AD_____

CONTRACT DAMD17-96-C-6069

TITLE: Breast Cancer Center Support Grant

PRINCIPAL INVESTIGATOR: Marc E. Lippman, M.D.

CONTRACTING ORGANIZATION: Georgetown University
Washington, DC 20057

REPORT DATE: September 1997

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

DTIC QUALITY INSPECTED 5

19980518 040

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY *(Leave blank)*

2. REPORT DATE
September 1997

3. REPORT TYPE AND DATES COVERED
Annual (1 Sep 96 - 31 Aug 97)

4. TITLE AND SUBTITLE
Breast Cancer Center Support Grant

5. FUNDING NUMBERS
DAMD17-96-C-6069

6. AUTHOR(S)
Marc E. Lippman, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Georgetown University
Washington, DC 20057

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

This document represents the annual report for our Breast Cancer Center Support Grant. Our grant consists of five areas, three projects and two cores. Projects include: Project 1 - Impact of Genetic Testing for Breast Cancer Susceptibility; Project 2 - A Coordinated Approach to Breast Cancer Diagnosis; and Project 3 - Development of Novel Antiangiogenic Therapies in Metastatic Breast Cancer. These projects are supported by Core 1 - Patient Accession Core, and Core 2 - Cancer Clinical and Economic Outcomes Evaluations Core. During the project period, each of the cores has become established and is fully functional, and each of the projects has begun to meet its objectives. Detailed summaries of the work in progress is provided in each of the project areas. Taken together, we believe that these projects, supported by their appropriate cores, have been successfully initiated and will be able to meet their statements of work, and to fulfill their scientific objectives during the granting period.

14. SUBJECT TERMS Breast Cancer

15. NUMBER OF PAGES
426

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

____ Where copyrighted material is quoted, permission has been obtained to use such material.

____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

✓ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

✓ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

PI - Signature 9/30/97
Date

TABLE OF CONTENTS

Front Cover 1

Standard Form 298 2

Foreword 3

Table of Contents 4

Principal Investigator's Introduction 5

Project 1 6
Impact of Genetic Testing for Breast Cancer Susceptibility

Project 2 11
A Coordinated Approach to Breast Cancer Diagnosis

Project 3 18
Development of Novel Antiangiogenic Therapies in Metastatic Breast Cancer

Core 1 37
Patient Accession Core

Core 2 48
Cancer Clinical and Economic Outcomes Evaluations Core

Appendix Packet 84

PRINCIPAL INVESTIGATOR'S INTRODUCTION

Since the inception of our Breast Cancer Center Grant, the participants have worked closely with one another to achieve the goals of the grant. While each of the projects has had significant problems to overcome, substantial success has already been achieved. For example, within **Project 1 (Impact of Genetic Testing For Breast Cancer Susceptibility)**, nearly 500 individuals have completed initial baseline interviews, and more than 284 have undergone testing for BRCA1 and BRCA2 mutations. Data are being gathered on both medical and psychological implications of these interventions. **Project 2 (A Coordinated Approach to Breast Cancer Diagnosis)** has also begun to accrue patients at a significant rate. It is of interest that at the recent retreat of the National Cancer Institute designed to set forth a research agenda for breast cancer research, one of the most critical diagnosis studies mentioned was, in fact, superimposible on the very study funded by the Army as our second project. Finally, **Project 3 (Development of Novel Antiangiogenic Therapies in Metastatic Breast Cancer)** has also made significant progress in terms of definition of protocols and is beginning accrual of patients. Detailed information about each of the projects and the cores which support them will be found on the following pages.

PROJECT 1: IMPACT OF GENETIC TESTING FOR BREAST CANCER SUSCEPTIBILITY

I. INTRODUCTION: Of the more than 180,000 cases of breast cancer that will be diagnosed this year in the United States, it is estimated that up to 18,000 are due to an inherited susceptibility to this disease. Advances in molecular genetics now allow women with a strong family history of breast and ovarian cancer the opportunity to determine whether they have inherited an increased predisposition to cancer. Two breast cancer susceptibility genes, BRCA1 and BRCA2, have been recently identified. Women who inherit an alteration in either of these genes have an estimated 55-85% risk of developing breast cancer (Struewing et al., 1997; Ford et al., 1994). The risk of ovarian cancer is thought to be 15-60% for women with a BRCA1 alteration and 15-20% for those with a BRCA2 alteration (Struewing et al., 1997; Ford et al., 1994). The impact of screening and prevention options, including preventive mastectomies or removal of the ovaries, in women with a BRCA1/2 alteration is unknown (Burke et al., 1997). While some studies have demonstrated a short-term impact of genetic testing on depressive symptoms and functional impairment in individuals from highly selected kindreds (Lerman et al., 1996; Croyle et al., 1997), it is important to gather both short- and long-term data on the psychological well-being of the more heterogenous group of high-risk individuals such as those represented in this study. Thus, the specific aims of this study are:

1) to identify determinants of who decides to undergo BRCA1/2 testing;

2) to evaluate the short- and long-term impact of BRCA1/2 testing on quality of life;

3) to evaluate the impact of genetic testing on prevention and surveillance practices;

4) to identify early predictors of psychological morbidity and nonadherence among participants in genetic testing programs; and

5) to develop a preliminary model to estimate the costs of BRCA1/2 testing per quality-adjusted life years ahead.

II. EXPERIMENTAL METHODS

A. ELIGIBILITY CRITERIA: The probability of obtaining an informative test result is maximized by first testing an individual within a family who has had breast or ovarian cancer at a young age. For this study, consistent with recommendations from the American Society of Clinical Oncology (1996), individuals who have at least a 10% chance of carrying a BRCA1/2 mutation are eligible for participation (see **Appendix 1** and **2** for eligibility criteria and estimated probabilities of identifying BRCA1/2 mutations based on eligibility). To help in promoting the program, we have named it the "CARE" or Cancer Assessment and Risk Evaluation Program. Considerable effort has been spent in maximizing patient accrual from internal providers at Georgetown and external provider referrals. Patients from Georgetown physicians have been ascertained primarily through the use of family history forms completed by patients during out-patient visits in medical oncology, radiation oncology, and surgery clinics (see **Appendix 3**). Patient lists from internal providers are also periodically reviewed to identify women with early onset breast and ovarian cancer. After obtaining permission from the treating physician, these patients are then contacted by letter and asked to call for more information about the CARE program. Written materials, including patient

brochures (see **Appendix 4**), have been sent routinely to external and internal providers to increase recruitment further. In addition, we have produced a booklet about genetic counseling and testing specifically designed for individuals who test positive to give to their relatives. The booklet also contains information about how to enroll in the study (see **Appendix 5**) and stresses that we would like to speak with individuals for brief phone interviews even if they are not interested in getting tested. Sample pedigrees of families with multiple participating relatives are included in **Appendix 6**.

B. STUDY PROCESS: Eligible individuals complete a 40 minute phone interview (see **Appendix 7**) which has been extensively refined and piloted. This interview covers medical and family history information as well as baseline levels of risk perceptions, depression, functional health status, preferences, and prevention practices. Within four weeks, participants meet with an experienced genetic counselor (under the supervision of a medical oncologist) for a one-on-one session in which a detailed evaluation of personal and family medical history is conducted along with a discussion of 1) characteristics of hereditary breast cancer and autosomal dominant inheritance; 2) possible outcomes of testing; 3) management options for carriers and non-carriers; 4) benefits, limitations, and risks of testing; and 5) consideration of alternative decisions and outcomes with respect to BRCA1/2 testing. Prior to this meeting, participants are asked to provide written informed consent. Comprehensive written material has been designed that reviews all of this information and is provided to patients at the conclusion of this session (see **Appendix 8**).

Those who opt for testing and who have signed the consent form can provide a blood sample at the conclusion of this initial session. Blood samples are not labeled with names but rather confidential identifiers. Testing for 12 common BRCA1/2 mutations is conducted at Georgetown University Medical Center's Institute for Molecular and Human Genetics. This panel of mutations has very high sensitivity for individuals of Jewish background, as three mutations are thought to account for the majority of mutations in this population. The panel is also useful for known familial mutations and offers the advantage of a rapid (i.e., 2-4 week) turnaround. All other testing is performed through the University of Pennsylvania by CSGE (conformation sensitive gel electrophoresis) analysis. These results are generally available in 3-6 months (for complete screening of the BRCA1 and/or BRCA2 gene), or within one month if only a single (familial) mutation is requested.

When results are available, individuals sign another consent form and meet with the genetic counselor and in some cases the medical oncologist for an in-person disclosure session. At this time, test results are explained with respect to cancer risks and medical management options. Risks to relatives are also reviewed and plans for communicating the information to others and coping resources are discussed. Standard supportive counseling is provided during the session. Study participants receive a phone call from the genetic counselor within 2 weeks of obtaining their results to see how they are doing and to answer questions. They also receive structured phone interviews at 1, 6, and 12 months to assess their psychological well-being, preferences for outcomes, and their decisions about screening and prevention options. In addition, all study participants receive a newsletter once or twice per year to keep them informed about recent developments in cancer genetics (see **Appendix 9**).

III. RESULTS AND DISCUSSION

A. STUDY ACCRUAL: To date, 474 individuals have completed the initial baseline phone interview, and 111 have declined genetic counseling and testing. About 90% of the individuals who completed baselines are Caucasian and 10% are minorities. Of note, 332 individuals have completed a pre-test genetic counseling session, and 284 have undergone testing for BRCA1/2 mutations. Of those individuals for whom results have been available, 70 tested positive for a BRCA1/2 mutation, 74 women from high-risk families had no mutation in the BRCA1 or BRCA2 genes, 15 had BRCA1/2 results of unknown clinical significance, and 42 relatives tested negative for the mutation identified in their family. The 185delAG mutation in the BRCA1 gene was identified in over 30% of positive individuals, and other common mutations in BRCA1 such as 1294del40 and 5382insC and the 6174delT in BRCA2 were carried by another 30% of participants. Most other mutations were family-specific.

Of the 70 individuals who tested positive for a BRCA1/2 alteration and who had relatives eligible for referral into this study (i.e., over 18 years of age and living within 6 hours of Washington), 79% informed at least one relative and provided a referral into the study; 14% told at least one relative but provided no referral into the study; and 7% did not share their results with any relatives. The number of 1, 6, and 12 month follow-ups completed thus far is 256, 123, and 28, respectively, and includes individuals who declined the initial visit. Based on current accrual, it is anticipated that we will be able to meet long-term recruitment goals and should therefore have sufficient power to perform statistical analyses.

B. INTEREST IN TESTING: In 1996, data from a companion study at Georgetown University called "Comparing Models of Pre-test Education for BRCA1 Testing" was analyzed in conjunction with preliminary data from the present study (Isaacs C, Peshkin B, Benkendorf J, Hughes C, Lerman C, 1996). Women from the former study were at low/moderate risk of having a BRCA1 mutation (n=314), whereas women from the current study were at high risk (n=93). We found that of the high-risk women, 72% reported that they were seriously considering testing versus 54% in the lower risk group (X^2; p=.001). Women cited learning about their children's risk, taking steps to prevent cancer, decisions for prophylactic surgery, and reducing uncertainty as the most important reasons to be tested. Losing insurance and effects of the test result on the family were the most important reasons reported for not wanting testing. Of the high-risk women, 69% had been tested or were taking steps to involve their affected relatives in testing. Of the low/moderate risk women, 44% had their blood stored for future testing. Once accrual is complete, we will conduct analyses to identify determinants of testing uptake in hereditary breast cancer families.

C. SCREENING PRACTICES: As screening practices are a critical measure of the medical impact of genetic testing, we investigated, at baseline, the breast and ovarian cancer screening practices for 152 high-risk study participants with no history of breast or ovarian cancer (Isaacs C, Peshkin B, Reutenauer J, Reed M, Main D, Lerman C, 1997). While the role of mammography in women age 40-50 is unclear, women at high risk for breast cancer and who test positive for a BRCA1/2 mutation are urged to begin mammography between age 25-35 (Burke et al., 1997). Our data revealed that over 85% of these women had a clinician performed breast exam at least yearly, and only 55% performed monthly breast self-exam. Mammography practices varied by age and race, with 82% of women over age 40 having their last mammogram within the last year, as compared with 60% of those 35-39, and only 34% of those 25-34. Just over 40% of women aged 25-34 had

never had a mammogram. Only 5% of our study subjects were participating in the NSABP Breast Cancer Prevention Trial of tamoxifen. In terms of ovarian screening, fewer than 20% of participants had either a CA-125 or a transvaginal ultrasound performed. Women from families with no history of ovarian cancer were significantly less likely to have had either of these two tests performed (16% vs 50%, p= .003). These data suggest that even in this high-risk population, approximately 20% of women over the age of 40 are not adhering to annual mammography recommendations and few women are undergoing ovarian cancer screening. Once study accrual is completed, we will assess the impact of genetic testing on screening and prevention practices and evaluate the cost effectiveness of such testing and subsequent screening. Genetic testing will also enable us to identify a cohort of women, particularly young women, who may benefit from advances in screening and prevention for ovarian cancer.

IV. RECOMMENDATIONS

- Continue current recruitment of study subjects referred from Georgetown providers and private practice surgeons as well as family members of known mutation carriers. Recruitment is currently on target.
- Through efforts of Patient Accession Core, increase recruitment of minority subjects
- Form contacts with other providers in the Washington, DC area to increase further the recruitment of minority subjects
- Continue cost-effectiveness analysis for this project

V. CONCLUSIONS: Genetic testing in high-risk families can have significant implications both medically and psychologically. It is therefore critical that such testing occur in the setting of comprehensive genetic counseling, both before and after testing. Identifying eligible patients for this study has been most successful by facilitating recruitment from internal providers and relatives of those who tested positive for a BRCA1/2 alteration. An initial assessment of baseline screening practices indicates that many women are not adhering to recommended guidelines, thus underscoring the role of genetic counseling and reinforcement of screening and prevention practices, even if individuals choose not to undergo genetic testing.

VI. REFERENCES

Burke W, Daly M, Garber J, Botkin J, Kahn MJE, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer: II. BRCA1 and BRCA2. JAMA 1997; 277: 997-1003.

Croyle RT, Smith KR, Botkin JR, Baty B, Nash J. Psychological responses to BRCA1 mutation testing: preliminary findings. Health Psychology 1997; 16: 63-72.

Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE, and the Breast Cancer Linkage Consortium. Risks of cancer in BRCA1-mutation carriers. Lancet 1994;343: 692-95.

Isaacs C, Peshkin B, Benkendorf J, Hughes C, Lerman C. Interest in testing for BRCA1: correlation between patient risk and desire for testing. Proc Am Soc Clin Oncol 1996; 15: 329.

Isaacs C, Peshkin B, Reutenauer J, Reed M, Main D, Lerman C. Cancer screening practices in women from high risk breast cancer families. Proc Am Soc Clin Oncol 1997; 17: 1916.

Lerman C, Narod S, Schulman K, Hughes C, Gomez-Caminero A, Bonney G, et al. BRCA1 testing in families with hereditary breast-ovarian cancer: a prospective study of patient decision making and outcomes. JAMA 1996; 275: 1885-1892.

Statement of the American Society of Clinical Oncology: Genetic testing for cancer susceptibility. J clin Onc 1996; 14: 1730-1736.

Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Eng J Med 1997;336:1401-8.

VII. APPENDICES (included in full packet following annual report text)

Appendix 1: Eligibility criteria
Appendix 2: Estimated likelihood of identifying BRCA1/2 mutations
Appendix 3: Family history form for patient completion
Appendix 4: CARE recruitment brochure (general)
Appendix 5: CARE brochure for relatives
Appendix 6: Sample pedigrees
Appendix 7: Baseline interview
Appendix 8: CARE written educational material
Appendix 9: CARE newsletter

PROJECT 2: A COORDINATED APPROACH TO BREAST CANCER DIAGNOSIS

I. INTRODUCTION: This project focuses on developing improved paradigms for breast cancer diagnosis using new methods of imaging and molecular markers of neoplasia measured in nipple aspirate fluid. The ultimate objective of such research is to reduce the number of unnecessary biopsies by improving the specificity and positive predictive value of diagnostic methods.

Currently, there are two parts of the imaging evaluation of women with possible breast cancer. In the first, the patient has a mammogram with two views of each breast obtained and may also have clinical breast examination. If any suspect region is found on the screening mammogram, then the patient proceeds to the second part. In the second part, a radiologist uses those imaging methods that are available to determine whether or not this suspect lesion is real, and whether the positive predictive value is great enough that biopsy is indicated.

Currently, approximately 10% (range 4-14 %) of women having a screening mammogram are called back for diagnostic mammography. In the diagnostic workup, special mammographic views such as compression spot views, magnification views or special mammographic projection views may be obtained. The patient may also have sonography and or breast magnetic resonance imaging with gadolinium. In some centers imaging with 99m Tc Sestamibi may be used. This radiotracer labeled agent, which was recently approved by the FDA, localizes in breast cancer.

After a full diagnostic workup, many patients are excluded from needing biopsy, but approximately 1/3 to 1/4 still need a biopsy. Of those who have a biopsy, 17-32% will have cancer based on the characteristics of the initial suspect region (some findings are more suspicious than others). With some patterns, the likelihood of cancer is close to 100%. But this still means that at least 2/3 of those having biopsy will not have cancer. This project, A Coordinated Approach to Breast Cancer Diagnosis (CABCAD) is designed to establish statistically supported criteria so that some of those women who now have biopsy and who are then found to have only benign disease, could be safely followed without biopsy.

II. BODY: In the CABCAD protocol, women with a suspect lesion identified by screening mammography and/or clinical breast examination and who have had a current standard diagnostic workup with the recommendation of biopsy are recruited into the study. Each woman who agrees is then studied with digital mammography, sonography, elastography, breast MRI with gadolinium, 99mTc Sestamibi and (in pre-menopausal women) has nipple fluid aspirated for cytogenetic analysis. The Sestamibi study is imaged with both a standard gamma camera and with a prototype high sensitivity high resolution dedicated breast gamma camera.

Each of these tests was selected because it looks at a different biological spectrum of disease. The digital mammogram looks at anatomy, the sonography looks at tissue texture, the elastography evaluates hardness, the MRI evaluates microvascularity, the Sestamibi evaluates an unknown factor that is related to p-glycoprotein and mitrochondrial localization probably based on molecular charge of the Sestamibi, the nipple aspirate fluid looks at cytogenetic lesions indicating biological change in the epithelium. Of the available imaging studies likely to be useful in this differentiation, only positron emission tomography is not included because of its great expense.

A. **PROGRESS:** In the first year there was a long delay caused by disagreements between the consent forms as approved by the Georgetown University Institutional Review Board and the US Army Human Subjects requirements. Multiple versions were submitted until we arrived at one form acceptable to both. Project 2, was therefore officially started June 30, 1997. Since that time, we have initiated the protocol and have recruited 48 women into it. In the initial start up phase, scheduling problems were encountered so that no all patients could have all studies. To a large extent these problems have been resolved and we are now recruiting two patients a week into the study and sometimes three or four. At this rate, we will be able to meet the required recruitment needs within the available time for the study. We will be working in this year to increase the recruitment rate slightly so that we are left with six months at the end of the four year project for data analysis. **Table 1** indicates the number of patients recruited into each arm of the study and the biopsy results to date.

Table 1: Biopsy Results of Patients Evaluated

Biopsy Results	No. Patients	Percent
Cancer	8	17
DCIS	2	4
LCIS	1	2
Atypical hyperplasia	4	8
Other benign	23	48
Results pending	5	10
No biopsy performed in spite of original recommendation for biopsy	5	10
Total Evaluated	48	100

Only 8 of the 38 (21%) women who have had biopsy and for whom we have the pathology results have had cancer. 10 of the 48 women did not have biopsy or the biopsy results are pending. Because the goal is to find features on imaging studies that indicate that the disease is a benign process, we need many benign cases for our analysis and consider this an appropriate ratio of benign to malignant lesions. The patients that have been recruited thus far are representative of the population of women who go for breast biopsy at Georgetown University Medical Center. We have a full range of ages included in the study as shown in **Table 2**. The average age is 50.6.

Table 2: Patients in Each Age Range

Age Range	No. Patients	Percent of Total
20-29	5	10
30-39	2	4
40-49	15	31
50-59	17	35
60-69	6	13
70-79	3	6

For the 48 patients evaluated to date, **Table 3** demonstates our success in completing the diagnostic studies and the reasons that studies were not conducted.

Table 3: Results of Procedures being Utilized

Procedure	Participants	Comments
Nipple aspirate fluid	attempted in 21 of 22 (95%)of pre-menopausal women	successful in 6
MRI	35 of 48 (73%)	1 excluded by criteria 5 refused 4 too large 3 not done due to scheduling problems on scanner
Nuclear Sestamibi imaging on Standard Gamma Camera	35 of 48 (73%)	5 refused 8 no available time on machine
Nuclear Sestamibi imaging on Special Gamma Camera	16 of 48 (33%)	5 refused 8 no available time slot for injection 9 lack of availability of machine 10 not done while awaiting new prototype of camera
Digital mammography	48 of 48 (100%)	
Ultrasound and elastography	38 of 48 (79%)	10 MD unavailable

During the start-up phase, many patients were unable to be scheduled for all studies. The situation has improved after discussions with each of the imaging areas. We have temporarily stopped using the breast dedicated gamma camera while we await the updated version of the prototype. A second prototype with improved sensitivity and a larger field of view is expected in November, 1997. There has been moderate patient resistance to both the MRI and the Sestamibi imaging. The causes of refusal are being noted as we believe that issues influencing patient unwillingness to have the study will be an important factor if these methods are determined to be important in the benign/malignant decision. This data is being recorded along with other indices of patient satisfaction with the study, to be used in cost-effectiveness and quality of life analyses conducted in conjunction with the Cancer Clinical and Economic Outcomes Evaluation Core (Core 2).

The low rate of uptake in the nipple aspirate studies reflects the fact that only 22 patients were premenopausal, the group most likely to yield breast fluid. The initial difficulties in scheduling influenced the lower than expected yield (6/22 = 27%). In the initial phases of the study, it was necessary to reserve specific time slots ahead of time for each modality to balance machine usage between clinical and research activities. Because the time allotted to each imaging modality was often exceeded in the initial period of the study, the Project Coordinator (who accompanied patients through all studies and also collected the nipple aspirate samples) was often rushed during the nipple aspiration procedure. This limited the time for the Project Coordinator to explain the nipple aspiration procedure, and for the patient to milk her breast (which usually requires several minutes). Succesful completion of the nipple aspiration technique requires adequate time for the milking procedure. These scheduling problems have been corrected in yield is now improving. In addition, we are beginning to attempt nipple aspiration of post-menopausal women as well as pre-menopausal, since the former may be expected to yield fluid in 25-50% of women below the age of 70.

1. New research information that is relevant to this study

a. Comparative evaluation of conventional vs. digital mammography: We have completed additional prospective evaluation of the digital mammography system that we are using in this protocol. We evaluated this system in a series of 134 cases which included 23 cancer cases. Six radiologists with no prior experience with digital mammography were, on average, better at distinguishing benign and malignant lesions on the digital images than on conventional high quality original mammograms. This result did not achieve statistical significance with this sample size, but the trend is clearly shown in Table 4. This article will be submitted for peer publication once we have a one year follow-up of the benign lesion cases so that we know that no cancers were missed. The data has been presented in the SPIE Medical Imaging Proceedings.

Figure 1: ROC Areas comparing digital mammography and screen-film mammography. Simulated diagnostic mode.

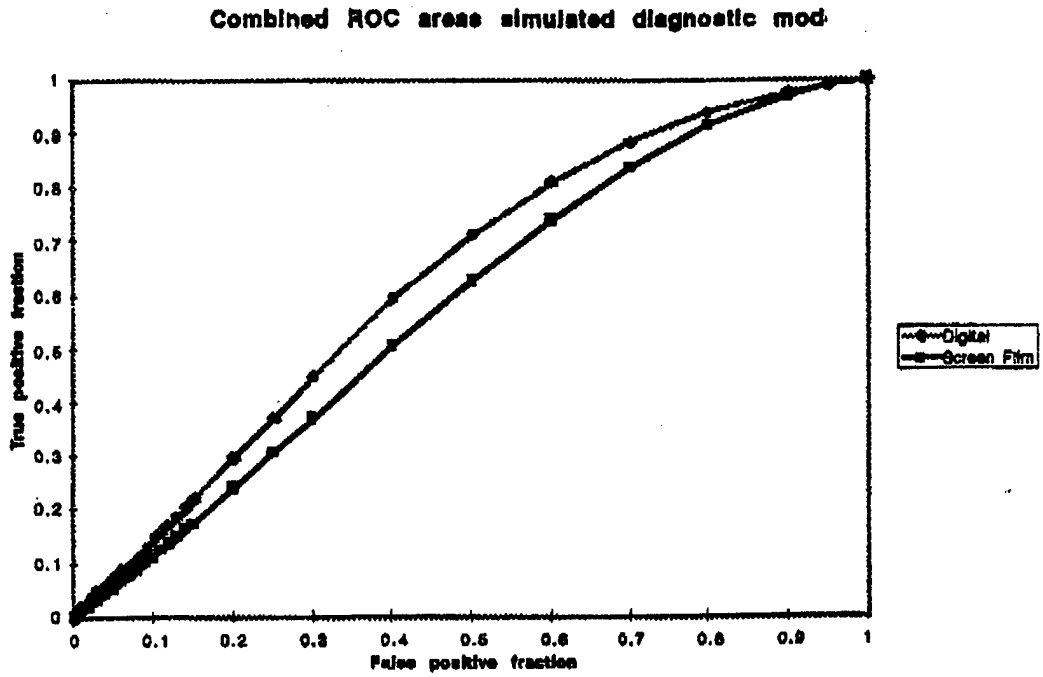


Table 4 demonstrates the average true positive fraction at each false positive fraction for the six readers in a study comparing 24 cancers and 25 lesions that at biopsy were shown to be benign. Digital and conventional images were compared.

Table 4

Reader	#1	#2	#3	#4	#5	#6	Average
Digital	0.600	0.656	0.735	0.697	0.462	0.643	0.633
Screen-film	0.609	0.616	0.556	0.575	0.495	0.644	0.583
p-value	0.923	0.637	0.085	0.069	0.741	0.992	

Table 4 shows the individual ROC areas under the ROC curves for each of the six readers as well as the average of these six values. The digital system is on average, better, but these results do not reach statistical significance with this relatively small sample size.

b. FDA approval for Sestamibi: At the time of the original grant submission, 99mTc Sestamibi had not completed evaluation by the FDA for use as a breast cancer imaging agent. This evaluation has now been completed and Sestamibi has received FDA approval for this purpose.

2. Changes in protocol: The Army reviewers of this original protocol recommended that we consider high resolution MRI instead of the MRI methods proposed in the funded protocol. We have evaluated these alternate protocols and have changed to this new protocol which is listed in below. High resolution MRI is becoming the standard method for MRI evaluation of suspect lesions in the breast. The technique allows one to study only the breast containing the suspect lesion. The other breast cannot be imaged with the same accuracy. For this reason we will be performing the ROC analysis limited to the one breast imaged rather than both breasts.

Richard Patt, MD, the Investigator for the MRI section of this protocol has left Georgetown. He has been succeeded by Susan Ascher, MD, an experienced MRI researcher whose CV is attached. She is the one who selected the current high resolution MRI protocol.

All BMRI will be performed on either of our 1.5 Tesla Siemens Vision magnets using a dedicated breast coil operating in the receive mode. Our MRI system affords maximal signal-to-noise ratio and spatial, contrast and temporal resolution, outperforming older systems. This should increase the sensitivity for the detection of minor degrees of gadolinium enhancement. The patient will lie prone in the magnet with both breasts being placed in the wells of the breast coil. We will use single breast technique for improved resolution. The breast undergoing examination will be flattened with foam pads to facilitate co-registration with other imaging methods. Markers will be placed on both the top and bottom of the breast if the CC projection is chosen, or on the inner and outer portion of the breast if the MR projection is chosen to allow for correction of shear deformation resulting in improved image registration. The imaging pulse sequence is a 3D FISP (fast imaging with steady state free precession) variant, a rapid gradient echo (GRE) technique that allows volume imaging of the breasts with 2.5 mm consecutive slice thickness. The pulse sequence parameters are as follows:

a. TE = 4.5 msec
b. TR = 10 msec
c. Flip angle (FA) = 40¡
d. Field of view (FOV) = up to 400 mm
e. Matrix size = 128 x 256 with 50% rectangular FOV in the phase encode direction
f. 64 partitions
g. 1 acquisition
h. Phase and frequency directions swapped depending on imaging plane
I. imaging time per sequence = 84 seconds

The scans will be performed once prior to contrast and three dynamic consecutive times following intravenous gadolinium bolus administration. No delays will occur between each of the three contrast-enhanced scans. Image calculation occurs after all 3 enhanced scans are completed. The gadolinium contrast agent will be administered at a dose of 0.1 mmol/kg using one of three FDA-approved paramagnetic agents: gadolinium diethylene triamene pentaacetic acid dimeglumine (Gd-DTPA, Berlex); gadolinium diethylene triament pentaacetic acid bis-methyl amide (Gd-DTPABMA, Winthrop); or gadolinium tirs (hydroxymethl) aminomethane (Gd-DO3A, Bracco) and given via the largest indwelling catheter able to be placed in a peripheral vein over 5 second. The contrast injection will be followed immediately by a 10 cc saline flush injection to clear the intravenous line of contrast. After the third post contrast acquisition, a very high resolution (1.28 mm effective slice thickness) 3D water excitation sequence will be performed with the following parameters:

a. TE = 9 msec
b. TR = 18 msec
c. FA = 25¡
d. FOV = 150 mm
e. Matrix size = 198 x 256
f. 1 acquisition
g. Phase and frequency directions swapped depending on imaging plane
h. Imaging time per sequence = 3:49 minutes

The data from the precontrast and three post contrast GRE sequences will then be subject to a subtraction post-processing algorithm developed by and provided to us for testing by the National Information Display Laboratories, a Division of Sarnoff Laboratories, Princeton, N.J. This program allows time intensity curves to be generated for each lesion observed.

The subtracted raw data will be viewed slice by slice as well as in 1 cm increments using maximum intensity projections and multiplanar reconstruction to allow image co-registration with other modalities. Each lesion with histopathologic correlation will be subject to the following types of evaluation:

a. Morphology-based on defined characteristic(s) of the lesion(s)' appearance
   Focal-well circumscribed vs. poorly circumscribed
   Diffuse-homogeneous vs. heterogeneous
   Margins-spiculated, poorly defined vs. well defined, branching
   Maximal bidirectional measurement

b. Contrast enhancement using the above semiautomated program which plots time-intensity curves as defined by the observer

With both the high resolution MRI limited to the evaluation of a single breast and the ultrasound and elastogram limited to the breast containing a suspect lesion, we have chosen to modify the ROC analysis so that it will be looking at only at the breast which contains the suspect lesion. We will thus have breasts that contain suspect lesions some of which are cancer and some of which are not cancer. Thus the ROC analysis will specifically address

the benign/malignant differentiation of suspect lesions. Based on an analysis of the ROC data we assembled in our study of digital mammography, we are also intending to redefine the ROC categories to correspond directly to the decision criteria recommended by the American College of Radiology Breast Imaging and Results and Decision System (ACR-BIRADS). These decision criteria are now becoming standard in US Radiological Practice. These new ROC categories are (1) Normal, (2) Benign finding, (3) probably benign finding recommend short term follow-up, (4) suspicious recommend biopsy, (5) cancer biopsy indicated.

3. **Clinical and Economic Outcomes:** We are collecting information on patient satisfaction, test acceptability, and costs using materials developed by Core 2.

4. **Data acquisition and analysis:** We are recording data as acquired. We perform routine demographic analysis of the study. Because of the small number of cases to data, we have not yet performed a statistical analysis of the imaging features being found.

III. CONCLUSIONS: Project 2, A Coordinated Approach to Breast Cancer Diagnosis is actively recruiting patients and is gathering data on patients with both benign and malignant disease. Initial scheduling problems have been addressed and recruitment is almost at the desired level. We have changed several aspects of the protocol based on the Army Reviewers recommendations and new knowledge. For the MRI evaluation we have changed to a high resolution single breast technique. We have modified the ROC statistical design to reflect the change to an evaluation of the involved breast only. These changes by producing images of higher quality, we believe, result in a stronger protocol that will result in more definitive final recommendations.

IV. REFERENCES

Freedman M, Steller Artz D, Hogge J, Zuurbier RA, Jafroudi H, Lo S-CB, Mun SK. An ROC Study of Screen Film Mammography and Storage Phosphor Digital Mammography: Analysis of Non-Concordant Classifications. Implications for the approval of digital mammography systems. Proc. SPIE Medical Imaging 1997. Harold Kundel Editor. 3606:281-291

American College of Radiology Breast Imaging Reporting and Data System (BIRADS). American College of Radiology, Reston VA 1993

V. APPENDIX (included in full packet following annual report text)

Appendix 1: NIH Biosketch for Susan M. Ascher, M.D.

PROJECT 3: DEVELOPMENT OF NOVEL ANTIANGIOGENIC THERAPIES IN METASTATIC BREAST CANCER

I. INTRODUCTION: The overall purpose of this proposal is to evaluate the clinical benefits of inhibitors of angiogenesis in regards to improving the care of patients with breast cancer. We are complementing these clinical trials with studies of the quality of life of participating patients, as well as with studies of the cost effectiveness of application of these agents in comparison to standard care.

As described in our original proposal, several possible angiogenic inhibitors are available for study. We selected two of these agents for our studies: the fumagillin derivative, TNP-470; and the sedative, thalidomide. Both had been shown to have anti-neovascular and anti-neoplastic properties in preclinical studies, and phase I studies of these drugs were either completed or underway at the time of our original proposal.

Clinical trials are now underway that will lead to accomplishment of our goals and aims. A Phase II study of thalidomide is actively accruing, and a Phase I pilot study of TNP-470 will open soon. Furthermore, additional trials are being started that will lead to a prospective randomized trial of the benefits of one of TNP-470 when added to the chemotherapeutic agent, paclitaxel. The following sections will describe our progress to date, as well as problems we have encountered and the actions we have taken to resolve them.

II. BODY

A. HYPOTHESIS/PURPOSE: We hypothesize that incorporation of well-tolerated antiangiogenic agents into standard treatment regimens for breast cancer will increase progression free survival, improve quality of life and, due to fewer treatment related side effects, decrease health care costs. Because these agents are unlikely to result in objective, measurable tumor regressions, we feel it is necessary to develop innovative trial designs to document their efficacy.

B. TECHNICAL OBJECTIVES:

1. To evaluate the antitumor activity of novel, non-cytotoxic antiangiogenic agents for the treatment of metastatic breast cancer in Phase II and Phase III trials. These studies will increase the availability of investigational agents to minority and under served patient populations with metastatic breast cancer.

2. To evaluate the impact on quality of life of non-cytotoxic antiangiogenic agents in a diverse spectrum of patients with metastatic breast cancer.

3. To evaluate the cost-effectiveness of non-cytotoxic antiangiogenic agents in patients with metastatic breast cancer.

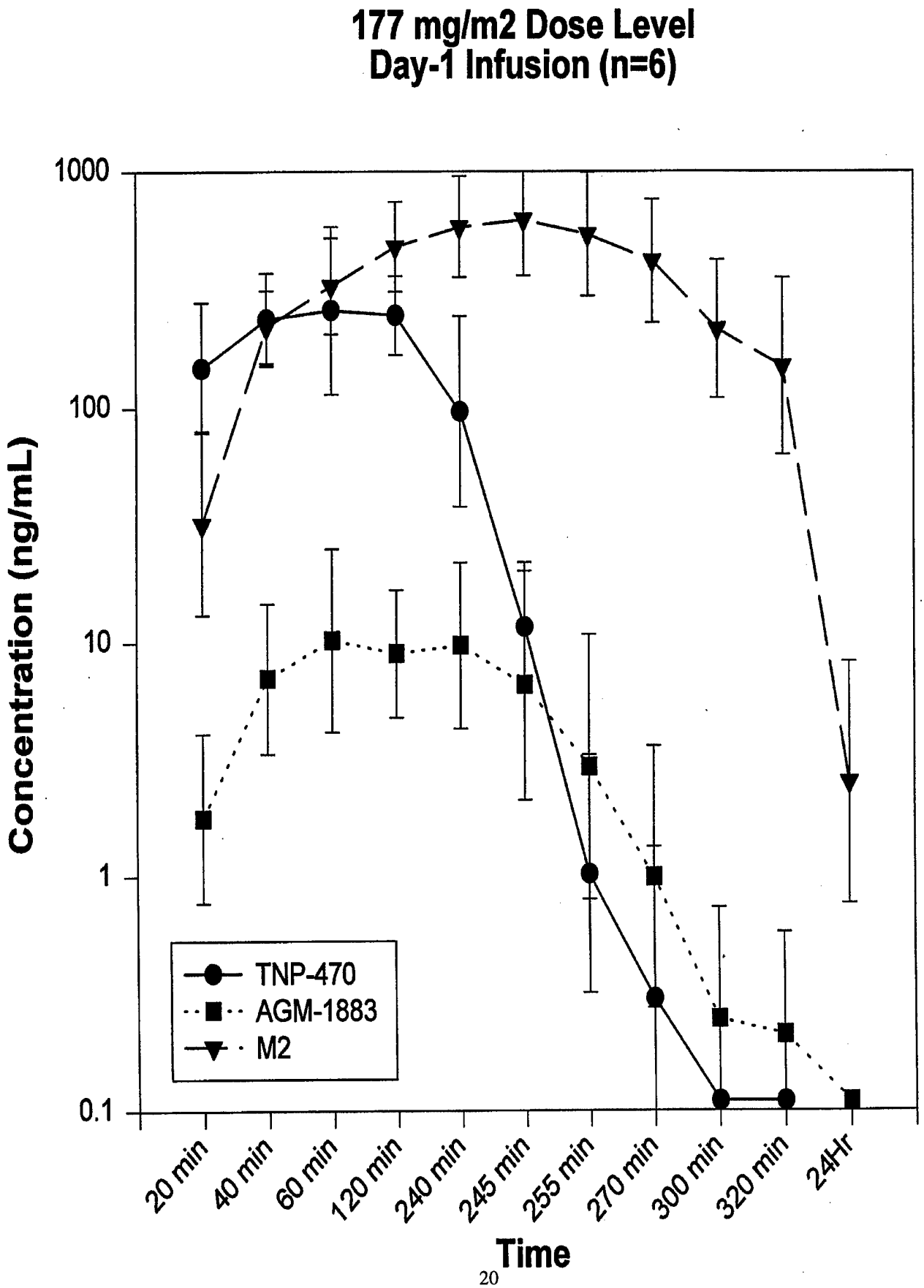
C. OVERVIEW OF CLINICAL TRIALS OF ANTI-ANGIOGENESIS: In our initial proposal, we planned two separate clinical trials of anti-angiogenic agents. In the first, we proposed to test the activity of the angiogenic inhibitor, TNP-470, using a novel trial design. In a second study, we proposed to test the efficacy of oral thalidomide, in a randomized phase II clinical trial. After some initial adjustments in trial design, we have now opened and are actively accruing to the

thalidomide study. However, a number of unforeseen obstacles have delayed implementation of the TNP-470 study, as we will describe below.

1. Clinical Trials of TNP-470: Originally, we had proposed a study in which patients with metastatic breast cancer who have not progressed after 6 cycles of induction chemotherapy would be randomly assigned to one of three investigational arms. In arm 1, patients would receive TNP-470 alone until progression, at which time they would be retreated with chemotherapy. In arm 2, patients would be observed off therapy until progression, at which time they would be offered TNP-470, and in arm 3 patients would continue with the same chemotherapy that they received for induction until they progressed, at which time they would be offered TNP-470 if they and their physicians felt that this approach would be in their best interest.

We remain enthusiastic about a randomized clinical study of TNP-470 as an angiogenic inhibitor in patients with breast cancer. However, we have elected to alter our clinical trial design from that which we originally proposed. We now plan to perform a prospective clinical trial in metastatic breast cancer, in which all patients will be randomly assigned to either the chemotherapeutic agent paclitaxel alone, or to paclitaxel plus TNP-470. We have made this decision for a number of reasons. One of the major factors is the absence of an optimal, easily administered dose and schedule for TNP-470. In our original application to DOD, we suggested that we would choose the dose recommended from our ongoing phase I trial. During the last year, completed phase I trials have demonstrated that this agent has a relatively short half-life is demonstrated in **Figure 1** (next page). These findings have necessitated a frequent dosing schedule to maintain potentially active drug levels (1).

Figure 1: TNP-470



Paclitaxel and breast cancer. A second reason we have altered our strategy rests in results from several recently reported studies regarding the anti-neoplastic agent, paclitaxel (Taxol). Paclitaxel has substantial activity in metastatic breast cancer, and recently published phase III studies suggest that use of paclitaxel as a single agent provides equal survival benefits and less toxicity when compared to paclitaxel and doxorubicin combinations (2). Indeed, in 1997, it is reasonable to consider paclitaxel as first-line therapy for hormone-refractory metastatic breast cancer (Coates, A. Commentary on presented abstracts. American Society of Clinical Oncology Meeting, May 1997). The ideal dose and schedule for paclitaxel administration have not been determined. Currently, the standard regimen is 175 mg/m2 over three hours. However, preliminary data have supported a dose and schedule-dependent relationship for response to this drug in breast cancer, favoring higher doses and longer administration (3). Data from several ongoing or recently completed randomized clinical trials that address these issues are not available, but uncontrolled phase II studies suggest that prolonged administration of the drug, such as for 96 hours, may result in increased activity (4).

Even if prolonged exposure to paclitaxel is advantageous, continuous infusions of this drug are cumbersome to deliver. Several studies have demonstrated that the drug can be delivered safely over a one-hour infusion, and that weekly 1h infusions of paclitaxel simulate prolonged exposure. For example, Seidman, et al, have reported administration of up to 100 mg/m2 for as many as 12 weeks (5). Breier, et al, have reported tolerance of 80 mg/m2/week for up to 6 months of continuous therapy (6).

Paclitaxel as an Angiogenic Inhibitor. As noted, the overall goal of this project is to identify clinically active inhibitors of angiogenesis in breast cancer. Paclitaxel itself may have angiogenic inhibitory properties. Results from preclinical studies have demonstrated that paclitaxel inhibits endothelial cell chemotaxis, invasiveness, proliferation, and in vitro cord formation (7). Oktaba et al have reported that paclitaxel inhibits neovascularization in the classic chick chorioallantoic membrane (CAM) model (8), and Klauber, et al, found that paclitaxel inhibits bFGF and VEGF induced corneal neovascularization (9). Similar results were observed by Winternitz, et al, especially when the paclitaxel was delivered in a sustained release formation (10).

Paclitaxel and TNP-470. Metabolic Interactions. Recently reported data suggest that TNP-470 and paclitaxel may be additive if not synergistic, based in part on a prolongation of the t1/2 of TNP-470 induced by the prior administration of paclitaxel. TNP-470 is metabolized by esterification to AGM-1883 (M-IV) which is an active metabolite. Further metabolism by cytochrome P450 microsomal epoxide hydrolase leads to the formation of inactive metabolites (M-II, M-III etc.).

In a an investigation of potential metabolic drug interaction between TNP-470 and anticancer agents, quantitative differences were observed in TNP-470 biotransformation in the presence of 25 μM paclitaxel (11). Combination of paclitaxel with TNP-470 led to a 50% decrease of M-II levels while unchanged TNP-470 and M-IV levels were increased by at least 2.5 fold as compared to control. These results suggest a possible inhibition of microsomal epoxide hydroxylase by paclitaxel thus decreasing the conversion of M-IV to inactive metabolites. Pharmacokinetic data from phase-I trials of TNP-470 alone were remarkable for the short half-life of TNP-470 and M-IV, which in theory would limit the duration of tissue exposure to these anti-angiogenic compounds. We propose that interaction between paclitaxel and TNP-470 will substantially prolong the half-lives and tissue concentrations of TNP-470 and M-IV. Concentrations of

paclitaxel <25 μM, which are typically achieved with the current dosing schedules of paclitaxel, have also been observed to inhibit microsomal epoxide hydroxylase, though to a lesser degree (personal communication, May 1997).

Based on these considerations, a phase I clinical trial is scheduled to open in October, 1997 at the Lombardi Cancer Center in which paclitaxel is being administered as a 96h infusion, with a 4h TNP-470 administration during the second day of therapy. Pharmacodynamic studies will determine whether the preclinical observation that paclitaxel induces a prolonged t1/2 for TNP-470 holds true in humans. Moreover, the toxicity of this regimen, in which the dose of TNP-470 will be escalated, will also be determined.

Paclitaxel and TNP-470. Biologic Considerations. TNP-470 and paclitaxel inhibit angiogenesis by distinct mechanisms, and when used together, would be expected to have an additive anti-angiogenic effect. In a study using AGM-1470 (TNP-470) in combination with paclitaxel in a CIA (collagen induced arthritis) model in rats, combination therapy resulted in significantly reduced clinical arthritis compared to either agent used alone (12). Female Louvain (LOU) rats were treated with 27.5 mg/kg of AGM-1470 on alternate days by subcutaneous injection or paclitaxel 7.5 mg/kg on alternate days by i.p. injection, alone or in combination, for 17 to 19 days after the induction of arthritis. Combination therapy was significantly better than single-agent AGM-1470 or paclitaxel in inhibiting clinical inflammation and bone destruction associated with the arthritis. Since inflammatory synovitis and pannus formation involve abnormal neovascularization, the greater efficacy of the combination was felt to be due to an enhanced anti-angiogenic effect. It was also demonstrated that the two agents could be used together safely in rats, although adverse effects of paclitaxel (transient weight loss, diarrhea, reversible granulocytopenia) appeared to be enhanced with concurrent administration of AGM-1470. Therefore, the combination necessitated a reduction of paclitaxel dose by 25% for subsequent cycles.

Revised Research Plans. Taken together, these results suggest that the combination of paclitaxel and TNP-470 might result in both direct tumor cell cytotoxicity due to the paclitaxel and, more germane to this proposal, to additive and perhaps synergistic suppression of angiogenesis due to both drugs. This anti-angiogenic effect may be enhanced if paclitaxel is administered in a fashion that results in prolonged exposure, either as a 96h continuous infusion or as a weekly 1h infusion. These results further suggest that the combination of the two agents might result in a prolongation of circulating TNP-470 levels and therefore enhanced activity. However, the precise dose, schedule and toxicities of combining these two agents have not been determined.

We therefore propose to delay initiation of our randomized trial while we perform two pilot phase I clinical studies to determine whether either continuous infusion or weekly administration of paclitaxel, coupled with simultaneous TNP-470, is preferable. The endpoints we will use to make this decision include pharmacokinetics (TNP-470 levels), toxicities, convenience of drug delivery, and overall cost of administration.

We fully plan to perform a randomized trial in patients with metastatic breast cancer. However, we will perform the pilot trials in patients with any metastatic malignancy that is refractory to standard therapy or for whom paclitaxel would be considered appropriate therapy. While we will preferentially place any patient with breast cancer for whom taxol is a reasonable treatment option on these trials, patients with other solid

tumors will also be eligible. We have chosen this strategy for the following reasons: 1) there is no reason to believe that the toxicities and pharmacokinetics observed in patients with other solid tumors would not be applicable to patients with breast cancer; 2) paclitaxel is active in many malignancies, and the two schedules to be tested are novel and may have even greater activity than that used in the standard clinical setting; and 3) wider eligibility will hasten our ability to complete these pilots and move on with the breast cancer-specific randomized trial.

Following completion of these two studies, which we anticipate will take approximately 12 months to complete, we will proceed with a randomized trial comparing paclitaxel vs. paclitaxel plus TNP-470 in patients with metastatic breast cancer, using a paclitaxel dose and schedule selected from these pilots.

We are requesting the same support as previously awarded to conduct these two pilot paclitaxel/TNP-470 trials, plus the thalidomide study described in the next section. The first of the pilot trials, in which paclitaxel will be administered as a 96h continuous infusion with TNP-470 on day 2 every three weeks, is partially supported by TAP Pharmaceuticals. However, the research nurse supported by the DOD will actively participate in regards to the quality of life and cost effectiveness analyses, which are not funded by TAP. TAP will provide TNP-470 for both pilot trials, but will not otherwise provide any financial support for the second pilot, in which paclitaxel will be administered as a weekly 1h infusion with TNP-470. Therefore, data management and other responsibilities of the research nurse, including QOL and CEA will be entirely supported by DOD funds.

Figure 2 illustrates our current clinical trial plan:

Year/Month	**1997**			**1998**												**1999**		
	10	**11**	**12**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**1**	**2**	**3...**
Thalidomide																		
TNP Pilot 1																		
TNP Pilot 2																		
Randomized Triall																		

TNP-470 PILOT TRIAL 1: Pilot Paclitaxel + TNP-470 Trial I. Continuous infusion 96h paclitaxel Plus day 2, 4h tnp-470

Since this trial was not previously described in our original proposal, details will be provided in this report. A full protocol, which is now being approved by the Georgetown University IRB, will be provided upon approval (Appendix 1).

1. OBJECTIVES

1.1 To determine the dose limiting toxicities (DLTs), maximum tolerated dose (MTD) and pharmacokinetics of TNP-470 and paclitaxel when administered together by intravenous (IV) infusion, TNP-470 over 4 hours and paclitaxel over 96 hours, once every 3 weeks in patients with advanced, incurable malignancies.

1.2 To document any objective antitumor responses that occur in patients treated on this protocol.

1.3 To obtain a metabolic profile on each patient with respect to P4502D6, P4503A4, P4502C18 and N-acetyltransferase and to evaluate the data obtained from this trial with respect to these parameters.

1.4 To describe quality of life (QOL) and cost of treatment for patients on this protocol.

2. PATIENT ELIGIBILITY

2.1 Patient must meet all of the following criteria:

2.1.1 Patients must have a histologically confirmed, incurable malignancy with locally unresectable disease or distant metastasis. Patients must have malignancies considered to be unresponsive or poorly responsive to the best cancer treatments currently available. Specifically, there must be no other mode of therapy which would have a greater chance of producing cure or significant palliation.

2.1.2 Patients must be 18 years of age or older.

2.1.3 Patients must have an anticipated survival of at least 8 weeks.

2.1.4 Patients must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible side effects), and must sign an informed consent.

2.1.5 Patients must be ambulatory, with an ECOG performance status of 0, 1 or 2 and must be maintaining a reasonable state of nutrition, consistent with weight maintenance.

2.1.6 Patients must have adequate organ function:

2.1.6.1 Hematologic: WBC 3,000/mm3, granulocytes 1,500/mm3 and platelet count 100,000/mm3);

2.1.6.2 Coagulation: PT and PTT within the normal range unless on anti-coagulants;

2.1.6.3 Hepatic: bilirubin # 1.2; SGOT, SGPT #2 x ULN; and

2.1.6.4 Renal: serum creatinine # 1.5 (or creatinine clearance 60 ml/min).

2.1.7 Patients must be on stable doses of any drugs which may affect hepatic drug metabolism or renal drug excretion (e.g.--non-steroidal anti-inflammatory drugs, corticosteroids, diphenylhydantoin, barbiturates, narcotic analgesics, probenecid). Such drugs should not be initiated while the patient is participating in this study unless required to ameliorate toxicity.

2.1.8 Patients must have recovered from the reversible side effects of prior therapy.

2.2 Contraindications to Enrollment

2.2.1 Recent major surgery (within 21 days).

2.2.2 History of a bleeding diasthesis

2.2.3 Recent (# 6 weeks) history of seizures.

2.2.4 History of peripheral neuropathy Grade 2.

2.2.5 Frequent vomiting or severe anorexia.

2.2.6 History of weight loss > 10% of current body weight within the last 4 weeks.

2.2.7 Pregnant (obtain pregnancy test in women with child bearing potential) or lactating women. (NOTE: women and men enrolled in the study are to practice an effective method of birth control while on the study and for at least six months after their last treatment on protocol).

2.2.8 Serious intercurrent medical illnesses which would interfere with the ability of the patient to carry out the treatment program.

2.2.9 The following therapies are prohibited and may not be administered to patients being treated on this protocol: chemotherapy other than that specified in this protocol, and immunotherapy. Limited field radiation is permitted for painful bony lesions or other palliation.

2.2.10. Patients who have been treated with a hormonal therapy for 6 months and who have evidence of progressive disease may be entered on this protocol and continued on their current hormonal therapy if the patient and their physician feel it is in the patient's best interest.

3. TREATMENT PLAN: Summary. Eligible patients who have signed the consent form will have their metabolic profile determined. TNP-470 will be administered as a 4-hour infusion on day 1. Taxol will be administered starting on day 8 as a 96-hour infusion. On day 9, once steady state concentrations of Taxol are achieved, TNP-470 will again be administered as a 4-hour infusion.

The second and subsequent cycles will be administered at 3 week intervals from the first day of Taxol infusion. For each cycle, Taxol will be administered as a 96 hour infusion with TNP-470 given as a 4-hour infusion on the second day of Taxol treatment. All treatment will be done on an outpatient basis. The 96-hour continuous infusion of Taxol will be accomplished using an ambulatory pump.

Day	First Cycle					Subsequent Cycles			
	D1	D8	D9	D10	D11	D1	D2	D3	D4
TNP-470	X		X				X		
Paclitaxol		X	X	X	X	X	X	X	X

In the absence of progressive disease, patients may be continued on treatment. Patients who experience dose limiting toxicities may resume treatment at a lower dose if the side effects resolve within 3 weeks.

The first 3 patients will begin on dose level 1. If no patients develop dose limiting toxicity during the first 4 weeks, then the next 3 patients will be started at dose level 2. If 1 of 3 patients experience dose limiting toxicity during the first 4 weeks of TNP-470, then an additional 3 patients will be started at that dose level. If less than 2 of 6 patients treated at any dose level experience dose limiting toxicity, the next patients will be started at the next dose level. As soon as two patients at a given dose level experience dose limiting

toxicity, no additional patients will be started at that dose level. If at least six patients have been studied on the previous dose level then that dose level will then be considered the MTD.

3.1. Dose limiting toxicities have been defined by shading the appropriate boxes in the NCI Common Toxicity Criteria in the protocol document.

3.2 Definition of the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D), which is the dose we will use in the prospective randomized trial of paclitaxel vs. paclitaxel + TNP-470. The MTD is defined as the highest dose level which results in Dose Limiting Toxicity (DLT, defined by the shaded boxes in the NCI Common Toxicity Criteria) in fewer than 2/6 patients. When >2 patients experience DLT at a given dose level, the MTD will have been exceeded and the previous dose level will be declared the MTD provided 6 patients were treated at that level. Often the RP2D will be the same as the MTD. However, if the toxicities observed at the dose level above the MTD or in 1 of 6 patients at the MTD were particularly severe, irreversible or fatal, and clearly related to drug administration, the next lower dose level would be declared the RP2D provided the side effects observed in all 6 patients treated at this dose level were acceptable. As explained above, tolerance to the RP2D will then be confirmed by the study of 10 additional patients.

3.3. Accrual of women and minorities. Characterization of drug metabolism, pharmacokinetics and pharmacodynamics in anticipation of a prospective randomized trial in women with metastatic breast cancer is a major objective of this pilot trial. However, as noted, although we will preferentially treat women with breast cancer on this study, it will not be limited to patients with breast cancer. If fewer than 50% of the patients treated at the RP2D are women, additional women may be accrued at the RP2D to evaluate any possible differences in drug processing. Since, by definition, minority patients (Black, Hispanic, Oriental, Native American) are less likely to be studied in any clinical trial, additional minority patients may be entered at the RP2D to obtain data relevant to these populations. Indeed, as described in the Patient Access Core section of this report, we are making a special effort to enroll minorities in these studies.

3.4 Patient dose escalation. Intrapatient dose escalation will be permitted from the second cycle onwards in the absence of side effects.

3.5 Dose levels.

Level	TNP-470 (mg/m^2)	Taxol (mg/m^2)
1	88.5	105
2	88.5	140
3	133	140
4	177	140

4. PHARMACOKINETICS

4.1 Collection of blood samples. Blood samples (9 ml) will be collected in heparinized (nonseparator) tubes. At each sampling time 1 ml of whole blood will be withdrawn and discarded to remove blood diluted with the heparin used to maintain catheter patency. Vacutainer collection tubes are to be immediately placed on ice and centrifuged at 4°C for 5 - 10 min. To 1 ml of plasma, add 100 :l of 2% (wt.%) H2SO4 (Mallinckrodt, Paris, KY, USA). The addition of sulfuric acid to the samples has the effect of acidifying the plasma to a pH of 4 to 5, a pH range in which TNP-470 is most stable. Acidification of the plasma also serves to partiality denature plasma proteins. Plasma is divided into 2 aliquots in screw top polyethylene tubes and then labeled and stored at -70oC or lower. Samples will be assayed by the Abbott Laboratories.

4.2 Time points for sampling.

4.2.1 TNP-470 pharmacokinetics. Complete pharmacokinetics are mandatory after the day 1 and 9 injections. Pharmacokinetics may be repeated in some patients who continue to receive TNP-470 past day 29. A blood sample should be obtained just prior to the injection and then 2 and 4 hours during the infusion and 5, 15, 30, 60, and 120 minutes after the end of the infusion and 24, 48 and 96 hours after the beginning of the infusion. The exact date and time that the infusion was started and completed, and each blood sample was obtained must be recorded.

4.2.2 Paclitaxol Pharmacokinetics. A blood sample should be obtained just prior to the infusion and then 48,72, and 96 hours after the start of infusion. The exact date and time that the infusion was started and completed, and each blood sample was obtained must be recorded.

4.2.3 Other fluids and tissues. If available, other fluids (e.g. pleural, peritoneal, cerebrospinal) or tissues (e.g. bone marrow) will be studied to determine if TNP-470 is transported into such sites. Fluids or tissues collected will be as part of standard medical management and not obtained solely for the purposes of this research.

5. TREATMENT MODIFICATIONS AND MANAGEMENT OF TOXICITY

5.1 Dose modification for toxicity. Dose limiting toxicities (DLTs) are identified by the shaded boxes in the NCI Common Toxicity Criteria. Specifically, hematologic DLT will be defined as granulocyte nadir <500 /:L for >7 days, platelet count <50,000/:L or febrile neutropenia (temperature >38▾C with AGC <1,000/:L). When DLT occurs, treatment with TNP-470 and taxol will be interrupted until the toxicity decreased by 2 grades or returns to baseline.

In case of hematologic DLT, the patient may be retreated at the same dose level with appropriate medical management of toxicity as described below. If, however, the hematologic DLT recurs despite appropriate medical management, the patient should be treated at the next lower dose level on subsequent cycles. In case of a non-hematologic DLT, the patient should be treated at the next lower dose level on subsequent cycles. Patients who experience a non-hematologic DLT on the first dose level should be restarted at 50% of the dose for both, TNP-470 and taxol. Hematologic DLTs should receive appropriate medical management without dose reduction. If the hematologic DLT recurrs despite appropriate medical management, the patient should be retreated at 50% of the doses for both, TNP-470 and taxol.

Patients who experience toxicities 1 Grade or more above DLT will be considered to have had potentially life threatening toxicity from TNP-470. In general these patients should not be restarted on TNP-470 once toxicity resolves unless there is some indication of patient benefit. In these cases the reason(s) for reinstituting TNP-470 must be clearly indicated in the case report form.

5.2 Management of anticipated toxicities.

5.2.1 TNP-470. Toxicities observed in phase-I trials of TNP-470 included mild fatigue, nausea and central nervous system (CNS) toxicities. CNS toxicities included ataxia, gait disturbance, dizziness, light-headedness, nystagmus, increased anxiety and emotional lability. These were dose limiting and resolved within 4 weeks of stopping the treatment. During the study, physical and neurologic exams and laboratory parameters (platelet counts and coagulation studies) will be closely monitored. TNP-470 will be discontinued at the first clinical evidence of bleeding (e.g.--cutaneous or retinal petechiae, guaiac positive stools), thrombocytopenia, coagulation abnormalities, seizures, or ataxia (see dose limiting toxicities that have been shaded in NCI Common Toxicity Criteria).

5.2.2 Paclitaxel. Blood counts will be closely monitored for myelosuppression, by far the commonest toxicity. For patients experiencing only dose limiting myelosuppression in the absence of other

non-hematologic DLT, granulocyte-colony stimulating factor ([G-CSF] filgrastim; Amgen, Thousand Oaks, CA) 5:g/kg/day will be administers subcutaneously on days 5 through 12 beginning 24 hours after the completion of the taxol infusion. G-CSF will be continued, if necessary, till the AGC is >2,000/:L for 3 consecutive days. Nausea and vomiting will be treated as per the anti-emetic guidelines at the Lombardi Cancer Center; diarrhea may be managed with anti-motility agents like loperamide; mucositis may be managed with mouth washes; arthralgias/ myalgias may be treated with analgesics e.g. tylenol with codeine. Peripheral neuropathies are generally transient and require no specific treatment. Febrile neutropenia will be treated as per current guidelines at Lombardi Cancer Center. Hypersensitivity reactions to taxol are rare; however as a prophylaxis, decadron 20 mg p.o. will be given 12 hrs and 6 hrs prior to taxol administration, followed by decadron 20 mg i.v., diphenhydramine 50 mg i.v. and famotidine 20 mg i.v. 60 minutes prior to taxol administration. Treatment for toxicities in individual patients will be determined by the principal investigator. Treatment will be held at the first evidence of non-hematologic DLT as defined by the shaded boxes in the NCI Common Toxicity Criteria.

5.3 Removal from study for prolonged toxicity. Patients who do not experience DLTs may continue to receive treatment. If DLT occurs, treatment must be interrupted and the patient assessed at weekly intervals. Treatment may be resumed according to the guidelines mentioned above. If it is not possible to resume therapy after a 4 week delay due to persistent treatment related toxicities, the patient should be taken off study.

5.4 Continued treatment of patients who are experiencing significant clinical benefit. It may be in the patient's best interest to continue on treatment despite the occurrence of prolonged or otherwise unacceptable toxicity. Patients who are experiencing a significant clinical response from treatment and in whom continued therapy is indicated may be continued at a reduced dose of TNP-470 as determined by the Principal Investigator.

5.5 Unavoidable treatment delays for non-medical reasons. Treatment interruptions for non-medical reasons (for any reason, at the discretion of the patient and physician) are at times unavoidable and are permissible under this protocol. However, every attempt should be made to avoid any non-medical treatment delays, especially during the first 4 weeks of treatment. Patients who require frequent or prolonged treatment interruptions should be taken off study. Patients who have their treatment interrupted for reasons not related to side effects during the first 14 days of treatment will not be included in the determination that it is safe to enter subsequent patients at the next higher dose level and an additional (replacement) patient will be started at this dose level.

6. TOXICITY MONITORING AND ADVERSE EXPERIENCE REPORTING

6.1 At each weekly visit during the first 4 weeks and every 2 weeks thereafter:

6.1.1 <u>an interim history</u> will be obtained and a directed physical examination (to include at a minimum ECOG performance status, weight, fundoscopic exam, examination of skin and mucosal surfaces for petechiae) will be performed;

6.1.2 <u>obtain a CBC</u>, differential, platelet count, coagulation studies;

6.1.3 <u>obtain a chemistry survey</u> (to include BUN, creatinine, LDH, SGOT/AST, alkaline phosphatase, total bilirubin, calcium, glucose, and uric acid), electrolytes and SGPT.

6.1.4 <u>Obtain a urinalysis</u> and stool guiac.

6.2 Laboratory studies will be repeated more frequently if clinically indicated, and any abnormalities potentially related to treatment will be followed until they have resolved, or have been determined to not be treatment-related.

7. CRITERIA FOR TERMINATING TREATMENT

7.1 Patients who experience substantial benefit attributed to treatment should continue to receive protocol therapy until progressive disease is discovered. Reasons for continued treatment are to be documented in the case records.

7.2 Rapid disease progression in the first month of treatment (50% enlargement of measurable disease) is grounds for termination of treatment. Patients with less rapid disease progression may remain on-study, at the discretion of the investigator after discussion with the patient.

7.3 Any disease progression (25%, or new metastases) occurring after the first month on study, requires treatment termination.

7.4 DLT that does not resolve within 3 weeks of stopping TNP-470.

7.5 Intercurrent illness which prevents further therapy.

7.6 General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator.

7.7 The patient or patient's physician is free to discontinue treatment and take the patient off study at any time, if this is believed to be in the patient's best interest.

8. STATISTICAL CONSIDERATIONS

8.1 This study will determine the Dose Limiting Toxicities (DLTs) and Maximum Tolerated Dose (MTD) for TNP-470 and Taxol administered by IV injection once every 3 weeks. The MTD is defined as the highest dose level which results in DLT during the first 4 weeks of treatment in fewer than 2/6 patients. When 2 patients experience DLT at a given dose level, the MTD will have been exceeded and the previous dose level will be declared the MTD.

8.2 TNP-470 will be assayed in plasma and urine for each patient treated on this study by Abbott Laboratories. Because the T½ of TNP-470 in other studies has been short, we anticipate that we will achieve steady state drug concentrations during the 4 hour infusion and will use standard pharmacokinetic analyses for infusions (36). We will determine the steady state concentration of TNP-470 by averaging the determinations taken at 1, 2, and 4 hours during the infusion. The T½ will be estimated using determinations obtained following the end of the infusion.

The total body clearance of TNP-470 will be determined for each patient by dividing the infusion rate by the study state concentration.

8.3. Patients will be characterized as extensive (EM) or poor (PM) metabolizers for each of 4 metabolic pathways: P4502D6, P4503A4, P4502C18 and N-acetyltransferase. Toxicity, anti-tumor responses and the PK parameters detailed above will be described in the context of the metabolic profile as determined for each patient. Given the small numbers of patients that will be treated on this trial, these characterizations are expected to provide, at most, data that can be further evaluated as subsequent trials of this agent are initiated.

8.4. Quality of Life (QOL) and Cost Effectiveness Analysis (CEA). Each patient will be assessed for QOL parameters prior to and during therapy. The methods and instruments to be used will be described in great detail in the Cancer Clinical and Economic Outcomes Evaluations Core section of this report. Of note, particular care will be made to assess patient choice regarding the effects of having a 96 hour infusion, including the inconvenience and cost of the transportable infusion pump.

TNP-470 PILOT TRIAL 2: Pilot Trial of Paclitaxel and TNP-470 II. *Weekly* 1 hr Infusion Paclitaxel plus TNP-470

In anticipation of initiating a prospective randomized trial of paclitaxel with or without TNP-470, we wish to determine whether one schedule of this combination might be preferable over another. We will preferentially choose the regimen that provides the most favorable pharmacokinetics for TNP-470. If the two regimens are roughly equal in this regard, then we will choose the more favorable schedule in regards to quality of life, and finally in regards to cost. Therefore, we are collecting all of these data in both pilot studies. Of note, if pharmacokinetic results favor one regimen, but it is associated with unacceptable quality of life correlations to the point that patient compliance is of concern, then we will over-ride pharmacokinetic considerations in favor of patient compliance.

We will conduct a second trial that takes advantage of the recently reported results of administration of paclitaxel at relatively high doses (80-100mg/m2) on a weekly schedule with acceptable toxicities. Since we will gather QOL and pharmacokinetic data from patients on both pilot studies, we will be able to choose one paclitaxel schedule over the other for the prospective randomized trial of paclitaxel +/- TNP-470 based on TNP-470 levels and patient preferences in the two studies.

1. OBJECTIVES

1.1 To determine the dose limiting toxicities (DLTs), maximum tolerated dose (MTD) and pharmacokinetics of TNP-470 and paclitaxel when administered together by intravenous (IV) infusion of paclitaxel over 1 hour followed by TNP-470 over 4 hours, once every week in patients with advanced, incurable malignancies.

1.2 To document any objective antitumor responses that occur in patients treated on this protocol.

1.3 To obtain a metabolic profile on each patient with respect to P4502D6, P4503A4, P4502C18 and N-acetyltransferase and to evaluate the data obtained from this trial with respect to these parameters.

1.4 To describe quality of life (QOL) and cost of treatment for patients on this protocol.

2. PATIENT ELIGIBILITY: Patient eligibility will be identical to that described in Pilot Trial I above.

3. TREATMENT PLAN: Summary. Eligible patients who have signed the consent form will have their metabolic profile determined. TNP-470 alone will be administered as a 4-hour infusion on day 1. Taxol will be administered starting on day 8 as a 1-hour infusion, followed by TNP-470 as a 4-hour infusion.

The second and subsequent cycles will be administered at 1 week intervals from the first day of Taxol infusion. For each cycle, Taxol will be administered as a 1 hour infusion with TNP-470 given as a 4-hour infusion on the same day as Taxol treatment. All treatment will be done on an outpatient basis.

	D1	D8	D15	D22	D29	D36
TNP-470	X	X	X	X	X	X
Paclitaxel		X	X	X	X	X

In the absence of progressive disease, patients may be continued on treatment. Patients who experience dose limiting toxicities may resume treatment at a lower dose if the side effects resolve within 3 weeks.

3.1. Patient dose escalation. Since this trial will involve weekly chemotherapy, intra- patient dose escalation will not be permitted. In the absence of TNP-470, the MTD for paclitaxel alone given on a weekly schedule is reported to be 80-100 mg/m2. Therefore we will not strive to exceed 100mg/m2 weekly, and we will stop the study if toxicity is satisfactory at dose level 6.

3.2 Dose levels.

Level	TNP-470 (mg/m^2)	Taxol (mg/m^2)
1	88.5	70
2	88.5	80
3	133	80
4	133	90
5	177	90
6	177	100

The first 3 patients will begin on dose level 1. If no patients develop dose limiting toxicity during the first 4 weeks, then the next 3 patients will be started at dose level 2. If 1 of 3 patients experience dose limiting toxicity during the first 4 weeks of TNP-470, then an additional 3 patients will be started at that dose level. If less than 2 of 6 patients treated at any dose level experience dose limiting toxicity, the next patients will be started at the next dose level. As soon as two patients at a given dose level experience dose limiting toxicity, no additional patients will be started at that dose level. If at least six patients have been studied on the previous dose level then that dose level will then be considered the MTD.

3.3 Dose limiting toxicities, definition of the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D), and accrual of women and minorities are identical to those described above for Pilot Trial I.

4. PHARMACOKINETICS

4.1 Collection of blood samples. Blood samples (9 ml) will be collected and processed as described above for Pilot Trial I.

4.2 Time points for sampling. TNP-470 pharmacokinetics. Complete pharmacokinetics are mandatory after the day 1 and 8 injections. Pharmacokinetics may be repeated in patients who continue to receive paclitaxel/TNP-470 past day 29. A blood sample should be obtained just prior to the injection and then and 4 hours during the infusion and 5, 15, 30, 60, and 120 minutes after the end of the infusion and 24 and 48 hours after the beginning of the infusion. The exact date and time that the infusion was started and completed, and each blood sample was obtained must be recorded.

4.2.1 Taxol Pharmacokinetics and other fluids and tissues. These specimens will be collected, processed, and handled as described above for Pilot Trial I.

5. TREATMENT MODIFICATIONS AND MANAGEMENT OF TOXICITY: These will be similar to those described in Pilot Trial I. Final details will be included in a full protocol which is currently under development.

6. STATISTICAL CONSIDERATIONS: This study will determine the Dose Limiting Toxicities (DLTs) and Maximum Tolerated Dose (MTD) for TNP-470 and Taxol administered by IV injection on a weekly schedule. The MTD is defined as the highest dose level which results in DLT during the first 4 weeks of treatment in fewer than 2/6 patients, unless Dose Level 6 is reached without DLT. In that case, Dose Level 6 will be used for subsequent studies. When ≥2 patients experience DLT at a given dose level, the MTD will have been exceeded and the previous dose level will be declared the MTD.

6.1 TNP-470 will be assayed in plasma and urine for each patient treated on this study by Abbott Laboratories. These studies will be performed as described for Pilot Trial I.

6.1.1 Quality of Life (QOL) and Cost Effectiveness Analysis (CEA). Each patient will be assessed for QOL parameters prior to and during therapy. These will be described in great detail in the Cancer Clinical and Economic Outcomes Evaluations Core. Of note, particular care will be made to assess patient choice regarding the effects of having weekly infusions, including the inconvenience and cost of the having to visit the outpatient infusion room at the Lombardi Clinic, and the 5-6 hours necessary for infusion each week.

Summary of TNP-470 Pilot Studies. In summary, preclinical and clinical data suggest that the combination of paclitaxel and TNP-470 may be additive if not synergistic as a result of prolonged half-life of TNP-470 and additive anti-angiogenic activities. Therefore, we plan to conduct a prospective randomized trial comparing paclitaxel and TNP-470 to paclitaxel alone in women with metastatic breast cancer. These two pilot studies will provide data that permit us to select a schedule and dose for this combination, based on pharmacokinetics, quality of life, and cost of the two regimens. We anticipate proceeding to the prospective randomized trial within 12-18 months.

2. Clinical Trial of Thalidomide. Overview. As described in our initial proposal, the sedative thalidomide has been shown to have potent anti-angiogenic activity in preclinical models. Indeed, it has recently been approved for clinical use in this country for non-neoplastic diseases, with the caveats necessary to avoid exposure to pregnant women.

We have therefore chosen to pursue studies of thalidomide in patients with breast cancer. Thalidomide was tried in the treatment of cancer in the early sixties. In a study by Olson, patients with advanced cancer were treated with thalidomide at a dose of 200mg three times daily. In the absence of toxicity, the dose was increased as tolerated to as high as 1400mg/day. Grabstald treated 71 patients with advanced cancer with a variable doses ranging between 300mg to 2000mg/day with the main side effect being sedation. In these studies, some symptomatic improvement was noted, and occasionally prolonged stabilization of the disease was reported.

Phase II Evaluation of Thalidomide in Patients with Metastatic Breast Cancer at Georgetown.

Initially, we opened a randomized phase II trial with relatively restricted eligibility requirements, especially in regards to measuring the rate of tumor growth in the preceding months prior to study entry. Although of course response rates would be determined, the main endpoint of the trial, as it was written, was to determine whether thalidomide, at one of two doses, would slow the rate of tumor progression. If so, then it would be considered an active drug and tested in a more "adjuvant-like" setting. However, using this trial design, we screened over 70 potential patients from March 1996 until December 1996, and only placed 1 patient on study.

Therefore, we met with representatives of the National Cancer Institute, who are supplying the drug, and we took two very important actions to enhance accrual: 1) We broadened eligibility, including deleting the requirement for preceding tumor growth measurements, so that time to progression has become the major endpoint; and 2) We expanded to other study sites, including the University of Chicago (Dr. Gini Fleming), the Dana Farber Cancer Institute (Dr. Charles L. Shapiro), and Duke University Medical Center (Dr. Lindsay Harris). These changes were fully approved by the Georgetown IRB in April, 1997, and since then we have accrued 6 additional patients. The study has just been opened at Chicago in September, 1997, and is currently under IRB review at DFCI and Duke. We anticipate that these additional sites will permit us to fully accrue to the original target during the next 12 months. The following is a more complete progress report of this study.

This study is a phase II evaluation of thalidomide in patients with metastatic breast cancer. It is a multicenter, open label, randomized study to evaluate the safety and efficiency of oral daily administration of thalidomide as a therapy for a maximum of 50 patients with metastatic breast cancer.

Pertinent documentation regarding the full protocol, including the approval of amendments, is included in **Appendix 2**.

1. **PRIMARY OBJECTIVE:** To assess the difference (if any) in activity (by evaluating time to progression) and safety profile between the low dose and high dose arm of thalidomide.

2. **SECONDARY OBJECTIVES**

2.1. To determine the objective response rate (complete and partial response rates) of thalidomide in patients with measurable metastatic breast cancer at both arms.

2.2. To determine time to response and survival.

2.3. To compare the post- versus the pre-treatment tumor growth rates in patients with a known rate of tumor growth over the 2-4 month period prior to starting thalidomide.

2.4. To analyze growth factors expression and matrix metalloproteinase activity in patients receiving thalidomide, and to study thalidomide pharmacokinetics.

2.5 To describe quality of life (QOL) and cost of treatment for patients on this protocol.

3. **CLINICAL TRIAL DESIGN:** Briefly, patients are randomly assigned to one of two doses of thalidomide. Each arm will have 14 patients. If response is observed in one patient an additional 11 patients will be accrued to that arm:

3.1. Low dose arm; 200mg/day, qhs. 9 pm.

3.2. High dose arm:800mg/day, qhs. 9pm. Increase by 200mg q2 weeks as tolerated up to a total daily dose of 1200mg/day, qhs. 9 pm.

3.3 Patients will receive the drug as long as there is no evidence of tumor progression, and as long as there is no dose limiting toxicity. The first tumor response assessment in the absence of new symptoms is performed at week 8 of therapy. Tumor assessment thereafter will be repeated every 2 months. Efficacy and safety will be assessed by histories and physical examinations, laboratory tests, and x-ray evaluations.

3.4 Patients will be evaluated for toxicity initially every 2 weeks during the first cycle (first 8 weeks) and then every month. Toxicities will result in dose modifications as described in section 10 of the protocol. Serum levels of TNF, VEGF, bFGF, plasma levels of MMP-9 and urinary bFGF will be

measured before entering the study and on week 2, 4, 6 and 8 of the first cycle and monthly after that. Samples for Thalidomide pharmacokinetics will be collected on the first and second day of the first cycle and week 2,4,6 and 8 of the first cycle then monthly after that. For patients who have accessible tumor and who are willing, a biopsy will be performed at entry, every 8 weeks, and at the time of removal from the study. Specimens will have angiogenic index determined together with assessment of tumor associated TNF, bFGF.

As noted, this study was recently changed to become a multicenter study in order to increase the rate of accrual. Currently University of Chicago has been approved. Dr. Gini F. Fleming is the responsible investigator at University of Chicago. We are expecting that Dana Farber Cancer Center and Duke University will join the study once they have IRB approvals.

3.5 Patient entry. Patients will be registered by the principal investigator, Said Baidas, MD, and the study coordinator, Barbara Brogan, RN, MS at Georgetown University hospital, 3800 Reservoir Rd, NW, Washington, DC 20007. Phone 202-687-2198. The protocol chairman (Dr. Baidas) at the coordinating center (Georgetown University) will be the single liaison with the NCI/CTEP and the Protocol Information Office (PIO). Dr. Baidas will coordinate the development, submission, and approval of the protocol as well subsequent amendment, result reports and publications. The coordinating center is responsible for developing common report forms, and all data should be submitted to the coordinating center on these forms. On-study informed consent and eligibility check should be submitted to the coordinating center no latter than 14 days after registration. Flow sheets should be submitted no later than 14 days after completing each cycle of treatment (8 weeks) and after the off study date. Each institution will batch their bioassay and pharmacokinetics specimens at –70oC until the trial is completed. These specimens will then be mailed on dry ice by Federal Express to Dr. Baidas at the Georgetown.

Pharmacokinetics will be performed at Georgetown in the laboratory of Dr. Robert Flockhart. Circulating bFGF, VEGF, and TNF levels will be performed at Georgetown in the laboratory of Dr. Anton Wellstein.

4. CURRENT STATUS OF CLINICAL TRIAL: As of September 1, 1997, six patients have been treated on the protocol. Since the trial is just opening at the other centers, all were accrued at Georgetown University Hospital. Five patients progressed after 8 weeks on treatment and the sixth was removed at the patient's request after 3 weeks for minor symptoms of sedation. Other than this patient, the other patients have generally tolerated thalidomide well. The main side effects have been mild early morning sedation, and mild constipation. No dose limiting toxicity has been encountered yet. No responses have been observed.

Table 1: Patients accrued on study

Center	Patient ID	DOB	Race	Date On	Date Off	Dose	Response
GU	669847	7/9/74	W	3/20/96	5/4/96	200	PD
GU	660948	9/3/12	W	6/18/96	7/9/96	800	NE
GU	5075041	7/4/51	W	12/17/96	2/13/97	200	PD
GU	819976	7/5/33	B	2/3/97	4/3/97	1200	PD
GU	889779	3/8/35	W	5/14/97	7/10/97	800	PD
GU	9469800	3/8/35	W	5/14/97	7/10/97	800	PD
GU	9469800	2/24/58	W	8/27/97	ON RX	200	ON TX

Of note, quality of life and economic evaluations for patients on this trial are being performed as described in detail in the Cancer clinical and Economic Outcomes Core section of this report.

5. CONCLUSION: Phase II evaluation of thalidomide in patients with metastatic breast cancer is a study that continues to accrue patients. In order to increase the rate of accrual, the eligibility has been widened and the study has been expanded to a multicenter study. We expect that accrual will be completed in the coming year.

III. OVERALL SUMMARY: As stated, the overall goals of this project are to evaluate the effects of angiogenic inhibitors in prospective clinical trials in patients with breast cancer. We are now successfully accruing to one study of thalidomide, which will provide insights into whether high dose (800-1200 mg) thalidomide is superior to standard doses (200 mg) in regards to both efficacy and toxicity. Furthermore, we have designed pilot trials that will lead to our proposed randomized trial regarding whether TNP-470 contributes added benefit, in regards to efficacy, QOL, or cost/benefit, to the chemotherapeutic agent, paclitaxel. We anticipate finishing these pilot studies during the upcoming 12 months, and initiating the randomized trial for patients with breast cancer within the next calendar year. Taken together, these studies should permit us to determine if inhibitors of angiogenesis have clinical value in metastatic breast cancer, and whether they should be studied in the adjuvant setting.

IV. REFERENCES

1. Bhargava P, Marshall J, rizvi N, Dahut W, Yoe J, Figueira M, et al. A study of TNP-470 in patients with advanced cancer. Proc Am Acad Cancer Res 1007;38:221a.

2. Sledge G, Neuberg D, Ingle J, Martino S, Wood W. Phase III trial of doxorubicin vs. paclitaxel vs doxorubicin + paclitaxel as first line therapy for metastatic breast cancer: An Intergroup trial. Proc Am Soc Clin Oncol 1997;16:1a.

3. Seidman A. The emerging role of paclitaxel in breast cancer therapy. Clin Cancer Res 1995;1:247-256.

4. Wilson W, Berg S, Bryant G, Wittes R, Bates S, Fojo A, et al. Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: A phase I/II trial of 96-hour infusion. J Clin Oncol 1994;12:1621-1629.

5. Seidman A, Murphy B, Hudis C. Activity of Taxol by weekly 1h infusion in patients with metastatic breast cancer. Proc Am Soc Clin Oncol 1997;16:148a.

6. Breier S, Lebedinsky C, Pelayes L. Phase I/II weekly paclitaxel at 80 mg/m2 i pretreated patients with breast and ovarian cancer. Proc Am Soc Clin Oncol 1997;16:163a.

7. Belotti D, Nicoletti I, Vergani V. Paclitaxel, a microtubule affecting drug, inhibits tumor induced angiogenesis. Proc AACR 1996;37:57a.

8. Oktaba A, Hunter W, Arsenault A. Taxol: A potent inhibitor of normal and tumor-induced angiogenesis. Proc AACR 1995;36:454a.

9. Klauber N, Parangi S, Flynn E, Hamel E, D'Amato RJ. Inhibition of angiogenesis and breast cancer in mice by the microtubule inhibitors 2-methoxyestradiol and taxol. Cancer Res 1997;57:81-86.

10. Winternitz C, Jackson J, Oktaba A, Burt H. Development of a polymeric surgical paste formulation for Taxol. Pharm Res 1996;13:368-75.

11. Placidi L, Cretton-Scott E, Sommadossi J. Potential metabolic drug interactions between the angiogenesis inhibitor TNP-470 and anticancer agents. Proc AACR 1997;38:51a.

12. Oliver S, Banguerigo M, Brahn E. Suppression of collagen-induced arthritis using an angiogenesis inhibitor, AGM-1470, and a microtubule stabilizer, Taxol. Cell Immunol 1994;157:291-9.

V. APPENDICES (included in full packet following annual report text)

Appendix 1: TNP-470 Pilot Trial 1
Appendix 2: Thalidomide protocol documentation

CORE 1: PATIENT ACCESSION CORE

I. INTRODUCTION: The overall goal of the Patient Accession Core (PAC) is to further **promote and facilitate increased participation, in current and proposed Lombardi Cancer Center Breast Center research protocols, by patients and high-risk women who have historically had difficulty accessing and benefiting from cancer prevention, diagnostic and treatment trials**. Two particular groups of patients and high-risk women will be the focus of these outreach efforts: 1) medically underserved populations, particularly African-American and elderly patients and 2) high-risk individuals who are members of health maintenance organizations (HMOs).

The following is an account of the progress made toward meeting the objectives specified for the Patient Accession Core of the Department of Defense-funded Breast Cancer Center of the Lombardi Cancer Center. In some cases, the PAC has been engaged in activities different from those specified in the original proposal. As such these are described within the discussion of original objectives or in the conclusion of this section. **The specific aims of the proposed PAC are as follows:**

1. Expand Lombardi's established links with the community-based Washington D.C. clinics already serving the primary care needs of the area's medically underserved. This will be done by forming a Community Advisory Board to the Lombardi Breast Cancer Center in order to review community-based education, protocol promotion, clinical referral, and patient transportation mechanisms. This will ensure that, while efforts are made to increase medically underserved patient participation in Lombardi clinical trials, continuity of primary care is maintained for illnesses and health problems unrelated to breast cancer.

2. Expand Lombardi's links with local and national Health Maintenance Organizations (HMO) serving the greater Washington D.C. area. This will be done by forming an HMO advisory board to the Lombardi Breast Cancer Center to review HMO member education, protocol promotion and clinical referral mechanisms and to participate in evaluating cost-effectiveness data from HMO members participating in breast cancer diagnosis and treatment trials at the Lombardi Center.

3. Expand Lombardi's existing breast cancer education materials and health promotion programs by making them available through the information superhighway (e.g. the Internet) for HMO members and by basing these materials and programs in medically underserved community settings. All messages, materials and programs will be made culturally and educationally appropriate for different racial/ethnic, age and socioeconomic breast cancer patient and high-risk groups.

4. Provide cultural awareness and sensitivity training to Lombardi Breast Cancer Center clinicians involved with prevention, diagnostic and treatment research protocols to ensure supportive patient care for all patients on clinical trials.

5. Provide free transportation, with the Lombardi Cancer Center van, for medically underserved patients for whom transportation to, and/or parking in, Georgetown may represent a barrier.

II. PROGRESS REPORT 1996-1997

A. COMMUNITY ADVISORY BOARD (CAB): Following the initial meeting of the Community Advisory Board in December, 1996, it became apparent that the research protocol

accrual issues for the primary care clinic representatives were not the same as those of the other community organization representatives. As a result, the CAB was divided in to two separate groups; the CAB-Outreach Group (CAB-OG)and the CAB-Primary Care Clinic Group (CAB-PCC). The objectives and activities for the CAB-OG focus on promoting awareness of the benefits of participating in LCC breast cancer research protocols and disseminating information about how members of these organizations or their relatives, who may be eligible for one or more protocols, can enroll. The objectives and activities of the CAB-PCC encompass those of the CAB-OG, but also include working out referral and transportation arrangements for their eligible and interested clinic patients. Thus, for example, the Zacchaeus Clinic instituted a chart review for each new patient visit, in July 1997, to identify candidates for the BRCA1/BRCA2 genetic testing and counseling protocol. While this change has resulted in a greater demand for staffing and meeting management, the content and discussions are more focussed. During the first year of the funding period there were six activities planned for the Community Advisory Board. The activities included;

- convene four meetings,
- examine sociodemographic data and cancer related statistics of organizations represented,
- review the clinical trial protocols of the Breast Cancer Center,
- identify potential barriers to patient accrual,
- review culturally appropriate education plan, and
- review newly developed education material.

At the first meeting, which took place on December 9, 1996, the proposed framework of the Community Advisory Board's role was reviewed along with ***sociodemographic data and it's relationship to breast cancer morbidity and mortality in the District of Columbia***. In addition, ***the three trial protocols of the Breast Cancer Center were reviewed*** in detail and included an explanation of patient eligibility, accrual and informed consent procedures along with potential transportation arrangements for patients recruited through their community-based organization (CBO's). It was at this meeting that the CAB recognized the need to split the group into two groups. Eight of the CAB members attended along with four Lombardi staff members.

The second meeting of the Community Advisory Board-Outreach Group (CAB-OG) took place on May 28, 1997. During the interim, between meetings, additional membership recruitment was conducted to increase the size and representativeness of the CAB-OG. Table 1 provides a listing of the original members of the CAB, as well as those who were invited to the board following its first meeting. The focus of the second meeting was to review the purpose of PAC for new members and to discuss, in detail, genetic testing and counseling by reviewing the Cancer Assessment and Risk Evaluation (CARE) Program. It was determined that this particular trial was the most applicable to members representing community organizations in that it contains a promising educational service opportunity and is directly associated with values to which these groups can identify; namely family. Furthermore, in the CARE program, it is possible for study participants to self-identify or make familial referrals. ***Barriers to genetic testing and counseling were discussed.*** Some barriers relate to common fears and concerns surrounding clinical trials. Such barriers as well as others (transportation and time) were addressed. Finally, ***recruitment needs and strategies were discussed*** including materials development and putting together a list of recruitment strategies that will be used as a guide during Year Two.

The third meeting of the CAB-OG was held on August 27, 1997 and continued to focus on the genetic testing protocol. A detailed flow chart of patient processing for the CARE program was presented along with a comparison of genetic testing as part of a clinical trial versus genetic testing through a commercial firm . ***A video put out by the National Action Plan on Breast Cancer, "Genetic Testing for Breast Cancer Risk: It is your Choice" was viewed and critiqued*** by the group as a potential educational piece to be utilized with CAB-OG constituents. This meeting resulted in some innovative recruitment ideas and strategies. For example, members on the CAB-OG who work with seniors shared their efforts to inform constituents about CARE and the other clinical trials of the Breast Cancer Center. Although seniors are not usually of interest in genetic testing studies, seniors serve as opinion leaders in their communities and their extended families. Thus, educating seniors about the important role they can play to influence the younger generations was explored. It was suggested that the Senior Beacon, a seniors newspaper in the metropolitan area, be used to advertise the CARE program. In addition, the upcoming National Council of Negro Women sponsored "Black Family Reunion" event on the mall, was mentioned as an opportunity for information sharing with members of the African American community.

From that discussion, ideas about identifying sub-groups from within the organizations already represented on the CAB-OG were discussed. Some of the sub-groups mentioned, were the employees who work at the organization that CAB members represent, and special events conducted by the community organizations (retreats and celebrations). Discussions between Lombardi health educators and CAB-OG representatives will take place one-on-one to further investigate potential channels for educating people about the need for clinical trial participation and further identification of CAB-OG member subgroups. In short, the benefits gained through the efforts of the CAB-OG include:

- Expansion of Promotional Channels - The CAB-OG distributed protocol promotion literature which included their organizational endorsement.

- Enhanced Outreach Capacity - The CAB-OG expanded as new members were invited and joined the group. (See Table 1 for additional board members).

- Development of Evaluation Strategies - Throughout Year One, continued communication with the CAB-OG included follow-up telephone conversations and one-one meetings initiated by health education staff members on the project. During those meetings, evaluation of mechanisms by which their constituents could be recruited to the clinical trials participating in PAC, were explored in detail.

- Specific Targets for Recruitment - Our CAB members have provided opportunities for the formation of linkages between; the American Cancer Society (informed their information specialist about LCC-BCC clinical trials), Chartered Health Plan (HMO's Director of Patient Services promoting clinical trials), Delta Sigma Theta Sorority, Inc. (Chartered Health Plan representative is also a sorority member).

- Establishing Recruitment Volunteer Networks - In the summer of 1997, one of the health education staff members met with the Delta Sigma Theta sorority member to explore a breast cancer/genetic testing program for the sisters of the sorority. At that meeting the development and adaption of a training curriculum for volunteers from the Delta

organization was discussed. These women would attend training workshops designed to get them ready to share information about clinical trials and the importance of participating in research with women within their communities. Another possible recruitment strategy being discussed as a result of that meeting is to design materials for the brother fraternity, the Kappa Alpha Psi Fraternity, Inc. These materials would be designed for men who may have concerns about breast cancer, genetic testing and counseling and clinical trials. Moreover, the material will address how these issues impact their loved ones and the roles men play.

Table 1: List of original members plus those added after PAC was funded.

Representative	Job Title and Organization	Rationale for Selection
Linden Griffith	Director - Washington Seniors Wellness Center	Offer health and nutrition programs geared towards seniors
Zora Brown	Director - Breast Cancer Resource Committee	Support groups and resources for women living with breast cancer.
Susan Anderson	Director - Health Insurance Counseling Project	Offer counseling services to seniors in how to obtain Medicaid and Medicare insurance.
Vivian Crest well	Volunteer - Breast Cancer Support groups for ACS & Greater Southeast	Breast cancer survivor to offer patient perspective
Edna Kane Williams	Senior Program Specialist - American Associations for Retired Persons	Sponsors African American Breast Care Campaign for increasing breast cancer screening among older women.
Julia Scott	Director - Public Education/Public Policy Office, National Black Women's Health Project.	Works with the DC Breast and Cervical Cancer Coalition.
New Representatives	**Job Title and Organization**	**Rationale for Selection**
Deborah J. Barnes	Education Outreach Coordinator Cancer Services Greater Southeast Community Hospital	Offer direct link to breast cancer patients through in and outreach activities
U. Michael Currie	Executive Director Maryland State Council on Cancer Control	Provides an extensive accounting of breast cancer rates and treatment trends across the D.C. metropolitan area
Linda Jackson	Director - Wellness Promotion & Disease Prevention Program The National Caucus and Center on Black Aged, Inc	Facilitating a partnership to access a breast cancer network of African American seniors, "Circle of Friends."
Caron Gwynn	Director - Public Education American Cancer Society	Offer link to national cancer education organization
Tylene Harrell	Program Associate - National Black Women's Health Project	Large promotional base aimed at reaching African American women with health specific information and self-help resources
Ginger Jevne	Health & Wellness Coordinator - Links, Inc.	Represents a large national network of African American professional women
Juanita E. Lyle	Metro Coalition Leader National Black Leadership Initiative on Cancer	Breast cancer survivor to offer patient perspective as well as breast cancer advocate and coalition leader

Representative	Job Title and Organization	Rationale for Selection
Cathy Miedel	Director - Providence Hospital Wellness Center	Offer Wellness programs
Valerie Rochester	Bethune Program Center National Council of Negro Women, Inc.	Working with LCC on the PORT project to validate messages intended for the African American women across the country
Lenora J. Sherard	Senior Health Educator - Department of Health and Human Services Health Promotion & Prevention	Access to two populations; an underserved population currently receiving services through the Mont. Co. Health Dept., and a large group of women that make of the Health Dept. employee base
Michael D. Thompson	Director of Marketing, Planning, & Community Outreach - Providence Hospital	Working closely to develop a partnership with this community based hospital which serves a predominantly African American aging population
Brenda Turner	Director - Aging Services Division Greater Washington Urban League, Inc.	Offer programs geared toward seniors
Kimberley D. Willis	Director, Patient Services DC Charted Health Plan, Inc.	Offer direct patient contact through DC Charted Health Plan, Inc as well as connections through her involvement with the Delta Sigma Theta Sorority, Inc

Primary Care Clinic Advisory Board: A sub-group of the original Community Advisory Board made up of representatives from five primary care clinics in the District of Columbia was formulated as a separate Advisory Board. Because many issues relating to the referral of patients to clinical trials are unique to primary care providers, it was decided to hold separate meetings of primary care clinic representatives apart from the other community-based service organizations. Primary Care Clinic representatives (CAB-PCC) have ***convened for two breakfast meetings*** held in May and August 1997. The first meeting was devoted to a ***review of the breast cancer research protocols*** and ***identifying barriers to participation***. The second meeting concentrated on ways of decreasing barriers to participation and promoting the clinical trials to eligible patients.

After a ***review of promotion materials prepared for the CARE and CAB CAD studies, it was determined that alternative materials needed to be developed*** that would be tailored to issues such as the inclusion of a family focus for genetic counseling and testing among Hispanic patients. Patient Accession Core staff will form a work group in the Fall of 1997 with clinic staff and volunteers to design educationally and ***culturally appropriate promotional materials*** for distinct patient populations. Please see notes from the two meetings in **Appendix 2** for additional information. ***Demographic data on the patient populations of each of the clinics has also been gathered*** and will be used to determine realistic targets for the pool of eligible patients that we can expect to accrue into the CARE and CAB CAD studies. It has been determined that the Thalidomide study is not a feasible protocol for accrual from the primary care clinics because once women have been diagnosed with breast cancer, it is not likely that they are in regular contact with a primary care clinic. A summary of the primary care clinic activities of the PAC is outlined in Table 2.

Table 2: Primary Care Advisory Board Representatives & Activities

Representative	Job Title and Clinic	Activities
Juan Romagoza, MD	Executive Director La Clinica del Pueblo	Supported Cancer Genetics Network grant proposal to allow CARE study to incorporate Spanish language capability, provided data on demographic background of patients, will refer women getting biopsies to CABCAD study, once staff orientation is completed.
Randi Abramson, MD	Medical Director Zaccheaus Free Clinic	Trained clinic coordinators to flag charts of women with family history of breast & ovarian cancer for referral to the CARE study. Volunteers will work with PAC health education staff to develop recruitment materials appropriate to clinics.
Catalina Sol	Health Education Coordinator Washington Free Clinic	Clinic volunteers will receive orientation from PAC staff about the studies during their training course. Charts of women with family history of breast or ovarian cancer will be flagged for referral to the CARE study. WFC staff will work with PAC health education staff to develop recruitment materials appropriate to their clinic population.
Sis. Kay Koppes, OSF, RN, FNP	Medical Coordinator Spanish Catholic Center	Supported Cancer Genetics Network grant proposal to allow CARE study to incorporate Spanish language capability, provided data on demographic background of patients, will refer women getting biopsies to the CABCAD study, once staff orientation to the study is completed.
Cheryl Williams, MD	Center Chief Woodbridge Neighborhood Health Center	Working to increase breast cancer screening services at the clinic and identify mechanisms for recruiting women into the CARE study.

During Year 2, the Primary Care Clinic Advisory Board will meet quarterly beginning in November, 1997. Prior to the initial meeting in Year 2, the materials development working group will be formulated and PAC staff will meet with clinic coordinators and volunteers working on the front lines of the clinics with patients to orient them to the breast cancer research studies, eligibility criteria, and discuss recruitment strategies.

B. HMO ADVISORY BOARD: During the conception of the HMO Advisory Board, over 30 individuals representing 12 health maintenance organizations were invited to serve on the HMO Advisory Board for the Patient Accession Core. Since that time, however, the status of many of these plans has changed and to an greater extent the senior management of major plans has been variable. During this funding period, mergers between several of the major plans have also occurred. For example, the Humana Health Care Plan has been purchased by the Kaiser Permanente Health Plan. M.D Individual Practice Association, Inc. has consolidated with other IPAs to form MAMSI.

One of the most difficult aspects to working with HMOs, aside from the dynamic nature of health plans, is the ability to get representatives to attend meetings with each other. To date, ***the board has met twice***. Prior to the first meeting a ***Key Informant Questionnaire (See Appendix 3) was mailed*** to HMO representatives. It was requested that HMOs either return the questionnaire by mail or bring it with them to the first meeting. With just one response, PAC allowed HMOs more time for

completion of the Questionnaire. At the second meeting PAC was informed that much of the data requested (cancer rates, member demographics, plan specifics and cost information) was either too difficult to procure or not routinely collected.

The first meeting of the HMO Advisory Board focused on broad issues relating to the concerns and tensions that rest between academic medical centers and health maintenance organizations around the area of clinical trials. The Advisory Board focused on issues that were specific to the Georgetown University Medical Center (parking, communications between physicians, follow-up) as well as issues for academic medical centers in general (trials not considered as approved clinical practice, paying for research-generated ancillary testing costs, capitated payment plans, patient retention). In the second meeting a ***detailed review of the PAC and each of the three DOD sponsored trials*** were discussed. Unfortunately, due to the difficulties in obtaining data, HMO cancer statistics were only discussed based on estimates. The second meeting revealed one of the primary concerns of the HMO representatives; costs to the health plans and cost effectiveness of the protocols. In response to the need to know more about the costs of studies incurred by the plans, PAC ***developed two cost support documents***; an assessment of ancillary costs to health plans for the Thalidomide protocol, the planned TNP 470 protocol and other breast cancer clinical trials, and a description of the recommendations for follow-up that result from genetic testing disclosures.

PAC agreed to convene a subsequent meeting of the HMO Advisory Board to focus on cost effectiveness and how the Cancer Clinical Economics and Outcomes Core will work to determine effectiveness of the three trials. It will occur during the latter part of the first quarter of the second project year. In the interim, PAC has been meeting with HMOs on an individual basis to work out individualized referral arrangements for the trials. To date meetings have occurred with the Capital Community Health Plan, MAMSI, and Chartered Health Plan. In reviewing the Key Informant Questionnaires with HMO representatives, two of these possessed patient populations that are likely to be too young (80-90% under the age of 25 years) for the three protocols. PAC has identified three HMOs for first level recruitment; MAMSI, Kaiser Permanente, and Blue Cross & Blue Shield. The progress made toward recruiting members from these plans for participation in LCC Breast Cancer clinical trials are as follows:

MAMSI - meetings and discussions have yielded responsibilities and tasks for each party. The LCC Breast Center's PAC agreed to the following tasks: 1) to share other known models of partnership between HMOs and academic medical centers, 2) work with CARE staff to develop a referral process for CARE, 3) determine whether the Thalidomide study will absorb the cost of scans required as part of the work up and whether required lab tests can be conducted at capitated laboratories, 4) explore with senior management the concept of clinical investigational research contracts, and 5) continue exploring the idea of a member patient satisfaction survey for cancer services. MAMSI agreed to: 1) explore clinical investigational research contracts with senior management and 2) produce an article for the physician's newsletter on CARE and encourage referrals to CARE.

Kaiser Permanente - the health plan is taking a less coordinated approach and placing referrals into the hands of direct providers. PAC has worked to contact specific physicians within that plan. PAC will also work to promote protocols through the physicians promotional materials (newsletters). PAC staff have begun to work to promote protocols to other providers in the plan (support group nurses). This year Kaiser acquired a huge increase in membership (over 30%) and made substantial changes

in its senior management structure. Although Kaiser has expressed interest in working with PAC to refer patients, such changes have restrained our ability to work through specific referral strategies.

Blue Cross & Blue Shield - PAC has been working to set up meetings with senior management of BC/BS. It is planned that a meeting will be set before November, 1997.

C. BREAST CANCER EDUCATION PLAN: During the first year of the program period much of the PAC's efforts pertaining to breast cancer education focused on the ***development of materials that support the recruitment of clinical trials participants***. In addition to the original CARE promotional brochure, an ***additional CARE recruitment piece*** has been developed by the PAC. The ***CAB/CAD recruitment brochure***, developed by CAB/CAD staff, was reviewed by PAC health educators and recommendations for revisions were presented. A ***second printing of the CAB/CAD brochure*** was provided for by PAC which included some of these recommendations. In addition, a generic brochure for clinical trials targeted to private practice providers and institutional partners was developed.

Due to difficulties in working with HMOs as a group, PAC has been unable, as yet, to assess the educational needs of the health maintenance organizations. However, an ***assessment of the structure of the HMOs*** reveals that each of the organizations represented on the Board possesses health education or public/member relations departments with professionally prepared staff responsible for developing educational and informational messages for the plans' membership. PAC health educators will begin working with these professionals to develop appropriate materials for promoting breast cancer research protocol participation.

Physician fact sheets (study profiles) were developed for each of the three trials. PAC has identified a need for materials produced for staff nurses in physicians' practices to educate them about trials open for accrual. Likewise additional materials are under development, using the NCI question and answer format, for ***patients considering participation*** in a clinical trial. All of these materials can be found appended to this report (**Appendix 4**).

Initially, it was planned that the PAC could produce culturally appropriate materials for each type of setting from which patients are being recruited (community organizations, health maintenance organizations, private physicians' practices, LCC waiting areas and lobbies). However, it has become apparent that ***materials relating to the specific trials will need to be developed for each individual health plan, community organization and hospital setting***. Thus, it is expected that health educators will be investing more time and resources than originally expected in materials development and production. In that the resources will not allow for materials for each and every partner, PAC will carefully chart progress toward the accrual targets specified in the Core's Strategic Plan (**Appendix 5**).

The PAC senior health educator recently met with the Breast Cancer Resource Committee (BCRC) to ***discuss the proposed media campaign*** for the PAC. Based on this discussion, BCRC will work to develop a statement of work, budget, and plan for the educational media campaign to be carriedout in Year Two. Health educators will work with BCRC to develop accompanying support materials for this campaign during Year Two.

D. CULTURAL AWARENESS TRAINING: The successful recruitment and retention of culturally diverse communities and individuals can be challenging for even the most experienced clinical investigators. The overall goal of the Patient Accession Core is to promote and facilitate increased participation, in current and proposed Lombardi Cancer Center Breast Center research protocols, by patients and high-risk women who have historically had difficulty accessing and benefitting from cancer prevention, diagnostic and treatment trials. After ***evaluating two training prototypes***, Education For Quality Living (EQL) an agency based here in Washington DC, was chosen to provide cultural awareness and sensitivity training to Lombardi Cancer Center clinicians who provide patient care for all patients on clinical trials. The training focuses on insights into how cultural distinctions impact knowledge, beliefs, attitudes, and behaviors associated with one's health and well being. The EQL offering focuses on the impact culture has on the practice of health care. The training experience is designed to engage participants in a self-analysis of their own culture, a comparison and contrast of their culture with differing cultures, and to explore how their culture and the understanding of different cultures impacts their professional capacities for providing clinical services to diverse populations.

Beginning in Year One and still continuing, the Lombardi PAC health educators have reviewed the EQL program and met with EQL training staff to review the time line for the training. Health education staff members and staff from EQL have been meeting bi-weekly to design a supplemental training component and its accompanying evaluation specific to cancer and clinical trials. This component will include issues specific to cultural barriers to genetic counseling, genetic testing and cancer diagnosis and treatment, and clinical trials. In Year Two (Fall, 1997), Ms. Anna Ryan (PAC health educator) is scheduled to participate in the EQL program to determine the most feasible approach for training all Lombardi clinicians involved in the Breast Cancer Research Center clinical trials. A version of a provider cultural competence self-assessment tool is being revised and the data from that survey will be used to help establish goals for cultural competence among clinical and data collection staff. In the second and third quarters of Year Two the cultural awareness training workshops will be offered to clinicians. These workshops will be offered on a semi-annual basis for new clinicians. A workshop schedule is being developed to assure that clinical and other research functions are not interrupted while staff participate in training. With a post-training self-assessment of provider cultural competence and patient satisfaction data, the PAC staff will identify those training components that appear most effective in Year 4 in order to determine how best to institutionalize them.

E. PATIENT TRANSPORTATION SUPPORT: The degree to which lack of transportation may present a barrier for potential participants in the breast cancer clinical trials has been discussed in detail during meetings with local hospital personnel, the CAB-OG and the CAB-PCC. Originally, the plan was to utilize the Lombardi Cancer Center van to pick up a group of patients at their referring hospital or clinic site. The logistics of such an endeavor are complicated in that the CARE and CAB/CAD studies require two to four hours of time for each individual to complete their sessions, and only one woman may attend a counseling session or receive diagnostic testing at one time. Therefore, asking a group of women to come to Lombardi to participate on the same day would require extra time to wait for each person to complete their appointment. As most of the women served by the primary care clinics are working or in school, lack of time during weekdays is a great barrier to participation in research studies.

To address transportation barriers, alternate mechanisms are in place for provision of parking and taxi vouchers. It is expected that many of the women referred from the primary care clinics to the CARE and CAB/CAD studies will need to take taxis to get to Georgetown. A system is already in place, for the CAB/CAD study, where women who need to take a taxi are identified during the intake session over the telephone and asked to call a taxi service under contract with Georgetown University Medical Center. When the patient arrives at Lombardi Cancer Center, the project coordinator for the study meets her taxi and provides the driver with a voucher. Likewise, when the patient leaves to go home, a taxi is called and a voucher is provided.

F. ADDITIONAL PATIENT ACCRUAL EFFORTS

1. Extramural Research Committee (ERC): During the first tear of the PAC, additional recruitment efforts were developed at the recommendation of the senior investigators and the Cancer Center's administration. The most intense effort has been the coordination between the PAC and the LCC Extramural Research Committee. This committee consists of two representatives from PAC, Dr. Jon Kerner (associate director for prevention and control) and Lenora Johnson (senior health educator), Dr. John Marshall (Associate Director for Extramural Research, Clinical Research Management Office and Associate Professor of Medicine), Caryn Steakley (clinical research coordinator), and Jan Hewitt (research nurse). This group meets monthly to coordinate those efforts underway to increase research referrals from external sources; mainly physicians' practices. To date, the activities of this group have been to:

- develop partnerships with three oncology practices in Washington D.C. and Winchester Va.;
- produce materials for physicians and their patients;
- identify barriers for physician referrals to protocols (focus group scheduled for 9/30/97); and
- coordinate external communications for all studies (letters to physicians, negotiations with other institutions - Providence Hospital, Holy Cross Hospital).

The Committee has served PAC well during the first year in alleviating the confusion associated with several entities of the same institution making agreements relating to patient accession to different clinical trials.

2. Community Hospital Partnerships: PAC is exploring new partnerships with community hospitals that may have an interest in participating in clinical trials. In April, PAC met with members of the Cancer Committee at Providence Hospital to discuss a potential partnership for cancer related clinical trials. Providence Hospital currently sees a sufficient number of cancer patients that they are now required to place a minimum of 2% of their patients onto clinical trials to maintain their American College of Surgeons accreditation. The members of the Cancer Committee present at the April meeting were the chairperson, the vice president of medical affairs, the health information management director, the vice president for quality assurance, and the director of marketing, planning, and community outreach.

Following that meeting, the LCC forwarded six binders containing the full protocols and recruitment materials already produced for those protocols. This material was to be reviewed and considered by the full Cancer Committee. However, given the summer downtime (they did not meet during the months of July and August) and the scope of their agendas, they were not able to focus on the LCC breast cancer protocols. As a result the Chair has recommended that LCC work with a much smaller group of professionals to focus only on this matter. This will expedite their moving forward in establishing structures for partnering for the purpose of clinical trial participation. PAC staff met with this smaller group on September 25, 1997.

Once these structures are in place for Providence Hospital, other hospitals in the Maryland suburbs will be approached.

3. **Physician Practices:** PAC has developed a database of all oncologists and oncology surgeons in the Washington Metropolitan Area. The list is approximately 250 members in size which includes multiple offices of a single practice. A letter is scheduled to be mailed to these practices that addresses referrals to clinical trials. PAC, along with the EMC, has designed a brochure that briefly explains clinical trials which will accompany this letter along with the materials already developed and produced for each of the three Breast Cancer Research Center protocols.

G. APPENDICES (included in full packet following annual report text)

Appendix 1: CARE Flow of Activities
Appendix 2: Primary Care Clinic Advisory Board Meeting Minutes
Appendix 3: Key Informant Questionnaire
Appendix 4: Materials
Appendix 5: Strategic Plan

CORE 2: CANCER CLINICAL AND ECONOMIC OUTCOMES EVALUATIONS CORE

I. INTRODUCTION: The goal of this **Cancer Clinical and Economic Outcomes Evaluation Core** is to use a **multi-disciplinary research team with broad methodological expertise** to conduct **patient-centered** evaluation of the costs and outcomes of new translational technologies for the prevention, early detection, diagnosis, and treatment of women at risk for or with breast cancer. Following a review of outcomes research in oncology, this section reviews the purpose, background, and general scope of work originally outlined for the Cancer Clinical and Economic Outcomes Evaluation Core (hereinafter referred to as the "Outcomes Core").

A. OVERVIEW OF ONCOLOGY OUTCOMES RESEARCH: The growing interest in the costs and quality of health care during the past decade has contributed to the dramatic growth of the field of outcomes research. One of the cornerstones of outcomes research is the measurement of quality of life (QOL). Increasing consumerism and patient participation in health care decisions has set the stage for the development of a plethora of tools to measure the QOL of cancer patients (Cella and Tulsky, 1990; Heithoff and Lohr, 1990; Strain, 1990). However, the incorporation of QOL outcomes into oncology research has been slow. For instance, a recent review of published phase III breast cancer randomized clinical trials (RCTs) noted that only 4% and 6% of trials published in 1985-1989 and 1990-1994, respectively, included any QOL assessment (Mandelblatt, 1995).

While the measurement of QOL has vastly improved the ability to describe the impact of health interventions, these measures do not presently lend themselves to incorporation into economic analyses. For that purpose, it is necessary to assess the importance of outcomes to individuals (or populations). This concept is broadly defined as *preference* or *utility* and is used in combination with length of time to yield quality-adjusted measures, such as years of life saved.

To date, the majority of cost-effectiveness analyses in oncology research have relied on physicians' estimations of utility (Hillner and Smith, 1991; Smith and Hillner, 1993; Desch et al, 1993; Hillner et al, 1993; Schulman and Yabroff, 1995; DeKoning et al, 1991). **The economic evaluations of the projects included in Breast Cancer Center are extending the current state-of-the-art by collecting prospective primary data from patients on their preferences for the outcomes observed within the course of the project observation periods; patients are also being asked to place themselves into generic health states which have existing community preference values, allowing comparisons of patient- and community-utilities for outcomes.**

B. BACKGROUND AND PURPOSE OF OUTCOMES CORE EVALUATIONS: This section reviews the context for the outcomes evaluations being conducted in each of the three projects included in the Breast Cancer Center.

1. <u>PROJECT 1: Genetic Testing For Breast Cancer Susceptibility</u>: Genetic testing holds promise as a route to the **prevention** of breast, ovarian, and potentially, colon cancer. Laboratory tests to detect genetic mutations associated with breast and ovarian cancer susceptibility are now commercially available. As yet, however, there are little data on the long-term health effects of such testing, including cancer incidence and mortality rates. Likewise, the economic implications of the availability of such cancer genetic testing have only received limited evaluation. Brown and Kessler (1995) conducted an analysis of the

potential impact of population-based screening for hereditary nonpolyposis colon cancer (HNPCC), compared to targeted screening of family members of colon cancer cases. They concluded that additional information on the population prevalence of mutations and efficacy of prevention and surveillance regimens was required prior to determining the most cost-effective public health strategy. However, it is interesting to note that their result of $55,000 per life year saved (LYS) is in the range of cost-effectiveness for common practices, such as mammography (Brown and Fintor, 1993) and autologous bone marrow transplant for metastatic breast cancer (Hillner et al, 1992).

Similar to HNPCC, female members of BRCA1 families have high risks of developing cancers at young ages, and there is the potential to save a large number of years of life through prevention, surveillance, and prophylactic surgery (Brown and Kessler, 1995; Schrag et al, 1997; Burke et al, 1997a,b). Additional savings might accrue from eliminating the need for intense and costly surveillance, based on knowledge of a negative genetic test result. However, these potential savings must be weighed against potential adverse affects on quality of life, as well as the costs and effects for identified mutation carriers who will undergo frequent surveillance and diagnostic procedures over a lifetime following genetic testing (Burke et al, 1997a,b; Hiatt, 1995). For general populations, there is concern about potentially large expenditures associated with testing lower risk individuals, and falsely reassuring them about their cancer risks (Healy, 1997; Couch et al, 1997).

The cost-effectiveness analysis (CEA) of breast and ovarian cancer genetic susceptibility testing and counseling in Project 1 is designed to address several of these important public health issues. Thus, the CEA will use primary data from Project 1 on the initial uptake and adherence to surveillance and prevention activities, and preferences for the proximal outcomes of BRCA1 testing and counseling. We are incorporating these data, together with secondary data from the literature, into an *exploratory model* of the cost-effectiveness of BRCA1 testing and counseling, compared to counseling alone, and to routine surveillance, among female members of hereditary breast and ovarian cancer (HBOC) families. Although much of the data are still preliminary, this model will allow us to identify the key parameters which drive the costs and effectiveness of genetic testing.

2. <u>PROJECT 2: New Coordinated Breast Cancer Diagnostic Technologies</u>: An estimated 600,000 breast biopsies are performed annually in the US (Osteen et al, 1991); as many as 80% of these yield benign results (Winchester et al, 1983; Artz and Blume, 1991). Thus, the potential economic and quality of life (Gram et al, 1990; Parker, 1993) impact of alternative diagnostic pathways is substantial. A few RCTs evaluating alternatives to excisional biopsy, such as fine needle aspiration and stereotaxic core biopsy, are currently in progress. To date there have been few economic evaluations of alternative breast cancer diagnostic techniques (Layfield et al, 1993; Linfors and Rosenquist, 1994; Lieberman et al, 1995; Hillner et al, 1996). The results of such evaluations indicate that any projected savings accruing from the use of different technologies depend most heavily on cost assumptions and the positive predictive value of the test. **The Core evalaution for this project centers on examining the costs and outcomes of simultaneously administered, promising new diagnostic technologies among a cohort of women requiring biopsy. These data will be critical to developing algorithms for care that yield the greatest health benefits for differing age- and race-groups at the lowest costs.**

3. **PROJECT 3: Novel Palliative Treatment of Metastatic Breast Cancer:** RCTs of palliative cancer treatments have begun to incorporate assessments of the effects of treatment on patients' QOL (Coates et al, 1987; Cassileth et al, 1992; Fraser et al, 1993; Bleehen et al, 1993; Joss et al,1995; Tummarlo et al, 1995; Ellis et al, 1995; Hopwood and Stephens, 1995). However, few studies have attempted to assess the cost-effectiveness of palliative cancer care (Smithe et al, 1993; Brown et al, 1994; Goldhirsch et al, 1989; Goodwin et al, 1988; Goodwin 1993; Jaakkimainainen et al, 1990; Glimelius et al, 1995), and we are not aware of any prior research evaluating the cost-effectiveness of palliative treatment of breast cancer. **For all phases of the trials examining palliative treatment strategies, the Outcomes Core will describe the QOL and cost-effectiveness of treatment, incorporating information from women on their assessment of their QOL and the value they place on their health.**

C. SCOPE OF THE OUTCOMES CORE RESEARCH: The overarching mission of this **Outcomes Core** is twofold: 1) to expand the technical capacity for outcomes evaluations for current and future research at the Lombardi Cancer Center; and 2) to provide expertise and support to the research projects included in this application. The Outcomes Core multidisciplinary team of researchers (including oncology, nursing, and primary care clinicians, economists, health services researchers, psychologists, and biostatistician) are providing the **methodological expertise** and **resources** to achieve this mission and accomplish the following technical aims:

1. Conduct **cost-effectiveness analyses** (CEAs) of each of the projects:

a. Develop an exploratory CEA model, combining primary and secondary data, to identify the key parameters which drive the costs and effectiveness of **genetic testing and counseling** as a strategy to **prevent** breast cancer and decrease cancer mortality among high-risk women.

b. Conduct an economic evaluation and develop a decision analysis model comparing the costs per cancer detected for new breast cancer **diagnostic evaluation** strategies.

c. Conduct a CEA of a **RCT of a novel palliative breast cancer treatment**.

d. Conduct **sensitivity and threshold analyses** to identify critical variables, assess the impact of uncertainty in estimates, and evaluate results for population sub-groups.

e. **Compare costs and outcomes** for women who enroll and do not enroll in the projects; assess the costs of outreach to increase accrual to under-served populations.

2. Evaluate the impact of tests or treatments on **quality of life** (QOL).

3. Provide methodological expertise to each project to measure and collect the **primary prospective data** and **secondary data** needed for the above Core analyses.

4. Develop a **centralized library of data** for use in cancer research on QOL, utility, and cost measurement tools and approaches, and provide consultation to investigators on the incorporation of such tools into new research initiatives.

II. BODY: Although the Outcomes Core evaluations will be done in a coordinated manner across all projects, for sake of clarity of presentation, the progress and methods applicable to each project are presented separately. **Table 1** presents an overview of the original Outcomes Core approach for each project. The narrative that follows highlights any additions/changes in approach, and preliminary results. Finally, this section concludes with a presentation of general Outcomes Core activities and progress that are cross-cutting in this Breast Cancer Center Project (ie, Technical Aims 3 and 4).

Table 1: Overview of Planned Outcome Evaluations

	Project 1: Prevention: Genetic Testing	**Project 2: Diagnosis: New Technologies**	**Project 3: Treatment: Novel Palliative Rx**
Design	Observational Cohort	Case Series	Phase I, II studies and a Phase III RCT
Outcomes	QOL Utility QALYs	Cancers Detected, Delayed, and Missed	QOL Utility Progression Time; QALYs
Costs	Direct; Time Costs	Direct and Time Costs	Direct and Time and Care-giver
Economic Analysis	CEA Model	Cost per Case Diagnosed; Decision Analysis Model	CEA

A. PROJECT 1: BRCA1/2 Genetic Testing: Develop an Exploratory Cost-Effectiveness Analysis (CEA), Combining Primary and Secondary Data, to Identify the Key Parameters Which Drive the Costs and Effectiveness of Genetic Testing and Counseling as a Strategy to Prevent Breast Cancer and Decrease Cancer Mortality among High-Risk Women: This prospective observational study is in the process of enrolling a target of nearly 520 white and African-American women from HBOC families to assess the impact of genetic testing and counseling for breast and ovarian cancer susceptibility on quality of life (QOL) and cancer prevention and surveillance practices in the 12 month period following enrollment. A secondary objective of the project is to develop a preliminary model to evaluate the cost-effectiveness of testing and counseling, compared to counseling alone, or routine practice. This section focuses on the latter objective, first summarizing our general approach to CEA, for this and other projects, followed by a summary of our progress to date in developing the CEA model for Project 1.

Overview of Cost-Effectiveness Analysis (CEA) Methods: CEA is a method of evaluating medical technology by calculating a ratio of the costs of an intervention to patient outcomes (health effects) (Mandelblatt et al, 1997). The general methods for applying CEA to medical technology have been specified in the literature (Gold et al, 1996a; Weinstein and Stason, 1977; Eddy, 1989; Eisenberg et al, 1987; Eisenberg, 1989; Schulman et al, 1995; Udvarhelyi et al, 1992). We will follow the recommendations of the Panel for Cost-Effectiveness in Health and Medicine (of which Dr. Mandelblatt was a member) for the conduct of all analyses (Gold et al, 1996a, Mandelblatt et al, 1996; Russell et al, 1996a,b; Weinstein et al, 1996; Seigel et al, 1996). These approaches will be briefly reviewed here. The **perspective** of a CEA is the viewpoint from which costs and benefits are assessed. Several different perspectives are possible: society, payor, hospital, or patient. Our primary analyses will adopt a societal perspective. Secondary analyses will examine other perspectives.

Clinical outcomes, or **health effects** of an intervention can be measured in terms of intermediate clinical outcomes such as time to progression or cancer cases detected, or as the more distal outcome of survival

(years of life), or quality-adjusted life years (QALYs). To quality-adjust outcomes, measures of preferences for health outcomes are necessary, reflecting the fact **that individuals with similar ability (or disability) to function may value that level of functioning differently**. This measure is broadly referred to as a **"utility" or "preference"** value or weight. While not strictly equivalent, the terms utility, preference, and value are used interchangeably here. A CEA that uses QALYs is also referred to as a cost-utility analysis. QALYs have been selected as the outcome measure for projects 1 and 3, although there are many critics of this approach (Cox et al, 1992; Mehrez and Gafni, 1989; 1993; Gafni and Birch, 1995).

There are many areas of debate among methodologists concerned with measuring utility, including, but not limited to, the perspective of the rater, the validity of values obtained from general populations, biases in utility measurement, and the best technique to measure utility (Patrick and Erickson, 1993). In certain situations conclusions about the value of an outcome for the population may be contrary to that for the individual (Ganz, 1994; Dean, 1990; Slevin et al, 1990). For example, a woman may prefer to incur the risks and toxicities of bone marrow transplantation for a low probability of cure of advanced breast cancer; from the societal perspective, the cost-effectiveness of this technology may exceed an acceptable threshold expenditure of cost for a given health gain.

Several instruments exist, or are in the process of development, based on different methods of assigning preference values (ie, *rating scales, willingness to pay, standard gamble (SG)*, and *time trade-offs (TTO))* (Patrick and Erickson, 1993; Torrance, 1976; Torrance, 1987; Torrance et al, 1982). The technique used should have validity, reproducibility, and be easily administered. Since several investigators have reported differences in utilities for similar conditions using different techniques (Fryback et al, 1993; Nease et al, 1995; Wolfson et al, 1992), projects 1 and 3 will use more than one measure.

The types of **costs**, or resources, that are generally included in CEAs fall into four categories: 1) **direct medical care costs** (e.g., costs of hospitalizations, medications, laboratory test, costs related to side-effects); 2) **direct non-medical care costs** (or "*indirect costs*", such as costs of transportation, time costs to receive treatment, and time costs of family members or other care givers; 3) **productivity costs**, or the costs associated with the lost ability to work due to illness or death; and 4) **intangible costs**, or the monetary value of pain and suffering. In CEA productivity and intangible costs are captured through decrements in utility.

In all projects, costs will be used, not charges. Where charges are the only available data source, a cost-to-charge ratio (such as in the Medicare Cost Reports, or the Medicare Resource Based Relative Value Scale) will be used to estimate costs. Second, time costs will be valued using average age-, gender- and race-specific wage rates. While there are problems with equity of current distributions of income inherent in this approach, this will provide results specific to the populations enrolling in the projects. Third, to sum costs derived from data across different time periods, current and past, all costs will be adjusted to one current time period (ie, 1997) using the medical component of the Consumer Price Index. All future costs and health effects are being discounted (at 3%; rates of 0% and 5% will also be evaluated). Finally, **incremental costs** per year of life gained are examined by comparing interventions to the next least costly strategy.

Project 1 CEA: Work to develop and complete this CEA has four basic components: 1) development of the CEA model, 2) analysis of data to establish model parameters, 3) primary measurement of participant utilities for the outcomes of genetic testing, and 4) estimating the costs of testing. Each of these components is described below.

Development of the CEA Model: The general principles described above for conducting a CEA apply to this analysis. There are several unique aspects of this analysis that have guided our approach, including the facts that 1) the impact of genetic testing on survival (and costs) occurs distal to the intervention in Project 1, and 2) much of the data on the effectiveness of prevention and early detection strategies for mutation positive women are still uncertain. Thus, a preliminary **mathematical simulation model** is being developed to extend the analysis time horizon and to **address questions of what the data parameters would need to be in order for the intervention to be considered cost-effective.**

The model will evaluate three strategies: genetic testing for BRCA1 mutations and counseling, counseling alone, and routine medical practice/surveillance. In terms of mapping primary data to the model, these three groups correspond respectively to the following groups in Project 1: women agreeing to testing and counseling, women counseled who decline testing, and women who decline testing and counseling.

The audience for this analysis consists of public health advocates, health services researchers, clinicians, and health plan decision makers faced with societal resource allocation decisions. The target population of the analysis is women at high risk for BRCA1 or BRCA2 genetic mutations (defined as those who are a first or second degree relative of a known mutation affected person; hereditary breast and ovarian cancer [HBOC] families). Such high risk women have at least a 25% chance of having a mutations themselves. Thus, the primary CEAs are restricted to the longitudinal evaluation of hypothetical cohorts of women who are members of HBOC families.

The time horizon of the CEA will be from the starting age at enrollment in Project 1 (18 or older) to death, or age 100. In this manner, we will capture all of the relevant down-stream costs and effects of that follow from testing and counseling decisions.

The computer simulation model represents the natural history of disease, and the impact of detection of genetic susceptibility mutations on outcomes. The model uses Monte Carlo simulation techniques to test the cost-effectiveness of each testing approach for longitudinal cohorts of women (Mandelblatt et al, 1996; Weinstein et al, 1980).

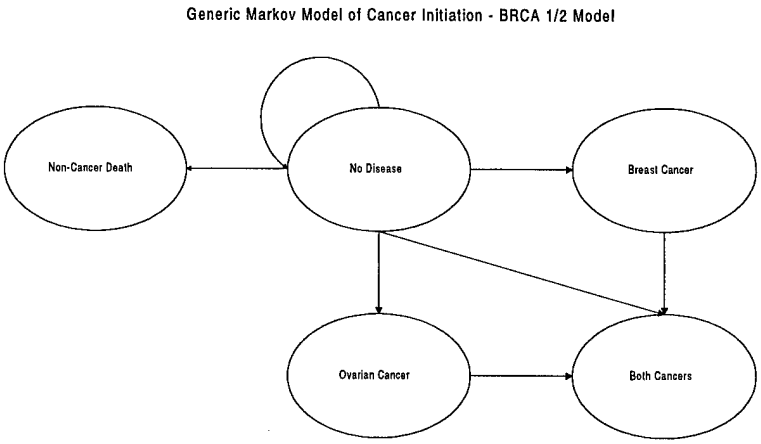
We are using a stochastic modeling approach (i.e., at each probability node a random number is generated and one branch is chosen based upon the number. This process will be reiterated many (about 100,000) times, and the results averaged across iterations). We chose a stochastic modeling approach over deterministic modeling for two major reasons: 1) it is easier to construct a stochastic model for the complex disease history we are portraying, and 2) it allows us to perform Monte Carlo simulations to establish confidence bounds on costs and effectiveness estimates and in multi-way sensitivity analyses of key parameters.

One problem faced in the design of this model is that we need to represent the simultaneous risk of the development of breast and ovarian cancer. While women with BRCA1/2 genetic mutations may be at risk for other cancers (e.g., colon cancer), there is currently not enough evidence to model this risk, so competing mortality from other cancers was assumed to occur at the same rates for women with and without the BRCA1 and BRCA2 mutations.

To model the simultaneous risk of these two cancers, and death from all other causes, we have decided to use a three-dimensional semi-Markov model (Beck and Pauker, 1983; Kassirer, 1976; Sox et al, 1988;

Sonnenberg and Beck, 1993; Weinstein et al, 1980) (**Figure 1**). This model uses a series of Markov processes to simulate a semi-Markov process. One fundamental rule of the Markov model is that the probability of transition to a state in the next cycle is dependent solely on the current state (i.e., the model has no memory of past health states). We will add limited memory to the Markov process by creating a model that switches to a separate Markov process (with different transition probabilities) when an event occurs that requires a "memory" of a past process (e.g. a women with a recurrence of local breast cancer may have a higher probability of an additional recurrence and progression of her treated cancer after the recurrence, compared to before the recurrence).

Figure 1. Three dimensional Markov model of BRCA testing.



Several critical issues in the natural history of breast and ovarian genetic cancers can be addressed in the models, such as the impact of lead time and length biases, whether the hazards for genetic cancers are additive or multiplicative, false-positive and negative test rates, assumptions about penetrance in different populations (Streuwing et al, 1997; Schatzkin et al, 1995; Tonin et al, 1995), and background rates of potential modifying risk factors (Healy, 1997; Collins, 1996)(e.g.,estrogen replacement therapy).

We consider three separate dimensions in the model portrayed above in **Figure 1**: 1) alive versus dead of non-cancer causes, 2) breast cancer (including breast cancer death) versus no breast cancer, and 3) ovarian cancer (including ovarian cancer death) versus no ovarian cancer. This technique offers the advantage of allowing us to model both cancer processes in an independent fashion. We are assuming conditional independence of the transition probabilities between dimensions since there are currently no data to estimate these dependencies. As new data become available, we can modify the model to address these dependencies.

Figure 2 summarizes our basic modeling approach. The first decision point is whether or not a woman decides to having BRCA1/2 testing and/or counseling. If she accepts, she has a certain pre-test probability of testing positive for the mutation (Couch et al, 1997; Shattuck-Eidens et al, 1995; Berry et al, 1997; Struewing et al, 1997; Krainer et al, 1997).

Each pathway is also associated with certain probabilities of morbidity and mortality. For instance, there may be decrements in quality of life associated with knowledge of mutation positivity, or anxiety associated with evaluation of positive (and false-positive) early detection tests, or mortality associated with prophylactic surgery. Ultimately, these paths would lead to death from breast or ovarian cancer or non-cancer related causes.

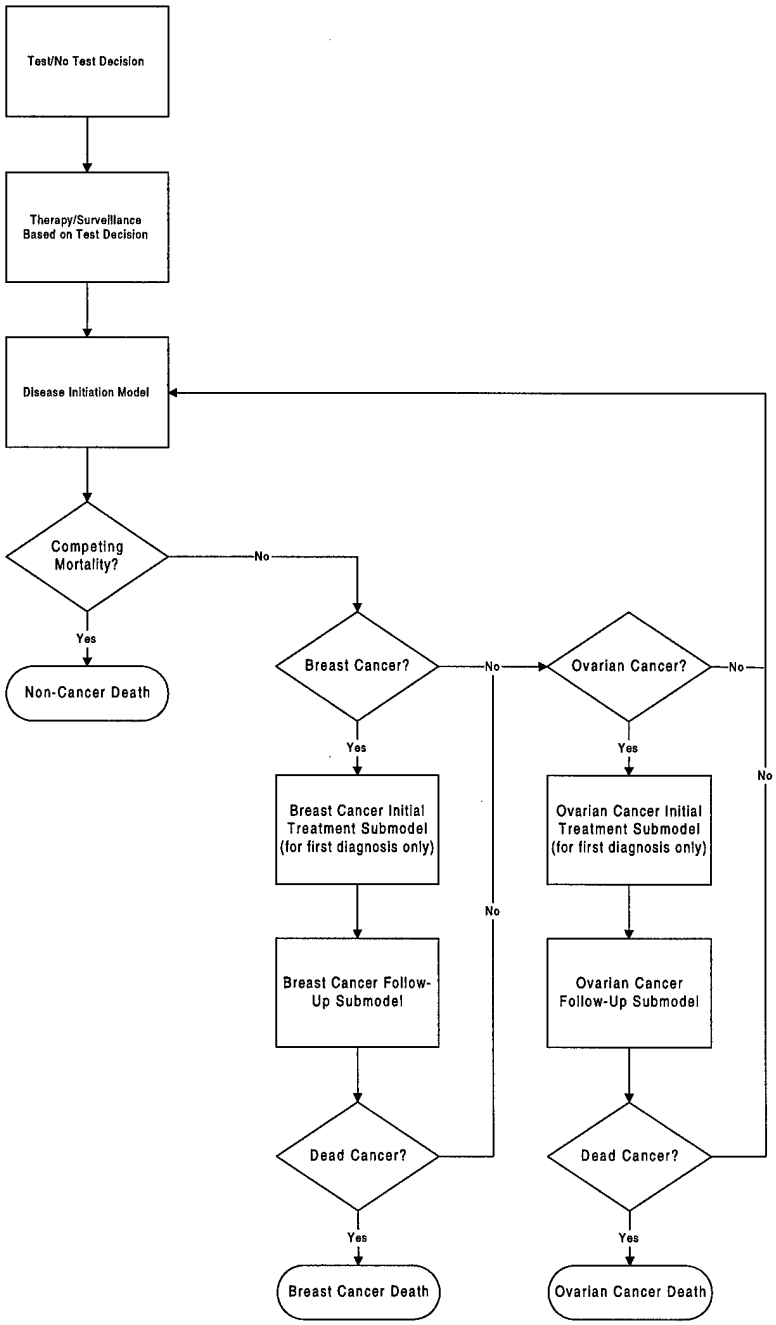
In the next set of choices, therapeutic prophylactic and early detection surveillance decisions are based upon the results of the test (or lack thereof). Therapeutic prophylactic (Schrag et al, 1997) and surveillance decisions (Hoskins et al, 1995; Weber at al, 1995) in turn, affect the probability of disease occurring, and if disease does occur, the probability of having a particular stage of disease at diagnosis. Whether or not disease occurs in any time period is evaluated in the disease initiation model; this part of the model

determines if breast or ovarian cancer has developed, and, for women both with and without cancer, determines if a women has died of a non-cancer-related cause in that period of time.

If the woman has not died, the breast cancer model determines if the woman developed breast cancer in the disease initiation model. If so, upon initial development of disease, the stage of disease is determined, and a treatment option is chosen. The treatment option will determine the probability of breast cancer recurrence or progression. If the person has not died of breast cancer, the ovarian cancer model determines if ovarian cancer has developed in the disease initiation model. If so, a procedure similar to that for breast cancer is performed. At the end of the cycle (1 year), we restart the whole process for all surviving women to evaluate the next time period, and so on.

Figure 2. Algorithm for BRCA model.

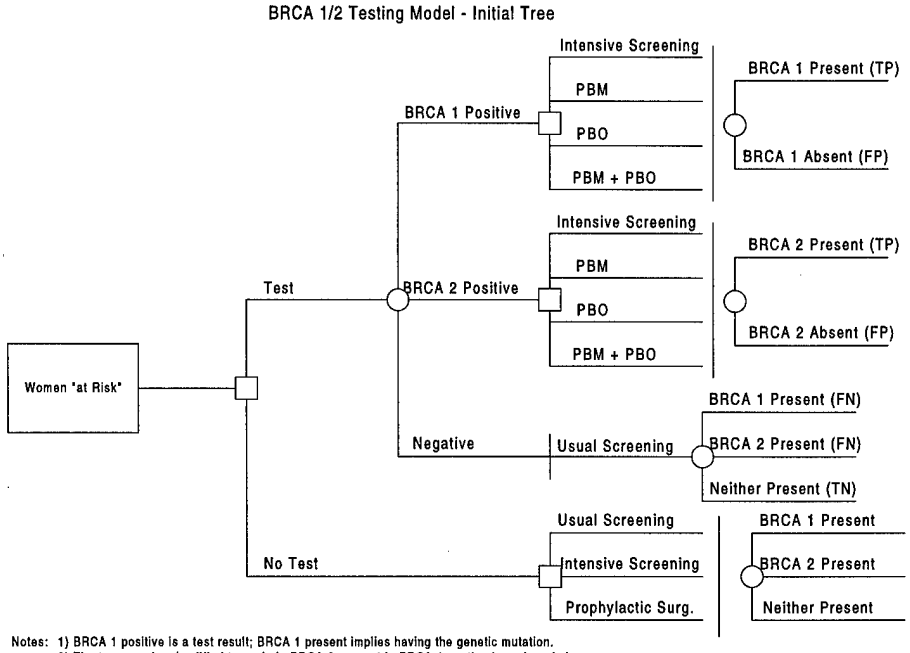
Flow Diagram of BRCA 1/2 Natural History Model



Initial Decision Tree: The decision tree shown in **Figure 3** describes womens' initial decision at the initiation of the model - whether to undergo testing and counseling or not. The figure shows a simplified version of the full tree, which includes three choices - agreeing to testing and counseling, agreeing to counseling alone, or deciding to have routine medical care. If a woman decides to be tested (and counseled), she has several potential outcomes: the woman could have a BRCA1 mutation (BRCA1 positive), she could have a BRCA2 mutation (BRCA2 positive), or she could have neither mutation (negative). We have decided not to include the option of having both a BRCA1 and a BRCA2 mutation, since there is little clinical natural history data for this combination, and this branch, being a rare event, should have minimal impact on the final CEA results. If a woman tests positive for one or the other mutation, then she would next decide what surveillance or prophylactic strategy she might use to avoid developing breast and/or ovarian cancer.

Whether she tests positive or negative, the result could be a true positive (TP) result or a false positive (FP) result.

Figure 3. Decision tree for testing.



Notes: 1) BRCA 1 positive is a test result; BRCA 1 present implies having the genetic mutation.
2) The tree may be simplified to exclude BRCA 2 present in BRCA 1 postive branch and vice-versa.
3) "Therapy" in this model could be one of several therapies. This representation will most likely be expanded to a decision node of several different therapies (eg. prophylactic mastectomy, prophylactic oophorectomy, intensive screening).
4) Endpoints of the model will be the BRCA 1/2 Cancer Initiation model, modified for appropriate branches of the tree.
5) Test negative patients would undergo usual screening if known mutation in family. If no known mutation, then they could receive options listed for the No Test branch.

For women with a positive test, we model several surveillance and therapeutic options. Women can chose intensive surveillance with frequent mammograms and clinical exams. Alternatively, women could decide to have a prophylactic bilateral mastectomy (PBM), which would reduce but not eliminate the risk of future breast cancer. Women may also opt to have prophylactic bilateral oophorectomy (PBO), which would reduce future risk of ovarian cancer. Finally, women could chose to have both PBM and PBO. The option chosen at this point in the model then determines future risk of developing breast and ovarian cancer, as well as the stage distribution at diagnosis. Each choice is also associated with certain probabilities of morbidity and mortality. For instance, there may be decrements in quality of life associated with knowledge of mutation positivity, or anxiety associated with evaluation of positive (and false-positive) early detection tests, or morbidity or mortality associated with undergoing prophylactic surgery.

If women test negative, there are two interpretations depending on the clinical setting. First, if the test is performed on a woman with a family member with a known mutation, then the test is negative for that mutation (true negative; TN). If the woman is at high risk for a mutation but does not have a known mutation in the family, then the test is indeterminate. In this case, the test is negative for the specific mutations tested for, but does not necessarily mean that the women does not have a genetic susceptibility for breast cancer (false negative - FN). Thus, if we are testing a woman with a known mutation in the family, we would model that she receive usual breast cancer screening if the test is negative. For the case of a woman with no known mutation in the family, however, we would examine the options presented to those with a positive test in addition to usual screening.

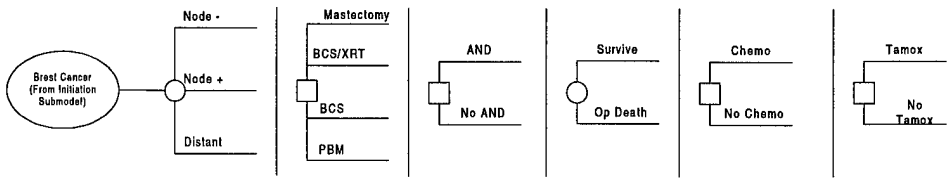
The "No Test" branch of the model currently incorporates the choices of having counseling, but declining genetic testing, and choosing not to be tested or counseled. The final decision tree will disaggregate these two "no test" options. The outcomes for women who chose not to have genetic testing will be based on clinical histories. For example, women with a family member with a known mutation who decline testing may chose diagnostic and therapeutic strategies ranging from usual age-specific screening, more intensive screening, PBM, PBO, or a combination of prophylactic surgeries. Womens' decisions will be affected by

whether or not they have had genetic counseling. Likewise, the probability of adhering to a screening regimen will be affected by counseling status.

BRCA1/2 Breast Cancer Initial Treatment Subtree: In any given year (model cycle), if the disease initiation model determines that a woman has developed breast cancer, the woman enters the breast cancer treatment submodel (**Figure 4**). This part of the model first determines the stage of disease at diagnosis (local=node negative, regional=node positive, distant metastases=distant). This stage categorization was chose to correspond to prognostic categories, as well as categories in which data are commonly reported (ie, in SEER). Women with cancer choose the treatment they prefer. The tree assumes unilateral cancer at the time of diagnosis, although the tree could be modified to include options for women with bilateral disease, if this is a sufficiently common occurrence in the population being evaluated. Local surgical treatment procedures for unilateral breast cancer include mastectomy, breast conserving surgery (BCS), with or without radiotherapy, and bilateral mastectomy (i.e. a mastectomy as treatment in the affected breast, and a prophylactic mastectomy in the unaffected breast). For any of the preceding local therapeutic decisions, axillary node dissection (AND) could also be performed. All surgical procedures have an associated operative mortality rate. In addition to local surgical treatments and regional evaluation strategies, women can have adjuvant chemotherapy and/or hormonal therapy with tamoxifen. This tree determines the starting node in the Markov model (below) of breast cancer follow-up (based upon stage of disease), and the probabilities of recurrence and progression of cancer (based upon treatment). A similar decision tree portrays ovarian cancer treatment, and will be fully developed in Year 2.

Figure 4. Decision tree for breast cancer treatment.

BRCA 1/2 Breast Cancer Initial Treatment Subtree

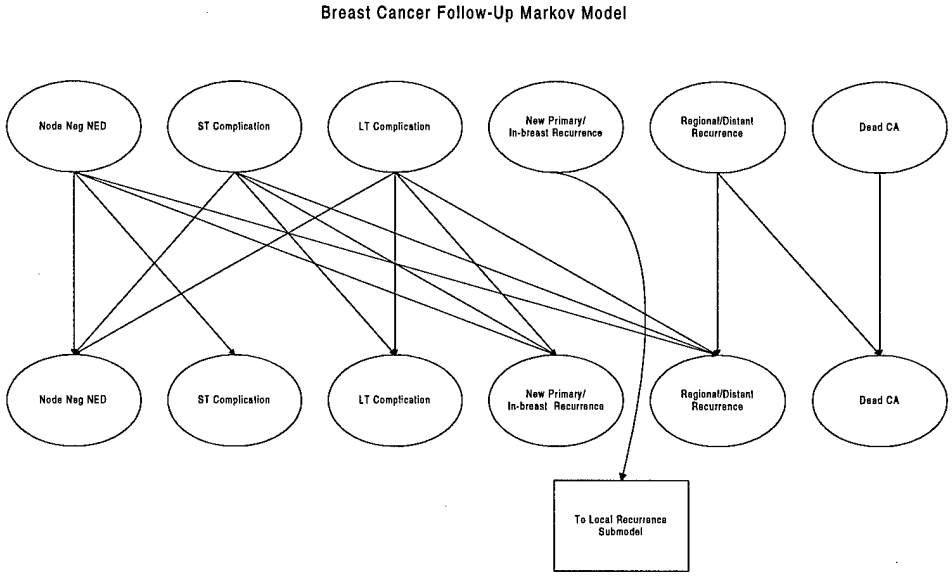


Notes: 1) This tree is a bridge between the disease initiation model and the breast cancer follow-up submodel. Endpoint of the tree will be an initial node in the breast cancer follow-up submodel.
2) Some nodes in the treatment tree will be excluded for some stages of disease (eg. a person with distant disease will most likely not receive BCS/XRT.

Breast Cancer Follow-Up Markov Model: Once a woman has been staged and treated, she enters the Markov model of breast cancer follow-up to determine the outcomes of of her disease course (**Figure 5**). Separate models will be set up for node negative and node positive disease, allowing for higher risk of recurrence and progression of disease in women with node positive cancer (only the node negative model is shown in the **Figure 5**). After initial treatment, women with node negative disease enter the model in the Node Neg. NED (no existing disease) state. In any time period (one year cycles), women have risks of complications of therapy. These complications can be either short or long term (ST or LT). Women also have certain probabilities of having an in-breast recurrence or a second local primary (and entering a separate recurrence submodel). This submodel will be of the same form but will allow for higher probability of recurrence and progression given that one recurrence has already occurred). Women can also progress to regional or distant disease. In this submodel, only women who have regional or distant disease can progress to death due to breast cancer. The model will allow for risk of competing non-cancer mortality, and for risk of ovarian cancer development and mortality once a woman has developed breast cancer.

A similar Markov model portrays ovarian cancer natural history, and will be fully developed in Year 2.

Figure 5. Breast cancer natural history model.



Notes: 1) Transition probabilities will be dependent on therapies chosen in the breast cancer treatment subtree.
2) The local recurrence submodel will have similar form to the model above, but will allow for a change of transition probabilites to reflect the possibility of increased regional/distant recurrence risk in the face of local recurrence. This will also allow a decision node for different treatments. This may be able to be simplified to stay in this Markov model.
3) Dead CA represents disease-specific mortality, which we assume can only occur with distant disease. Competing mortality is handled in the disease initiation submodel.

Analysis of Data to Develop Model Parameters: For the CEA, we will estimate the effects of all possible events that flow from the initial testing choices, the probability of each event, and the probability of transition from one state to the next. Since the majority of events in the CEA model take place outside of the time-frame and scope of Project #1, an extensive review of the medical literature (secondary data) will be conducted to estimate all model parameters. For secondary data used in the model, the data will be derived from the best designed and least biased studies available (e.g., well designed randomized clinical trials and observational studies, and administrative databases, such as SEER)(Mandelblatt et al, 1996; 1997). Meta-analytic techniques will be used to derive effect size estimates (e.g., the expected cancer risk reduction associated with bilateral mastectomies [Schrag et al, 1997]). An illustrative list of parameters to be collected or estimated is presented in **Table 2**, below.

Some of these data are in the process of being collected, or are still largely unknown. We will rely on the clinical expertise of Project 1 investigators, other Lombardi oncologists, and national experts in the field to estimate unknown variables and update data as they become available. For uncertain parameters, we can use the model to evaluate whether the parameter impacts on overall results, and, if so, what the range of values would need to be for genetic testing to be cost-effective.

Data collection to finalize estimates of model parameters will continue in Years 2 and 3. In this manner, we can finalize the entire model structure, in conjunction with the clinical input of Project 1 staff and the Outcomes Core Advisors, and conduct focused literature reviews to finalize the best estimates for each parameter in the entire CEA model.

Table 2. Preliminary Model Parameter Estimates

Parameter	Estimate (Range)	Sources
Prevalence of BRCA1/2 mutation	.37 [1] (.25 - .90)	Wooster, 1994; Miki 1994; Easton, 1993; Shattuck-Eidens, 1993; Langston, 1996; Neuhausen, 1996; Berman, 1996
BRCA1/2 test accuracy [2] Sensitivity Specificity	 .45 (.4 - .9) .99 (.8 - 1.0)	 Shattuck-Eidens, 1995; BCIC, Tavtigian, 1995 NCHGR Breast-Cancer Information Core (BCIC), Expert opinion
Surgical mortality: BCS MRM BM	.009 (.002 - .02) .009 (.002 - .02) .009 (.002 - .02)	Herbsman, 1981; Turnbull, 1978; Becker, 1989
Relative risk of breast cancer with BM	.05 (0 - .10)	Slade, 1984; Pennisi, 1989; Expert Opinion
Relative risk intra-abdominal carcinomatosis with oophorectomy	.05 (0 - .10)	Nguyen, 1994; Piver, 1993; Struewing, 1995
Rate of 2nd primary (per year) BRCA1/2 positive	.036[3] (.024 - .058)	Ford 1994; Easton, 1995, Marcus et al., 1996
Rate of 2nd primary (per year) BRCA1/2 unknown	.005 (.004 - .01)	Broet, 1995
Rate of ovarian cancer (per year) with BRCA1	.019[3] (.010 - .024)	Ford 1994, Easton, 1995
Rate of ovarian cancer (per year) with BRCA2	.007[3] (.003 - .15)	Expert opinion
Rate of in-breast recurrence with BCS (events/year)	.009[3,4] (.004 - .030)	Fisher, 1995; Recht, 1996
Rate of regional/distant metastases (events/year/ years 0-4)	.047[3,4] (.030 - .110)	Fisher, 1989; Recht, 1996; Early Breast Cancer Trials Collaborative Group, 1992
Mortality rate (deaths/year) Metastatic disease Population (female)	 .343[3,4] (.303 - .354) Age/race dependent	 Parker, 1996; Ries, 1991 Statistical Abstract, 1995

[1] This estimate is an example and represents the prevalence of women under 40 years old with breast cancer who have a sister diagnosed with breast cancer before age 40. Then we will examine a full range of prevalences based upon risk factors for BRCA1/2 mutations.
[2] Accuracy for detecting a BRCA1/2 mutation (using sequencing as "gold standard").
[3] Yearly rate estimated using DEALE method (Sox et al., 1988).
[4] The final parameter estimate will be dependent on prognostic factors including tumor size and grade, nodal status, Er, PR, S-phase and ploidy status, as well as local and systemic treatment regimens.

Preference/Utility Measurement: As noted above, the final health effects, or outcomes of the different testing and counseling strategies will be measured in terms of quality-adjusted life years (QALYs). Thus, life-table methods will be used to measure the survival associated with each clinical pathway in the above models; time in the health state associated with each path will be weighted by the average utility, or

preference value for that state, and cumulated over each pathway to yield QALYs. Such quality-adjustment allows us to incorporate the fact that women with similar ability (or disability) to function may value that level of functioning differently. This concept is broadly referred to as a "utility" or "preference" value or weight; although these terms are not strictly equivalent, we use the term utility in the remainder of this discussion to reflect this concept (Gold et al, 1996b; Patrick and Erickson, 1993).

There are many areas of debate among methodologists concerned with measuring utility (Gold et al, 1996b; Mandelblatt and Eisenberg, 1996; Cox et al, 1992; Mehrez and Gafni, 1989;1993; Gafni and Birch, 1995; Ganz, 1994b; Dean, 1990; Slevin et al, 1990; Torrance, 1976b; 1982; 1987; Fryback et al, 1993; Nease et al, 1995; Wolfson et al, 1992). Thus, we are using three complementary approaches, including a patient linear rating scale (LRS), hypothetical time-trade-off (TTO) scenarios, and a generic health state tool - the Health Utilities Index (HUI)(with available population-based utilities values (Torrance et al, 1972; 1984; Drummond et al, 1987; Ontario Ministry of Health, 1990). The TTO scenarios portray and measure utility for several of the key choices individuals might be faced with (e.g., prophylactic surgery)(Singer et al, 1991; Yellen et al, 1994; McQuellen et al, 1995; Ashby et al, 1994).

The LRS and the TTO scenarios measure womens' individual preference values, and the HUI, in which women place themselves into a health state for which population-based utilities exist, provides a societal utility. Thus, we can generate QALYs from the perspective of both women (women at risk for breast cancer) and society. All three utility measures are being obtained from women enrolled in Project 1 at baseline, 1, 6 and 12 months using telephone administration. In this manner we will be able to include data needed for the CEA model and also test the effect of genetic testing and timing of assessment on utility values. Project 1 staff have been trained to administer all utility assessments.

Time Trade-Off Scenarios: The time-trade-off (TTO) method of utility assessment provides a holistic assessment of the respondent's preference for a state of health. This assessment technique has the advantage of being usable for rating preferences for hypothetical states of health (e.g., rating a woman's preference for mastectomy to treat local stage breast cancer, even if that woman does not actually have cancer). Another advantage of this approach is that TTOs do not measure risk adversity, as do standard gambles, an otherwise closely related technique for evaluating utility. The TTOs ask the respondent to make a choice between living for a specified time in the state of health of interest, or living for a shorter period of time in excellent health. For example, if a woman felt that living 30 years with a mastectomy for early stage breast cancer was as desirable as living 25 years in excellent health, her utility would be the ratio of the two times, 25/30=0.83. The TTO results are expressed on a scale from 0, representing death, to 1, representing excellent health.

In Year 1, these TTO scenarios have undergone extensive piloting, revision, and validation in the target population. Piloting was conducted in-person and over the telephone, since Project 1 is collecting these data over the telephone. There were several interesting findings noted in the piloting process. First, we found that women at high risk for having a mutation had extremely high utilities for mastectomy and BCS following early stage breast cancer diagnosis (e.g., of the first 12 participants surveyed, 42% gave mastectomy and BCS a utility of 1.0, or a utility equivalent to excellent health). After review with the Outcomes Core Advisors and a survey of comparable results in other settings, we concluded that the pilot scenarios did not capture the disutility of womens' concerns/fears about the return of cancer. Therefore, we revised the scenarios to include the statement "... is free from known cancer, although from time to time she worries about the cancer coming back".

Second, the initial TTOs were worded in the first person. When we revised the scenarios to the third person, the range of utility values increased, and fewer women rated having a breast cancer surgical procedure as equivalent to excellent health (mean utility first person for mastectomy=.95, mean third person=.89, p=.056 for difference).

Third, based on the experience of one of our Advisors (David Cella, Ph.D.), we piloted trading off different time periods (30 years, 1 year, 5 years)(**Table 3**).

Table 3. Pilot TTO Results

Scenario	**Mastectomy**	**BCS**	**Metastases**
Time Frame (long)	30 yr.	30 yr.	5 yr.
N	10	10	10
Mean Utility	0.93	0.96	0.54
Time Frame (short)	1 yr.	1 yr.	1 yr.
N	10	10	9
Mean Utility	0.88	0.92	0.85
P value (short v. long)	0.33	0.46	0.02

There was no significant difference between the scenarios using the 1 year vs 30 year life expectancy for local disease, there was an important difference between the two time periods for evaluation of metastatic disease, with the 5 year time frame yielding more valid results for then the one year time frame. However, it would not be logical for women to be rating early stage disease using a 1 year time frame and then metastatic disease using a five year time frame for life expectancy. Thus, the final TTOs use the third person and a 30 year life expectancy for local disease and five years for distant disease. We are planning additional methodological studies on these, and related issues in utility assessments for cancer in the later years of the Outcomes Core activities.

The final TTO scenarios for Project 1 are included in **Appendix 1**; these scenarios include 10 key clinical pathways in the CEA model. To lessen respondent burden, each participant receives 3 randomly selected TTO scenarios at each measurement point.

Linear Rating Scale: The linear rating scale (LRS) utility assessment technique asks the respondent to directly rate the health states represented in the TTO scenarios on a scale from 0, representing death, to 100, representing the best state of health imaginable. The LRS assessment technique used is similar to that of the EuroQOL (EuroQoL Group, 1990), modified for telephone administration. We decided to add the LRS to our utility assessments for two reasons. First, we wished to have a comparison method of utility measurement to cross-validate the TTO results. Second, the LRS is cognitively easier for respondents than the TTO. However, it should be noted that LRSs are not be a "true utility measure" (Gold et al, 1996). Pilot data for the LRS utility assessment are summarized in **Table 4**. These results demonstrate that, as for the TTOs (data in **Table 3**, above), women rate BCS slightly more highly than mastectomy, and that the LRS

results yield somewhat lower utility values than the TTOs. This latter result is commonly noted in utility assessment (Gold et al, 1996). Researchers have found also found that a plateau function based upon LRS utilities reasonably explains the variance in TTO utilities (O'Leary, et. al., 1995), thus we will consider using a plateau function to modify the LRS scale results for incorporation into the CEA model.

Table 4. Linear Rating Scale Pilot Data

Scenario	**Mastectomy**	**BCS**	**Metastases**
Mean LRS (Std.Dev.)	77.4 (16.2)	79.6 (13.1)	38.4 (20.5)
Range	50-100	50-100	10-80
N	19	20	19

Health Utilities Index: The above two utility assessments provide a holistic assessment of the respondents personal preferences for a state of health. Since a CEA performed from a societal perspective should include societal utilities for the outcomes, we are also using the Health Utilities Index (HUI) (Feeny et al, 1992). The HUI is a brief questionnaire that can estimate societal utilities based upon ratings of several domains of health-related quality of life (sensory perception, mobility, emotional function, cognitive function, self-care, pain, and fertility). To minimize respondent burden, we have developed a modified version of the HUI 15 Q, deleing items or sub-items with low expected variability in function in the target population (**Appendix 1**).

We have modified our original measurement strategy by deleting the Years of Healthy Life (YHL) instrument (Erickson et al, 1995), since this was developed using HUI values and would be redundant.

Costs: The non-medical direct costs of patient identification and recruitment through the Patient Accession Core (see **Appendix 2**), counseling, genetic testing, and time costs (e.g., patient time costs to receive counseling and testing, travel, and costs of caregivers to provide care for dependents while the woman receives testing/counseling, etc.) are being measured using primary data from women enrolled in Project 1 and other related cancer genetic studies at Lombardi Cancer Center (**Appendix 1**). Productivity costs and intangible costs will be captured through the decrements in utility.

Direct medical care costs and non-direct medical care costs occurring outside of the scope and time frame of Project 1 will be measured in Years 2 and 3. Since costs are decreasing over time as a result of economies of scale, experience, and improvements in techniques (Gershon, 1995), we will evaluate a range of likely costs for testing and counseling. Costs incurred outside of the time frame and scope of primary observation of Project 1 (e.g., life-time screening surveillance, diagnostic test costs, and/or treatment costs) will be estimated using nationally representative average costs. Age- and stage-specific treatment costs for breast and ovarian cancer will be estimated using existing data (Riley et al, 1994; 1995; Taplin et al, 1995; Baker et al, 1991); race-specific data will be used to the extent possible. The use of such "gross" costing techniques is sufficient in the context of these analyses, where the events are high-cost and are occurring far in the future relative to genetic testing (Gold et al, 1996a; Eisenberg, 1989). Analyses will use costs, not charges. Where charges are the only available data source, a cost-to-charge ratio will be used to estimate costs. Time costs will be valued using average age-, gender- and race-specific wage rates; all costs will be adjusted to one time period (ie, 1998) using the medical component of the Consumer Price Index. As noted

above, since many of the costs (and health effects) occur far into the future relative to genetic testing (e.g., for women who develop cancer, the costs of treatment may occur 10 to 20 years after genetic testing), all future costs (and health effects) will be discounted at 3%.

B. PROJECT 2: Coordinated Approach to Breast Cancer Diagnosis: Technical Aim: Conduct an economic evaluation, develop a decision analysis model comparing the costs per cancer detected for new breast cancer diagnostic evaluation strategies, and assess test-related patient QOL: Project 2 is prospectively enrolling a cohort of approximately 400 white and African-American women, from several DC-metropolitan area clinics, hospitals, and HMOs, who have abnormal breast physical examination, mammography, and/or standard sonography results and have been recommended to have a breast biopsy. The goals of the project include evaluating the accuracy of several simultaneously administered new technologies, including digital mammography, magnetic resonance imaging (Gd-DTPA enhanced MRI), nuclear medicine evaluation (Tc-99m-sestamibi scanning), special ultrasound evaluation (radio frequency elastography imaging), and nipple aspirate fluid (NAF) cytology via correlation with pathological results of **surgical excisional biopsy**. Women with negative biopsies will receive 12-month follow-up mammography and CBE.

The Outcomes Core objectives for this project are to: 1) conduct an **economic evaluation** to compare the costs per cancer detected for each for each of the innovative diagnostic technologies; 2) using the general methods of decision analysis and modeling described above for the genetic testing project, use the primary data on test sensitivity, specificity, and costs, combined with natural history data (e.g., molecular markers in NAF), to develop a **decision analysis model** for hypothetical cohorts of women comparing the costs per intermediate outcome (correct early diagnosis, delayed diagnosis, and missed diagnosis) for alternative diagnostic tests (or combination of tests) and surgical excisional biopsy; and 3) to evaluate the acceptability of, and satisfaction with, the tests.

Economic Evaluation: The following discussion summarizes the Outcomes Core approach to conducting the economic evaluation. The outcomes for this economic evaluation are intermediate outcomes (e.g., the number of correctly diagnosed, delayed, and missed breast cancers, average size of invasive cancer by modality). The primary intermediate outcome for the economic evaluation will be the number of cancers correctly diagnosed. The preliminary economic evaluation will be conducted in Years 2 and 3, and the final analysis is Year 4. This analysis will tally, for each diagnostic technique, the average costs per test and divide this by the number of correctly diagnosed cancer cases (based on excisional biopsy pathology results and the test scoring procedures in the project). Since some tests may correlate with biopsy based on chance alone, the 95% confidence intervals associated with the test ROC curves will be used to assess the concordance of test interpretation and pathology results beyond chance expectations (McNeil and Hanley, 1984). The costs per correct diagnosis will also be evaluated for clinically relevant sub-groups (ie, palpable/non-palpable mass, pre/post-menopausal; hormone use yes/no, etc); since the costs will not vary substantially, these analyses will be detecting differences in test performance across sub-groups. We will also evaluate the costs per cancer correctly diagnosed for different combinations of the four diagnostic tests.

Costs will include the costs of the tests as well as non-medical direct costs, such as patient time costs, travel, caregiver costs while taking the tests, etc. Procedure costs will be collected in Years 2,3, and 4, while patient-related costs are being collected prospectively from women on the day of the tests (see **Appendix 3** for the instrument that includes these items).

In addition to beginning above the economic evaluation as originally planned, we have also added a brief assessment of womens' willingness to pay for these alternative diagnostic tests in order to avoid a surgical biopsy (Froberg and Kane, 1989; Patrick and Erickson, 1993; Kartman et al, 1996). The questions measuring willingness to pay are included in **Appendix 3** and discussed below, in the QOL/Acceptability section. While such a descriptive economic evaluation is useful in preliminary investigations, it will ultimately be important to assess the impact of false-positive and false-negative test results on the costs and benefits of alternative diagnostic strategies as they are projected to occur in clinical settings. This goal will be accomplished using the decision analysis model described in the following section.

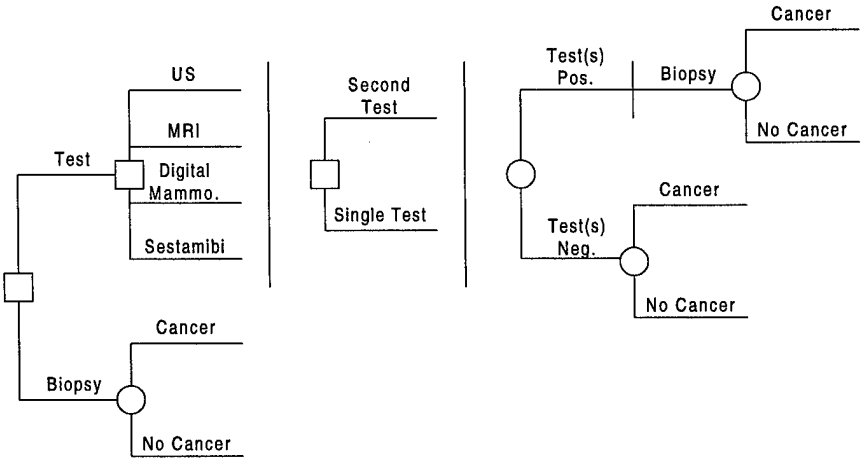
Decision Analysis/CEA Model: The goal of this portion of the Outcomes Core assessment is to extend the intermediate outcomes (and costs) in the above economic evaluation to include all projected downstream events (and costs) that might follow from the clinical application of these tests, either alone, or in combination, compared to surgical excisional biopsy. To accomplish this goal, we have begun work in Year 1, in conjunction with one Outcomes Core Advisor - Dr. Bruce Hillner, to extend prior work (Hillner et al, 1996) and develop a decision analysis/CEA model. This model will calculate the incremental cost per cancer diagnosed (intermediate outcome) and years of life saved (final outcome) for the use of single and paired combinations of diagnostic tests for follow-up of an abnormal mammogram and/or clinical breast examination, compared to a surgical excisional biopsy.

The audience for these analyses (to be conducted in Year 4) consists of clinicians and health plan decision makers interested in algorithms to maximize the negative predictive value of a diagnostic algorithm for follow-up of clinical or radiologic breast abnormalities, as well as public health advocates, health services researchers, clinicians, and health plan decision makers faced with societal resource allocation decisions.

The strategies to be compared include digital mammography, sestamibi scan, breast ultrasound, and breast MRI, singly and in paired combination, compared to surgical excisional biopsy for follow-up of suspicious breast abnormalities (on mammogram [films interpreted as suspicious or positive for cancer] or clinical breast exam). We will examine two time frames: one short-term frame (through the completion of the diagnostic evaluation of the breast abnormality), and one long-term (from point of diagnostic evaluation through death). For the short-term time horizon of analysis, we will not discount results to present value; the long-term analysis will discount future costs and health effects at a rate of 3%.

A decision model will be used to estimate the number of true positive and false negative diagnoses, based upon the prevalence of disease in the population. **Figure 6** includes a preliminary decision tree for this model. Data for parameters in the model will be derived from Project 2, the published literature, other Outcomes Core related projects, and Dr. Hillner's prior research. An important goal of Project 2 (and the decision/CEA analysis) is to identify the optimal

Figure 6. Decision Tree for Diagnostic Evaluations.



diagnostic algorithm for follow-up diagnostic testing for women with suspicious mammographic abnormalities or clinical breast examinations. This goal guided the development the decision model. All testing algorithms are compared to the standard diagnostic work-up of surgical excisional biopsy. We consider the four potential diagnostic tests in comparison to biopsy. For each test, the choice could be made to use the test alone, or add a second diagnostic test (of the remaining 3 tests). We have chosen to simplify the analysis by restricting consideration to single diagnostic tests or to paired combinations; in sensitivity analysis, we will examine more than two tests in combination. In the decision tree, women with screen-detected abnormalities may have palpable or non-palpable masses; diagnostic tests (or pairs of tests) may be interpreted as positive, negative, or indeterminate for a cancer; negative women will return to routine screening; women with falsely negative results will have delayed diagnosis; women with indeterminate results can either have other tests performed immediately or under-go interval re-screening (ie, 3-4 months later); women who are positive may have cancer or not; etc. In this manner we will calculate the number of women correctly diagnosed with cancer, and the impact of test results on life expectancy.

We will also address two important issues in these analyses. First, the results of combinations of tests can be interpreted either in series or in parallel. If tests are performed in series, the first test is performed, and if positive, the second test is performed. If tests are performed in parallel, then both tests are performed, and if either test is positive then the woman is considered to have a positive diagnostic work-up, and a biopsy would be recommended. For our base analyses, we will assume parallel use of paired tests, as this strategy most closely matches the experimental conditions of Project 2 and maximizes the overall sensitivity of the combination of test pairs (ie, minimizes the number of false negative diagnoses).

The second issue that must be addressed is that of conditional dependence of diagnostic accuracy between the tests (Mandelblatt et al, 1996). Typically in decision analyses, if two diagnostic tests are to be used, analysts assume conditional independence of test results (i.e. the results of the second test are independent of the findings of the first test). This approach is usually necessary because there are no data on test dependencies. In the case of Project 2, all four diagnostic tests are being performed for all women, we can examine conditional dependence of test results. For instance, we can calculate the probability that an ultrasound will provide a true positive result given that a sestamibi scan was negative. We can then incorporate these conditional diagnostic accuracies into the model when we are examining paired combinations of tests, allowing for more clinically valid model results.

The costs for this decision model/CEA will include test costs and patient-related costs as measured in Project 2, and all downstream costs (from secondary sources). The general approach to estimating down-stream costs will be similar to that described for the CEA of BRCA1/2 genetic testing, above.

QOL/Acceptability: In this portion of Project 2, the Outcomes Core is measuring several specific domains of QOL pertaining to a woman's experiences with the diagnostic tests, including satisfaction, and pain, discomfort, and embarrassment. We are measuring satisfaction with the diagnostic tests using a modification of the Medical Outcomes Study Visit Rating Questionnaire (Rubin et al, 1993). We have also developed questions that ask about pain and discomfort and embarrassment associated with the tests.

In addition, as noted above, we have added a measure to assess womens' preferences for having one of the diagnostic tests compared to a surgical biopsy, using the willingness to pay (WTP) technique. The WTP questions ask respondents how much money they think women like themselves would be willing to pay out-of-pocket to an alternative diagnostic test instead of a biopsy. We have chosen to word these questions in the third person, based on our experience with the TTO utility assessments in Project 1 (noted above). Since

the WTP technique is sensitive to economic status, we are calculating results as the amount a woman thinks women like herself would be willing to pay as a proportion of the respondents household income. We are using two WTP scenarios: the first asks about willingness to pay to have a test instead of a biopsy, if the test were as accurate as a biopsy at diagnosing cancer; and the second asks about WTP if the test were nearly (95%) as accurate as a biopsy. We hypothesize that women's preferences for the diagnostic tests, as measured by the WTP, will be lower for the tests that are not as diagnostically accurate as a biopsy, compared to those that are. The survey instrument for all of these domains is included in **Appendix 3**.

C. PROJECT 3: Trials of Novel Palliative Treatments for Metastatic Breast Cancer: Project 3 is enrolling white and African-American women from several DC-metropolitan area settings (including cancer centers, community practices, and managed care organizations) who have advanced metastatic breast cancer (clinical stage 4) and who have no tumor progression after $\geq$ 6 cycles of induction chemotherapy. After phase I and II evaluations are completed, women will be enrolled in phase III randomized treatment interventions of anti-angiogenic agents alone and in combination with standard chemotherapy. In all trial phases, the Outcomes Core will provide descriptions of the QOL of life of participants, the acceptability of the regimens (e.g., inconvenience, time spent), and the quality-adjusted costs and costs-per unit of clinical outcome.

Quality of Life: For the TNP-470 and the Thalidomide trials we are measuring the following general and breast cancer-specific domains of QOL: physical well-being, social/family well-being, relationship with doctors, emotional well-being, functional well-being, additional concerns related to breast cancer, breast cancer symptoms, and performance status. In evaluating existing tools for use in a palliative care setting, several elements were considered, including respondent burden, ability of the instrument to detect floor effects (ie, when patients with the lowest possible scores deteriorate (Ganz et al, 1988; Bindman et al, 1990; Ganiats et al, 1992), relevance of domains (ie, physical and emotional functioning and ADLs), and practical considerations, such as availability of self-, interviewer-, or telephone-administration formats.

To balance respondent burden and sensitivity to detecting changes in QOL over time, we will collect all data at study enrollment and at selected follow-up clinical visits (e.g., for the thalidomide protocol, every two weeks from start through week 8, and then every four weeks); QOL, acceptability, and utility measures will rotated. The instruments are included in **Appendix 4**. The Outcomes Core has trained the Project 3 research nurses for all data collection.

These next sections outline our experience piloting instruments for reliability and validity in the target population, and our final choice of measures. It should be noted that all measures were acceptable and comprehensible to women participating in the pilot evaluations.

FACT-B: We are using the Functional Assessment of Cancer Therapy - Breast Cancer (FACT-B) as our general QOL measure. This questionnaire measures both general and breast cancer specific domains of health, including physical well-being, social/family well-being, relationship with the woman's doctor, emotional well-being, functional well-being, and additional concerns related to breast cancer. This survey has been previously validated in women with breast cancer, including those with metastatic disease (Cella et al, 1993). We originally chose this instrument for its pertinence to breast cancer, and for the ability to measure a broad range of health states. We piloted this instrument among women who had stage 4 breast cancer, but were early in their course of disease ("early metastatic disease"), and several women with advanced metastatic disease, who represent women in the terminal phases of breast cancer ("late metastatic disease"). We have recently completed piloting with 10 additional women in this latter category. Since we

are interested in detecting treatment-related differences in QOL in women over the course of disease, from study enrollment to death, piloting efforts for this, and the other QOL measures centered on the ability of the instrument to detect differences among well functioning women (ie, not having a "ceiling effect"), as well as among severely ill women (ie, not having a "floor effect"). The FACT-B can be scored either with a summary score or with scores for the separate domains of health. The summary scores for our pilot are presented in **Table 5**. The maximum score achievable on the summary score is 152, representing the best health measured by the survey. No woman scored either at the ceiling or the floor of the summary scale, although ceiling effects were seen for some of the individual scales. Most notably, 67% of participants scored at the ceiling for the Relation with Doctor scale, that is, they rated their relationship with the doctors(s) and medical care staff as the best possible relationship. Overall, given the published data on the FACT-B, and our pilot data, we have incorporated this measure into our final Outcomes Core data collection instrument (**Appendix 4**).

Table 5. FACT-B Pilot Data

	"Early" Metastatic	"Late" Metastatic
N	12	6
Mean (S.D.)	119 (17)	94 (33)
% Ceiling	0%	0%
% Floor	0%	0%

Table 6. NHP Pilot Results

% Ceiling Effects by Scale	"Early" Metastatic	"Late" Metastatic
EL	91%	33%
P	82%	33%
ER	36%	33%
S	36%	33%
SI	82%	33%
PA	73%	0%

N= 11 Early, 6 Late

Nottingham Health Profile: The Nottingham Health Profile (NHP) (Hunt et al, 1981) was one of the originally proposed measures of general QOL. The NHP is a measure of general health status which is most responsive to detecting differences among individuals in very poor health. The NHP has 6 domains: energy level (EL), pain (P), emotional reactions (ER), sleep (S), social isolation (SI), and physical activities (PA). Unfortunately, in piloting, a large proportion of women early in the course of metastatic breast cancer functioned so highly that they scored at the top (ceiling) of several of the scales (**Table 6**). This finding, together with the overlap of domains with the FACT-B, led us to decide to drop this measure from our Core assessment package.

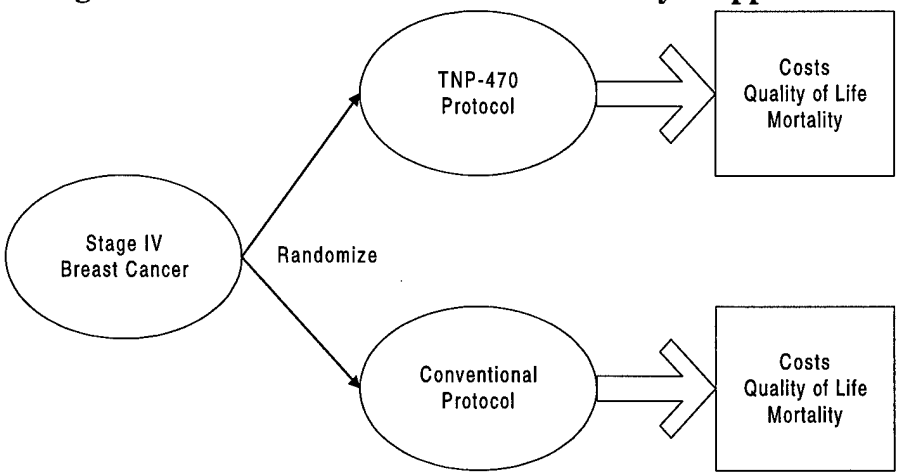
Rotterdam Symptom Checklist: Breast cancer-specific symptoms are measured using the symptom scale from the Rotterdam Symptom Checklist (Dehaes et al, 1990). This scale asks about 30 different symptoms that cancer patients may experience, and patients can rate the degree of bother from the symptom on a scale that ranges from "not at all" to "very much". In the pilot sample, the two symptoms with the highest average bother score were depressed mood and decreased sexual interest. The variability of responses was also good over the sample, and we are continuing to include this measure in our Core assessment.

Karnofsky Performance Scale: The preceding instruments measure patient-rated QOL. We also include the Karnofsky Performance Scale (KPS) to measure clinician-rated QOL/functional status. This scale has scores ranging from 100 (no evidence of disease) to 0 (dead). In our pilot survey, the mean (s.d.) KPS score for 12 "early metastatic" patients was 88 (7.5), and the mean KPS score for 5 "late metastatic" patients was 78 (8.4)(p=.07).

Economic Evaluation (Quality-Adjusted Costs per Unit Outcome): The Outcomes Core will be performing economic evaluations of the antiangiogenic therapies for use in metastatic breast cancer, including the phase II trial of thalidomide, and a phase I/II and a phase III trial of TNP-470. In the phase I and II studies, we will provide a description of the costs of care and utilities for outcomes for study participants. In the phase III portion of the research, we will perform a formal cost-effectiveness analysis of the use of a TNP-470 based regimen, calculating incremental costs per quality-adjusted life year saved. In addition, for all phases, we can evaluate the costs per specified clinical intermediate outcome of interest (e.g., costs per months of progression-free survival, costs per unit of improvement in functional status, etc). In this section we describe our approach for a phase III RCT, although the approach and data collection for intermediate analyses would be similar.

To conduct the CEA, we will model the CEA, collect primary data form women on their preferences/utilities for outcomes, and measure direct and non-direct medical care costs. The CEA will calculate the incremental cost-effectiveness of using a regimen containing the antiangiogenic agent TNP-470 compared to standardized chemotherapeutic regimens for women with metastatic breast cancer. As before in other analyses, the audiences for this analysis also consists of public health advocates, health services researchers, clinicians, and health plan decision makers faced with societal resource allocation decisions. The results of the CEA will be presented in incremental cost-effectiveness ratios, with health effects expressed as QALYs and costs expressed in dollars.

Figure 7. Schematic of cost-effectiveness analysis approach.



We will evaluate all women who meet the eligibility criteria for entry into the phase III RCT (women with stage IV breast cancer who have been stable, without progression) following 6 cycles of cytotoxic chemotherapy. The time horizon of the CEA will parallel that of the RCT, from enrollment to progression or death. An overview of the CEA structure is shown in **Figure 7**. Participants will be randomized to receive either the TNP-470 protocol or the conventional chemotherapy protocol. Direct and indirect costs of medical care, patient utilities, and survival/ progression data will be collected in the trial. Participants who die during the trial will be considered to have a utility of 0 (by definition) at the time of death.

The utility and cost components of the Core instruments are included in **Appendix 4**. To our knowledge, none of the existing utility-based health state tools (with the exception of the Quality of Life and Health)(Hadorn et al, 1995a,b) have yet been applied to comparable palliative cancer treatment trials. Thus, it is unclear what approach will be most sensitive to the differences in preferences for health states by treatment arm. Recognizing this, and considering respondent burden and comprehensibility of the task, we decided to use two measures of utility- a linear rating scale (LRS) and the HUI. The LRS and the HUI have been described above in the description of Project 1; their uses are similar in this Project. The pilot data for the performance of a LRS in women with stage 4 breast cancer is summarized in **Table 7**. Given the wide

range health experienced by women eligible for Project 3 protocols, ranging from asymptomatic with laboratory or radiologic evidence of metastases to extremely symptomatic from the cancer, these data are presented for two groups of women - women with "early" metastatic disease (little functional and symptomatic impact of the metastases), and "late" metastatic disease (significant functional and symptomatic impact of the cancer). As can be seen in the table, where scores can range from zero for a state equivalent to death to 100 for perfect health, only 1 of 11 women with early disease rated their health at the top of the scale, and no other participants rated themselves at either extreme of the scale. The mean LRS scores for the two groups were significantly different from each other (p=.015).

Table 7. LRS Data for Project 3

	"Early" Metastatic	**"Late" Metastatic**
N	11	6
Mean (S.D.)	82.4 (10.0)	55.8 (17.7)
% Ceiling	9%	0%
% Floor	0%	0%

The HUI is being used to measure societal preferences for the participants' health. These societal preferences will be used in the societal perspective CEA. We use the full version of the HUI (16 questions)(as opposed to the abbreviated version used in the genetic testing study) to capture a wider range of states of health. The pilot data for the HUI yielded utilities at the top of the scale in 3 of 10 women with "early metastatic" disease, and none of women with "late metastases scored at the bottom of the scale.

Thus, we feel that the LRS and the HUI will be useful measures to track changes in utility overtime, to discriminate among women with different treatment outcomes, and to provide both womens' and societal preferences for palliative care outcomes.

For cost data collection, we are measuring the costs of out-reach, medication, laboratory tests, procedures, physician and nurse time, hospital inpatient and outpatient visits, patient out-of-pocket costs, and patient and family/care-giver time costs. To maximize generalizability, protocol-induced costs that would not be necessary in real-world settings will be identified separately, so that the analysis can be conducted both including and excluding these costs. Thus, we are collecting data from the Patient Accession Core (see below), from women on their travel time, transportation costs, time spent in treatment, and caregiver costs, and from the project staff on use of medical care services and protocol-related costs (**Appendix 4**). We will costs out these data in Years 3 and 4 of the project. Productivity costs and intangible costs are captured through decrements in utility.

One issue that will be addressed in these economic evaluations is that of estimating the **cost of new investigational drugs or biological agents**, such as TNP-470. The research and development (R&D) costs associated with the "first-copy" production of such agents will over-estimate their ultimate cost, if and when they are produced for mass marketing. This reflects the fact that improvements in development and economies of scale can be achieved when pharmaceuticals, or other products, are produced for large-scale consumption. To address this the investigators will separately estimate R&D costs, production costs, distribution costs, and provision costs. In this manner, TNP costs, inclusive and exclusive of R&D costs, can be calculated for evaluation in the CEA analysis. Alternatively, we can estimate the projected wholesale costs of the drug if it should be mass-marketed. Costs of standard chemo-therapy will be estimated from pharmaceutical wholesale prices.

In this manner, we will, in Years 3 and 4, calculate means and standard errors for both QALYs and costs in the trial, and compute an incremental cost-effectiveness ratio for the use of an antiangiogenic agent in metastatic breast cancer. Due to the short expected time horizon of this study (from trial enrollment to death, which is expected to be in the range of months to one-two years), we will not discount future costs and outcomes.

The incorporation of QOL and economic evaluations into protocols such as those in Project 3 is important, since traditional endpoints of tumor progression and survival often do not capture important treatment differences. For instance, even if overall survival were lower with an agent such as TNP-470, but progression were delayed by the projected 2 months, compared to traditional chemotherapy, the QOL improvements and costs savings associated with this delayed progression and lower toxicity might yield a more favorable outcome from the point of view of the patient and society.

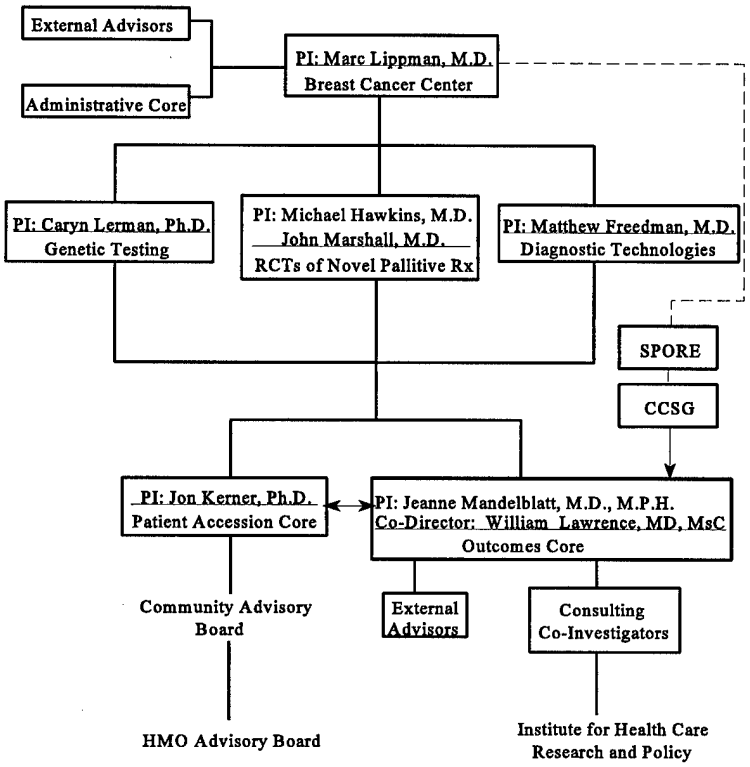
D. TECHNICAL AIM 3: Provide the Methodological Expertise to Measure and Collect the Data Needed for Core Analyses in Projects 1,2, and 3: As described in the preceding sections for each individual project, the Outcomes Core has provided expertise in the selection, piloting, and finalization of instruments to be used to collect primary, prospective data. In addition, for all instruments, the Outcomes Core has provided project-specific staff training. In Years 2, 3, and 4 the Outcomes Core will provide in-service re-training as needed and monitor data on a quarterly basis for quality assurance and rapid detection of unanticipated problems with instrument performance. In addition, in future project years, the Outcomes Core will continue work on abstracting secondary data for use in all project evaluations.

E. TECHNICAL AIM 4: Develop a Centralized Library of Data for use in Cancer Research on QOL, Utility, and Cost Measurement Tools and Approaches, and Provide Consultation to Investigators on the Incorporation of Such Tools into New Research Initiatives: After a review of the Outcomes Core organization structure, highlighting a few minors changes from the original, this next section summarizes the Outcomes Core's progress in each of these arenas encompassed by Technical Aim 4.

1. Organization of the Outcomes Core: The multi-disciplinary research team constituting the **Outcomes Core** is directed by Jeanne Mandelblatt, MD, MPH. In Year 1, Dr. William Lawrence, a general internist and decision analyst, was hired as co-director of the Outcomes Core. Also in the course of Year 1, Dr. John Eisenberg, chairperson of the Department of Medicine, took a leave of absence from Georgetown to assume leadership of the Agency of Health Care Policy and Research.

The overall Center organization, including the **Outcomes Core** structure is shown in **Figure 8**. As can be seen in the figure, the Core is structured to maximize **interactions** with the individual research projects, the Patient Accession Core, and existing Lombardi Cancer Center resources. In Year 1, the Outcomes Core members have met approximately bimonthly to discuss Core activities, and have met with the Principal Investigators of the projects and Cores monthly to ensure maximal coordination of activities. As previously noted, the **Outcomes Core** and **the PAC** have also collaborated to ensure the incorporation of patient out-reach costs and patient subgroup analyses into all evaluations, to the extent feasible. Review of **Outcomes Core** analysis design and results by the PAC Community and HMO advisory boards is intended to enhance the dissemination of results, diffusion of outcomes methods, and relevance of future research. Finally, in Year 1 the Outcomes Core held an Advisory Meeting, which included the three External Advisors (Drs.

Figure 8: Core Organization And Interactions



Cella, Hillner, and Weeks), the project Principal Investigators, and the Outcomes Core members (**Appendix 5**).

2. Outcomes Core Library: The development of this comprehensive cancer outcomes library is planned to occur over the entire fours years of the project, with most activity targeted for Years 2 and 3. This timeline has been adapted to allow us to focus on piloting and completing data primary patient collection instruments in Year 1, and to allow sufficient time for analyses and publication of project-specific Outcomes Core data in Year 4. In this first year we have: 1) hired an Outcomes Core Coordinator (supported by the Lombardi Cancer Center [LCC]) to develop the database and coordinate the complex data collection activities across the three projects; 2) met with the LCC computer support staff to discuss the optimal software configuration for the database; 3) attended meetings (e.g., Medical Decision Making and Quality of Life and Cost-Effectiveness conferences) to identity the current state-of-the-art in outcomes materials; and 4) begun to review and collect materials for the library, including existing instruments, summaries of their psychometric properties, and literature reviews on current use of these tools in cancer research(e.g., Patrick and Erickson, 1993; Kornblith and Holland, 1995; Tchekmedyian and Cella, 1990; Spilker et al, 1990; Scott and Anderson; BRS Technologies). The current list of library materials is included in **Appendix 6**. Finally, we are considering a private-public partnership to apply for an SBIR grant to make such a library available on the worldwide web and/or CD rom.

3. Consultations: In Year 1 we have developed a preliminary process for Outcomes Core consultations. Briefly, individuals interested in including a QOL and/or economic evaluation into their research contact Dr. Lawrence. Dr. Lawrence disseminates the request to Core members, and, based on area of expertise, assigns the appropriate person to provide the consultation. We have provided consultation to several Lombardi Cancer Center members (see **Appendix 7**), and have developed several new research initiatives (below). In addition, Outcomes Core members have begun attending clinical meetings, to provide a stimulus for new initiatives. Finally, LCC has made further commitments to developing the Outcomes Core as a cancer center-wide shared resource by investing funds to hire additional decision analysis/QOL staff. Together with funds from new research initiatives, we anticipate hiring this additional staff person in the first half of 1998. Our goal, by the end of the period of Department of the Army funding, is to have this shared resource fully self-sustaining using new grant and consultation support.

4. New Research Initiatives: Since submission of this Breast Cancer Center Grant, Outcomes Core members have contributed to, or have been the lead investigators for six newly funded peer-reviewed grants highlighting clinical and/or economic outcomes. Six new grant applications are also in the progress of being (re-)submitted (**Table 8** and **Appendix 8**).

Table 8: Core 2: Cancer Clinical and Economic Outcomes Evaluation Core: Grant Funding

Principal Investigator(s)	Core Members	Title	Agency	Status
FUNDED				
Burnett C	Burnett Mandelblatt	Cancer Screening Adherence: Underserved Elderly Women	National Institute on Aging (NIA)	Approved, pending 10/97
Fahs M Mandelblatt J	Mandelblatt Lawrence	CEA of Breast Cancer Control for African Americans	National Cancer Institute	Approved, pending 10/97
Gold K	Gold	Statistical Computing Program and Research Computing Laboratory	Georgetown University	Funded 1/97-1/98
Hadley J	Hadley Mandelblatt	Cost-Effectiveness of Treatments for Local Breast Cancer in the Elderly	Department of the Army	Funded 8/94-8/98
Hadley J Mandelblatt J	Hadley Mandelblatt Gold	Care, Costs and Outcomes of Local Breast Cancer in Older Women	Agency for Health Care Policy and Research (AHCPR)	Funded 9/94-9/99
Hadley J Mandelblatt J	Hadley Mandelblatt Gold	Care, Costs and Outcomes of Local Breast Cancer: Older African-Americans	AHCPR	Approved, pending 10/97
Lerman C	Mandelblatt Lawrence	Decisions and Outcomes of BRCA1 Test for Breast Cancer Patients	National Cancer Institute	Funded 7/97-6/02
Mandelblatt J	Mandelblatt Lawrence	Cost-Effectiveness of HPV Screening for Cervix Cancer	National Cancer Institute (NCI)	Funded 7/97-12/99
PENDING				
Burnett C	Burnett Mandelblatt Gold	Regular Mammogram Use in Elderly African Americans: an RCT	NCI/ NIA/National Institute of Nursing Research	To be re-submitted 3/98
Ganz P	Rowland Mandelblatt Lawrence	Breast Cancer: Preparing for Survivorship	National Cancer Institute	To be submitted 11/97
Mandelblatt	Mandelblatt Lawrence	Cost-Effectiveness of Cancer Genetic Testing	National Cancer Institute	Pending 9/97
Lawrence W	Lawrence Mandelblatt Gold Burnett	Racial, Age, and Payor Differences in the Treatment of Prostate Cancer	American Cancer Society	To be submitted 4/99
Lerman C	Mandelblatt Lawrence	Comparing Models of Counseling for BRCA1/2 Testing	National Cancer Institute	Pending 3/97
Schlitz Rowland J	Rowland	Life Experiences and Meaning Systems as They Relate to QOL & Survival Among Women with Metastatic Breast Cancer	Department of the Army	Pending

5. Outcomes Core-Related Publications: **Table 9** summarizes the 25 publications and selected presentations of Outcomes Core members for the period corresponding to Year 1 of the Breast Cancer Center Grant (see also **Appendix 8**).

Table 9: Core 2: Cancer Clinical and Economic Outcomes Evaluation Core: Selected Relevant Core Member Publications and Presentations*

PUBLISHED

Burnett CB, Steakley CS, Tefft M. Return to Breast Cancer Screening for African American Women Over 50 years of age. American Cancer Society, 4th National Conference on Cancer Nursing Research, 1997.[Abstract]

Fahs MC, Plichta SB, Mandelblatt JS. Cost-Effective Policies for Cervical Cancer Screening. PharmacoEconomics, 1996;9(3):211-230.

Fryback DG, Lawrence WF. Dollars may not buy as many QALYs as we think: A problem with defining quality-of-life adjustments. Med Decis Making 1997; 17:276-284.

Fryback DG, Lawrence WF, Martin PA, Klein R, Klein BEK. Predicting Quality of Well-Being Scores from the SF-36: results from the Beaver Dam Health Outcomes Study. Med Decis Making. 1997; 17:1-9.

Ganz PA, Rowland JH, Desmond K, Meyerowitz B, Wyatt G. Life after breast cancer: Understanding women's health-related quality of life and sexual functioning. J Clin Oncol. (in press).

Gold K. Adaptive assessment of functional status: prototype for the Short Form 3600? Med Decis Making. 1996; 16:457. [Abstract]

Gross RE, Burnett CB, & Borelli, M. Coping responses to the diagnosis of breast cancer in post-mastectomy patients. Cancer Practice . 1996; 4(4):204-211.

Lawrence WF, Fryback DG, Martin PA, Klein R, Klein BEK. Health status and hypertension: results from the Beaver Dam Health Outcomes Study. J Clin Epidemiol. 1996;49:1239-1245.

Lawrence WF, Fryback DG, Klein R, Klein BEK. Community-based, quality-adjusted life expectancy: results from the Beaver Dam Health Outcomes Study. Med Decis Making. 1996;16:454. [Abstract]

Schapira MM, Lawrence W, Nattinger AB. Utility assessment of impotence and incontinence states before and after treatment for localized prostate cancer. Med Decis Making. 1996;16:455. [Abstract]

Mandelblatt JS, Eisenberg JM. Historical and Methodological Perspectives on Cancer Outcomes Research. Oncology, 1996;9:23-32.

Mandelblatt J, Fryback D, Weinstein M, et al, and members of the Panel on Cost-Effectiveness in Health and Medicine. Assessing the Effectiveness of Health Interventions. In: Cost-Effectiveness in Health and Medicine. Editors: Gold M, Seigel J, Russell L, and Weinstein M. Oxford University Press, New York, 1996.

Mandelblatt J, Andrews H, Kao R, Wallace R, Kerner J. Late Stage Diagnosis of Colorectal Cancer: The Relationships Between Poverty, Race, Gender, Age, and Settings of Care. AJPH 1996;86:1794-1797.

Mandelblatt, J, Freeman H, Williams S, Trowers R, Cagney K, Winczewski D, Kerner J. The Implementation of breast and cervical cancer screening in a public hospital emergency room. Ann of Emerg Med, 1996;28:493-498.

Mandelblatt JS, Freeman H, Winczewski D, Cagney K, Kerner JF. The costs and yields of emergency room screening for breast and cervix cancer. Amer J Public Health 1997;87:1182-1189.

Mandelblatt J, Fryback D, Weinstein M, et al, and members of the Panel on Cost-Effectiveness in Health and Medicine. Assessing the Effectiveness of Health Interventions. J of General Internal Medicine, in press, 1997.

Neill K, Armstrong N, Burnett CB Choosing Reconstruction after Mastectomy: A Qualitative Analysis. Oncology Nursing Forum (in press).

O'Malley A, Mandelblatt J, Kerner J, Gold K, et al. The Role of Primary Care in Breast and Cervix Cancer Screening Among Multi-Ethnic Populations. Arch Internal Med, (in press), 1997.

Rowland JH. Outcomes assessment: Cancer-specific quality-of-life measures — the research setting. In: *American Society of Clinical Oncology (ASCO) Educational Book.* Alexandria, VA, ASCO, 1997.

Rowland JH. Psychosocial aspects of breast cancer. In: Blechman EA, Brownell KD (eds.). *Behavioral Medicine for women: A comprehensive handbook.* New York, Guilford Press (in press).

Russell L, Seigel J, Daniels N, Luce B, Mandelblatt J, and members of the Panel on Cost-Effectiveness in Health and Medicine. Cost-Effectiveness Analysis for Decision Making in Health: Roles and Limitations. Editors: Gold M, Seigel J, Russell L, and Weinstein M. Oxford University Press, New York, 1996.

Russell L, for members of the Panel on Cost-Effectiveness in Health and Medicine (Mandelblatt, panel member). The Role of Cost-Effectiveness Analysis for Decision Making in Health. JAMA 1996;276:1172-1177.

Seigel J, for members of the Panel on Cost-Effectiveness in Health and Medicine (Mandelblatt, panel member). Reporting the Results of Cost-Effectiveness Analysis. JAMA 1996;276:1339-1341.

Swan JS, Fryback DG, Lawrence WF, et al. MR and conventional angiography: Work in progress toward assessing utility in radiology. Acad Radiol 1997; 4:475-482.

Weinstein M, for members of the Panel on Cost-Effectiveness in Health and Medicine. Recommendations for Conducting Cost-Effectiveness Analysis (Mandelblatt, panel member). JAMA 1996;276:1253-1258.

MANUSCRIPTS UNDER REVIEW

Abrahams EB, Burnett CB, Information Seeking and Postoperative Coping in the Total Joint Arthroplasty Patient. [Under review - Orthopaedic Nursing]

Lawrence WF, Smith SS, Fiore MC, Baker TB. Public health benefit of prescription vs over-the-counter Nicoderm nicotine replacement therapy for smoking cessation. [Under review - Am J Public Health].

Mandelblatt J, Ganz P, Kahn K. Quality of Breast Health Care in Managed Care Settings.

Weinfurt KP, Rowland JH. Brief forms of the Profile of Mood States for cancer patients.

PRESENTATIONS

Mandelblatt JS, "Assessing the Effectiveness of Health Interventions in a CEA". Roll-Out Conference Presenting the findings of the Panel on Cost-Effectiveness in Health and Medicine, Washington, DC, Feb, 1997.

Burnett CB, " Return to Breast Cancer Screening for African American Women Over 50 years of age. American Cancer Society, 4th National Conference on Cancer Nursing Research, Newport Beach California, January, 1997

Lawrence WF. Costs and benefits of cancer screening and prevention. Presented at: The American Association of Clinical Chemistry Annual Meeting, 7/97.

Lawrence WF. Costs of cervical cancer screening. Presented at: Alternatives in cervical cancer screening and treatment in low-resource settings: Board of Trustees Workshop, JHPIEGO Corporation, 5/97.

*Core members are underlined.

6. Assess the Costs of Patient Accession: As noted above in the description of the individual projects, we are working with the Patient Accession Core to evaluate the costs of outreach and accrual of non-Lombardi Cancer Center patients/individuals to the three projects. Our general approach is summarized in **Appendix 2**.

III. CONCLUSIONS: The science of conducting outcomes research, including economic evaluations in oncology practice, is a relatively new discipline and one which is rapidly evolving. This **Outcomes Core** is extending the state-of-the-art by consisting a unique cross-disciplinary research team with the methodological expertise to evaluate the costs and benefits of new and existing cancer services. Incorporating clinical and economic outcomes into center-wide research focused on translating new advances from the laboratory to individuals, and from a cancer center to community-based hospitals,

managed care organizations, and community groups is allowing Lombardi Cancer Center to expand its leadership position to informing on-going clinical, policy and resource allocation debates. As we continue balance efforts to contain costs while providing care that maximizes health and quality of life, cost-effectiveness and other outcomes analyses, such as those outlined in this Core, will be critical to understanding which treatments work best, under which circumstances, for which populations, and at what cost.

IV. REFERENCES

Artz D, Blume E. Too many breast biopsies? Watching vs. cutting. *J Natl Cancer Inst* 1991; 83: 1207-9.

Ashby J, O'Hanlon M, Buxton MJ (1994). The time trade-off technique: How do the valuations of breast cancer patients compare to those of other groups? *Quality of Life Research*, 3, 257-265.

Baker MS, Kessler LG, Urban N, Smucker RC. Estimating the treatment costs of breast and lung cancer. *Med Care* 1991; 29: 40-49.

Beck JR, Pauker SG. The Markov process in medical prognosis. *Med Decis Making* 1983; 3(4):419-458.

Becker TM, Goodwin JS, Hunt WC, et al. (1989). Survival after cancer surgery of elderly patients in New Mexico, 1969-1982. *Journal of the American Geriatric Society*, 37, 154-159.

Berman DB, Wagner-Costalas J, Schultz DC, et al. (1996). Two distinct origins of a common BRCA1 mutation in breast-ovarian cancer families: a genetic study of 15 185delAG-mutation kindreds. *American Journal of Human Genetics*, 58, 1166-76.

Berry DA, Parmigiani G, Sanchez J, Schildkraut J, Winer E. Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. *J Natl Cancer Inst* 1997;89:227-38.

Bindman AB, Keane D, and Lurie N: Measuring health changes among severely ill patients. The floor phenomenon. *Medical Care* 28;1142-52, 1990.

Bleehen NM, Girling DJ, Machin D, Stephens RJ. A randomised trial of three or six courses of etoposide cyclophosphamide methotrexate and vincristine or six courses of etoposide and ifosfamide in small cell lung cancer (SCLC) II: Quality of life. *Brit J or Cancer* 1993, Dec.; 68(6): 1157-66.

Breast Cancer Information Core (1996). National Center for Human Genome Research. Internet.

Broët P, de la Rochefordière A, Scholl SM, et al. (1995). Contralateral breast cancer: annual incidence and risk parameters. *Journal of Clinical Oncology*, 13, 1578-83.

Brown ML, Kessler LG. The use of gene tests to detect hereditary predisposition to cancer: economic consideration. *J Natl Cancer Inst* 1995 Aug 2; 87 (15): 1131-1135.

Brown ML, Fintor L. Cost-effectiveness of breast cancer screening: Preliminary results of a systematic review of the literature. *Breast Cancer Res Treat* 1993; 25: 113-118.

Brown ML, Nayfield SG, Shilby LM. Adjuvant therapy for stage III colon cancer. Economics returns to research and cost-effectiveness of treatment. *J Natl Cancer Inst* 1994; 8 (6): 424-30.

BRS Information Technologies: Health and psychosocial instruments (HAPI). McLean, VA.

Burke W, Petersen G, Lynch P, Botkin J, Daly M, Garber J, Kahn MJE, McTiernan A, Offit K, Thomson E, Varricchio C. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. JAMA 1997a;277:915-919.

Burke W, Daly M, Garber J, Botkin J, Kahan MJE, Lynch P, McTiernan A, Offit K, Perlman J, Petersen G, Thomson E, Varricchio C. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA 2. *JAMA* 1997b;277:997-1003.

Cassileth BR. Breast cancer surveillance: On increasing its effectiveness while reducing its negative psychological effects. J Natl Cancer Inst. 1992; 84:2-3.

Cella DF and Tulsky DS: Measuring quality of life today: methodological aspects. *Oncology* 4;29-38, 1990.

Cella DF, Tulsky DS, Gray G, et al: The functional assessment of cancer therapy (FACT) scale. development and validation of the general measure. *Journal of Clinical Oncology* 11;570-579, 1993.

Coates A, Gebski V, Stat M, for the Australian-New Zealand Breast Cancer Trials Group. Improving the quality of life during chemotherapy for advanced stage breast cancer. *N Engl J Med* 1987; 317: 1490-95.

Collins FS. BRCA1 - lots of mutations, lots of dilemnas. *N Engl J Med* 1996;334:186-8.

Couch FJ, DeShano ML, Blackwood A, Calzone K, Stopfer J, Campeau L, Ganguly A, Reebeck T, Weber BL. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med* 1997;336:1409-15.

Cox DR, Fitzpatrick R, Fletcher AE, et al. Quality-of-life assessment: can we keep it simple? *J R Statist Soc A* 1992; 155, Part 3: 353-393.

Dean HE. Political and ethical implications of using quality of life as an outcome measure. *Sem in Onc Nursing*, 1990; 6: 303-08.

DeHaes JCJM, van Knippenberg FCE, Neijt JP. Measuring psychological and physical distress in cancer patients: Structure and application of Rotterdam Symptom Checklist. *Brit J of Cancer* 1990; 62: 1034-1038.

DeKoning HJ, van Ineveld BM, van Oortmarssen GJ, de Haes JCJM, Colletter HJA, Hendriks JHCL, van der Mass PJ. Breast cancer screening and cost-effectiveness; Policy alternatives, quality of life considerations and the possible impact of uncertain factors. *Int J Cancer* 1991; 49: 531-537.

Desch CE, Hillner BE, Smith TJ, et al: Should the elderly receive chemotherapy for node-negative breast cancer. *J Clin Oncol* 11; 777-782, 1993.

Drummond MF, Stoddard GL, and Torrance GW: *Methods for the Economic Evaluation of Health Care Programmes.* New York: Oxford University Press, 1987.

Early Breast Cancer Trialists' Collaborative Group (1992). Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet*, 329, 1-15, 71-85.

Easton DF, Bishop DT, Ford D, et al. (1993). Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *American Journal of Human Genetics*, 52, 678-701.

Easton DF, Ford D, Bishop DT, et al. (1995). Breast and ovarian cancer incidence in BRCA1-mutation carriers. *American Journal of Human Genetics*, 56, 265-71.

Eddy DM. Screening for breast cancer. *Ann Intern Med* 1989; 111: 389-399.

Eisenberg JM, et al. What is the cost of nephrotoxicity associated with aminoglycosides? *Ann Int Med* 1987; 107: 900-09.

Eisenberg JM. Clinical Economics: A guide to economic analysis of clinical practices. *JAMA* 1989; 262: 2879-86.

Ellis PA, Smith IE, Hardy JR, Nicolson MC, Talbot DC, Ashley SE, Priest K. Symptom relief with MVP (mitomycin C, vinblastine and cisplastin) chemotherapy in advanced non-small-cell lung cancer. *Brit Jour Cancer* 1995, Feb; 71(2): 366-70.

Erickson P, Wilson R, Shannon I. *Years of Healthy Life. Statistical Notes. Number 7, 1995.* US Department of Health and

Human Services, PHS, Centers for Disease Control and Prevention, National Center for Health Statistics, Hyattsville, Maryland. DHHS Publication No. (PHS) 95-1237 4-1485 (4/95).

EuroQoL group. EuroQoL - A new facility for the measurement of health-related quality of life. *Health Policy*. 1990; 16:199-208.

Feeny DH, Fulong W, Barr D, et. al. A comprehensive multi-attribute system for classifying the health status of survivors of childhood cancer. *J Clin Oncol*. 1992; 10:923-928.

Fisher B, Anderson S, Redmond C, et al. (1995). Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *New England Journal of Medicine*, 333, 1456-61.

Fisher B, Redmond C, Poisson R, et.al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*. 1989; 321:689-690.

Ford D, Easton DF, et al. Risks of cancer in BRCA1-mutation carriers. *Lancet* 1994; 343: 692-95.

Froberg DG, Kane RL (1989). Methodology for measuring health-state preferences. II: Scaling methods. *Journal of Clinical Epidemiology*, 42, 459-71.

Fraser SCA, Dobbs HJ, Ebbs SR, et al. Combination or mild single agent chemotherapy for advanced breast cancer? CMF vs epirubicin measuring quality of life. *Brit J Cancer* 1993; 67(A): 341-46.

Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: Initial catalog of health-state quality factors. *Med Decis Making* 1993; 13: 89-102.

Gafni A, Birch S. Preferences for outcomes in economic evaluation: An economic approach to addressing economic problems. *Social Sciences and Medicine*. 1995; 40:767:776.

Ganiats TG, Palinkas LA, and Kaplan RM: Comparison of quality of well-being scale and functional status index in patients with atrial fibrillation. *Medical Care* 30;958-64, 1992.

Ganz PA. Quality of life and the patient with cancer. Individual and policy implications. *Cancer* 1994b;74:1445-52.

Ganz PA: Quality of life measures in cancer chemotherapy, methodology and implications. *PharmacoEconomics* 5;376-388, 1994a.

Ganz PA, Haskell CM, Figlin RA, et al. Estimating the quality of life in a clinical trial of patients with metastatic lung cancer using the Karnofsky performance status and the functional living index-cancer. *Cancer* 1988; 61: 849-56.

Gershon D. DNA diagnostics tool for 21st century. *Nature Med* 1995; 1; 102-103.

Glimelius G, Hoffman K, Graf W, Hagland U, Nyren O, Pahlman L, Sjoden P-O. Cost-effectiveness of palliative chemotherapy in advanced gastrointestinal cancer. *Annals of Oncology* 1995; 6: 267-274.

Gold M, Seigel J, Russell L, and Weinstein M, eds. *Cost-Effectiveness in Health and Medicine*. Oxford University Press, New York, 1996a.

Gold M, et al. Identifying and Valuing Outcomes. In: Gold M, Seigel J, Russell L, and Weinstein M, eds. *Cost-Effectiveness in Health and Medicine*. Oxford University Press, New York, 1996b, pages 82-134.

Goldhirsch A, Gelber RD, Simes RJ et al. Costs and benefits of adjuvant therapy in breast cancer: A quality adjusted survival analysis. *J Clin Oncology* 1989; 7: 36-44.

Goodwin PJ, Feld R, Evans WK, Pater J. Cost-effectiveness of cancer chemotherapy: An economic evaluation of a randomized trial in non-small cell lung cancer. *J Clin Oncol* 1988; 6: 1537-47.

Goodwin PJ. Economic factors in cancer palliation - methodologic considerations. *Cancer Treatment Reviews* 1993; 19 (supp A): 59-65.

Gram IT, Lund E, Slenker SE. Quality of life following a false-positive mammogram. *Br J Cancer.* 1990; 62:1018-1022.

Guyatt GH, Feeny DH, and Patrick DL: Measuring health-related quality of life. *Annals of Internal Medicine* 118;622-629, 1993.

Hadorn DC, Uebersax J. Large-scale outcome evaluation: how should quality of life be measured? I: Calibration of a brief questionnaire and a search for preference subgroups. *J Clin Epidem* 1995; 48(5):607-618.

Hadorn DC, Uebersax J, Holte J. Large-scale outcome evaluation: how should quality of life be measured? II: Questionnaire validation in a cohort of patients with advanced cancer. *J Clin Epidem* 1995; 48(5): 619-29.

McNeil BJ, Hanley JA. Statistical approaches to the analysis of receiver operating characteristic (ROC) curves. *Med Decis Making.* 1984; 4:137-150.

Healy B. BRCA genes - bookmaking, fortunetelling, and medical care. *N Engl J Med* 1997;336:1448-9

Heithoff KA, and Lohr KN: *Effectiveness and outcomes in health care.* Washington, DC, National Academy Press, 1990.

Herbsman H, Feldman J, Seldera J, et al. (1981). Survival following breast cancer surgery in the elderly. *Cancer*, 47, 2358-63.

Hiatt RA. Ethics and Economics of genetic testing for breast cancer. In Basil A. Stoll (ed.), *Reducing Breast Cancer Risk in Women*, 1995. Netherlands: Kluwer Academic Publishers, pages 55-65.

Hillner BE, Bear HD, Fajardo LL. Estimating the cost-effectiveness of Stereotaxic Biopsy for non-palpable breast abnormalities: A decision analysis model. *Acad Radiol.* 1996; 3:351-360.

Hillner BE, Smith TJ, and Desch CE: Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. *JAMA* 267;2055-2061, 1992.

Hillner BE and Smith TJ: Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. *The New England Journal of Medicine* 324;160-8, 1991.

Hillner BE, Smith TJ, Desch CE.Assessing the cost-effectiveness of adjuvant therapies in early breast cancer using a decision analysis model. *Breast Cancer Res Treat* 1993; 25: 97-105.

Hopwood P, Stephens RJ. Symptoms at presentation for treatment in patients with lung cancer: Implications for evaluation of palliative treatment. *Brit J of Cancer* 1995, Mar.; 71(3): 633-36.

Hoskins KF, Stopfer JE, Calzone KA, Merajver SD, Rebbeck TR, Garber JE, Weber BL. Assessment and counseling for women with a family history of breast cancer: A guide for clinicians. *JAMA* 1995, Feb. 15; 273(7): 577-85.

Hunt S, McKenna SP, McEwen J, et al. The Nottingham Health Profile: Subjective Health Status and Medical Consultations. *Soc Sci Med* 15A; 221-229, 1981.

Jaakkimainainen L, Goodwin PJ, Pater J et al. Counting the costs of chemotherapy in a National Cancer Instititute of Canada randomised trial in non-small cell lung cancer. *J Clin Oncol* 1990; 8:1301-9.

Joss RA, Alberto P, Hunry C, Bacchi M, Leyvrz S, Thurlimann B, Cerny T, Martinelli G, Stahel R, Ludwig C for the Swiss Group for Clinical Cancer Research. Quality versus quantity of life in the treatment of patients with advanced small-cell lung cancer? A randomized phase III comparison of weekly carboplatin and teniposide versus cisplatin, adriamycin, etoposide alternating with cyclophosphamide, methotrexate, vincristine and lomustine *Annals of Oncology* 1995; 6: 41-48.

Kartman B, Andersson F, Johannesson M. Willingness to pay for reductions in angina pectoris attacks. *Med Decis Making.* 1996; 16:248-253.

Kassirer JP. The principles of clinical decision making: An introduction to decision analysis. *Yale J Biol Med* 1976; 49: 149-64.

Kornblith AB, Holland JC. *Handbook of measures for psychological, social and physical function in cancer, volume I: Quality of life*, 1995. New York: Memorial Sloan-Kettering Cancer Center.

Krainer M, Silva-Arrieta S, Fitzgerald MG, Shimada A, Ishioka C, Kanamaru R, MacDonald DJ, Unsal H, Finkelstein DM, Bowcock A, Isselbacher KJ, Haber DA. Differential contributions of BRCA1 and BRCA 2 to early-onset breast cancer. *N Engl J Med* 1997;336:1416-21.

Langston AA, Malone KE, Thompson JD, et al. (1996). BRCA1 mutations in a population-based sample of young women with breast cancer. *New England Journal of Medicine*, 334, 137-42.

Layfield LJ, Chrischilles EA, Cohen MB, Bottles K. The palpable breast nodule: A cost-effectiveness analysis of alternate diagnostic approaches. *Cancer* 1993; 72: 1642-1651.

Lieberman L, Fahs MC, Dershaw DD, Bonaccio E, Abramson AF, Cohen MA, Hann LE. Impact of stereotaxic core breast biopsy on cost of diagnosis. *Radiology* 1995; 195: 633-637.

Mandelblatt J, Fryback D, Weinstein M, Gold M, Russell L, Hadorn D, and members of the Panel on Cost-Effectiveness in Health and Medicine. Assessing the Effectiveness of Health Interventions. *Journal of General Internal Medicine*, in press, 1997.

Lindfors KK, Rosenquist CJ. NEedle core biopsy guided with mammography: A study of cost-effectiveness. *Radiology* 1994; 190: 217-222.

Mandelblatt J, Fryback D, Weinstein M, Gold M, Russell L, Hadorn D, and the members of the Panel on Cost-Effectiveness in Health and Medicine. Assessing the Effectiveness of Health Interventions. *J Gen Internal Medicine*. in press, 1997.

Mandelblatt J, Fryback D, Weinstein M, Gold M, Russell L, Hadorn D, and members of the Panel on Cost-Effectiveness in Health and Medicine. Assessing the Effectiveness of Health Interventions. In: *Cost-Effectiveness in Health and Medicine*. Editors: Gold M, Seigel J, Russell L, and Weinstein M. Oxford University Press, New York, 1996.

Mandelblatt JS, Eisenberg JM. Historical and Methodological Perspectives on Cancer Outcomes Research. *Oncology*, 1996;9:23-32.

Mandelblatt JS. Historical and Methodological Perspectives on Cancer Outcomes Research. Presented at the 1995 Quality of Life Symposium: Economic and Quality of Life Outcomes in Oncology. St. Mary Medical Center, Long Beach, California, April 4, 1995.

Marcus JN, Watson P, Page DL, et al. (1996). Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. *Cancer*, 77, 697-709.

McQuellen RP, Muss HB, Hoffman SL, Russell G, Craven B, Yellen SB: Patient preferences for treatment of metastatic breast cancer: a study of women with early-stage breast cancer. *J Clin Oncol* 13;858-868, 1995.

Mehrez A, Gafni A. Quality-adjusted life years, utility theory, and healthy-years equivalents. *Med Dec Mkg* 1989; 9(2): 142-149.

Mehrez A, Gafni A. Healthy-years equivalents versus quality-adjusted life years: In pursuit of progress. *Med Dec Mkg* 1993; 13(4): 287-192.

Miki Y, Swensen J, Shattuck-Eidens D, et al. (1994). A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science*, 226, 66-71.

Miller SM (1987). Monitoring and blunting: validation of a questionnaire to assess styles of information seeking under stress. *Journal of Personality and Social Psychology*, 52, 345-53.

Nease RF, Kneeland T, O'Connor GT, Sumner W, Lumpkins C, Shaw L, Pryor D, Sox, HC. Variation in patient utilities for outcomes of the management of chronic stable angina: Implication for clinical practice guidelines. *JAMA* 1995, April 19; 273

(15): 1185-1190.

Neuhausen S, Gilewski T, Norton L, et al. (1996). Recurrent BRCA2 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. *Nature Genetics*, 13, 126-28.

Nguyen HN, Averette HE, Janicek M (1994). Ovarian carcinoma: A review of the significance of familial risk factors and the role of prophylactic oophorectomy in cancer prevention. *Cancer*, 74, 545-55.

O'Leary JF, Fairclough DL, Jankowski MK, et al. (1995). Comparison of time-tradeoff utilities and rating scale values of cancer patients and their relatives: Evidence for a possible plateau relationship. *Medical Decision Making*, 15, 132-37.

Ontario Ministry of Health: *An Overview of the Survey Content of the Ontario Health Survey.* Ontario Health Survey Bulletin, 1990.

Osteen RT, Cady B, Chmiel JS, et al. 1991 national survey of carcinoma of the breast by the Commission on Cancer. *J Am Coll Surg* 1994; 178: 213-219.

Parker RG. The "cost-effectiveness" of radiology and radiologists. *Radiology* 1993; 189: 363-369.

Parker SL, Tony T, Bolden S, et al. (1996). Cancer statistics, 1996. *California Cancer Journal Clinician*, 65, 5-27.

Patrick DL and Erickson P: Health Status and Health Policy. *Quality of Life in Health Care Evaluation and Resource Allocation*, New York, Oxford University Press, 1993.

Pennisi VR, Capozzi A (1989). Subcutaneous mastectomy data: A final statistical analysis of 1500 patients. *Aesthetic Plastic Surgery*, 13, 15-21.

Piver MS, Jishi MF, Tsukada Y, et al. (1993). Primary peritoneal carcinoma after prophylactic oophorectomy in women with a family history of ovarian cancer: A report on the Gilda Radner Familial Ovarian Cancer Registry. *Cancer*, 71, 2651-55.

Recht A, Come SE, Henderson IC, et al. (1996). The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. *New England Journal of Medicine*, 334, 1356-61.

Ries LAG, Hanlsey BG, Miller BA, et al. (1991). *Cancer Statistics Review 1973-1988.* National Cancer Institute. NIH Publication No. 91-2789.

Riley GF, Potosky AL, Lubitz JD, Brown ML. Stage of cancer at diagnosis for Medicare HMO and fee-for-service enrollees. *Amer J Pub Health* 1994, Oct.; 84(10): 1598-1604.

Rubin HR, Gandek B, Rogers WH, Kosinski M, McHorney CA, Ware JE. Patients' ratings of outpatient visits in different practice settings. *JAMA*. 1993; 270:835-840.

Russell L, Seigel J, Daniels N, Luce B, Mandelblatt J, and members of the Panel on Cost-Effectiveness in Health and Medicine. Cost-Effectiveness Analysis for Decision Making in Health: Roles and Limitations. Editors: Gold M, Seigel J, Russell L, and Weinstein M. Oxford University Press, New York, 1996a.

Russell L, for members of the Panel on Cost-Effectiveness in Health and Medicine (Mandelblatt, panel member). The Role of Cost-Effectiveness Analysis for Decision Making in Health. *JAMA* 1996b;276:1172-1177.

Schatzkin A, Goldstein A, Freedman LS. What does it mean to be a cancer gene carrier? Problems in establishing causality from the molecular genetics of cancer. *J Nat Cancer Inst* 1995; 87(15): 1126-30.

Schrag D, Kuntz KM, Garber JE, Weeks JC. Decision analysis - effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA 2 mutations. *N Engl J Med* 1997;336:1465-71.

Schulman KA, Glick HA, Yabroff KR, Eisenberg JM. Introduction to clinical economics: Assessment of cancer therapies. *J Nat Cancer Inst Monographs* 1995; 19: 1-9.

Scott J and Erickson P: The on-line guide to quality-of-life assessment (OLGA). Kensington, MD.

Seigel J, for members of the Panel on Cost-Effectiveness in Health and Medicine (Mandelblatt, panel member). Reporting the Results of Cost-Effectiveness Analysis. *JAMA* 1996;276:1339-1341.

Shattuck-Eidens D, et al. A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene: Implications for presymptomatic testing and screening. *JAMA*, 1995; 273(7): 535-40.

Singer PA, Tasch ES, Stocking C, Rubin S, Siegler M, and Weischselbaum R: Sex or survival: trade-offs between quality and quantity of life. *Journal of Clinical Oncology* 9;328-34, 1991.

Slade CL (1984). Subcutaneous mastectomy: Acute complications and long-term follow-up. *Plastic Reconstruc-tive Surgery*, 73, 84-90.

Slevin ML, Stubbs L, Plant HJ, Wilson P, Gregory WM, Armes PJ, Downer SM. Attitudes to chemotherapy: Comparing views o patients with cancer with those of doctors, nurses, an general public. *Brit Med J* 1990; 300: 1458-60.

Smith TJ, Hillner BE, and Desch CE: Efficacy and cost-effectiveness of cancer treatment: rational allocation of resources based on decision analysis. *J of the National Cancer Institute* 85;1460-1474, 1993.

Smith TJ and Hillner BE: The efficacy and cost-effectiveness of adjuvant therapy of early breast cancer in premenopausal women. Journal of Clinical Oncology 11;771-776, 1993.

Sonnenberg FA, Beck JR. Markov models in medical decision making: A practical guide. *Med Decis Making* 1993; 13:322-338.

Sox HC, Blatt MA, Higgins MC, Marton KI. *Medical Decision Making*, 1988. Boston: Butterworth-Heibnemann.

Spilker B, Molinek FR Jr, Johnson KA, Simpson RL Jr, and Tilson HH: Quality of life bibliography and indexes. *Medical Care* 28;DS1-DS77, 1990b.

Strain JJ: The evolution of quality of life evaluations in cancer therapy. *Oncology* 4;22-27, 1990.

Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, Brody LC, Tucker MA. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among ashkenazi jews. *N Engl J Med 1997*;336:1401-8.

Struewing JP, et al. (1995). Prophylactic oophorectomy in inherited breast/ovarian cancer families. *Journal of the National Cancer Institute*, 17, 33-35.

Struewing JP, Abelievich D, Peretz T, et al. (1995). The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. *Nature Genetics*, 11, 198-200.

Struewing JP, Lerman C, Kase RG, et al. (1995). Anticipated uptake and impact of genetic testing in hereditary breast and ovarian cancer families. *Cancer Epidemiology, Biomarkers and Prevention*, 4, 169-73.

Taplin SH, Barlow W, Urban N, Mandelson MT, Timlin DJ, Ichikawa L, Nefcy P. Stage, age, comorbidity and direct costs of colon, prostate, and breast cancer care. *J Natl Cancer Inst* 1995, Mar 15; 87(6): 417-26.

Tavtigian SV, Simard J, Rommens J, et al. (1995). The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. *Nature Genetics*, 12, 333-37.

Tchekmedyian NS and Cella DF, guest editors: Quality of life in current oncology practice and research. *Oncology* 4(s);21-232, 1990.

Tonin P, Serova O, Lenoir G, Lynch H, Durocher F, Simard J, Morgan K, Naord S. BRCAI mutations in Ashkenazi Jewish women. *Am J Hum Genet* 1995; 57:189.

Torrance GW. Social preferences for health states: an empirical evaluation of three measurement techniques. *Socio-Econ Plan*

Sci 10;129-136, 1976b.

Torrance GW. Utility approach to measuring health-related quality of life. *J Chronic Dis* 40;593-600, 1987.

Torrance GW and Zipursky A. Cost-effectiveness of antepartum prevention of Rh immunization. *Clin-Perinatol* 11;267-81, 1984.

Torrance GW, Boyle MH, and Horwood SP. Application of multi-attribute utility theory to measure social preferences for health states. *Operations Research* 30;1043-69, 1982.

Torrance GW, Thomas WH, and Sackett DL. A utility maximization model for evaluation of health care programs. *Health Serv Res* 7;118-33, 1972.

Turnbull AD, Gundy E, Howland WS, et al. (1978). Surgical mortality among the elderly. An analysis of 4,050 operations (1970-1974). *Clinical Bulletin*, 8, 139-42.

Tummarlo D, Graziano F, Isidori P, Cellerino R. Symptomatic, stage IV, non-small-cell lung cancer (NSCLC): Response, toxicity, performance status change and symptom relief in patients treated with cisplatin, vinblastine and mitomycin-C. *Cancer Chemotherapy Pharmacol* 1995; 35: 249-53.

Udvarhelyi S, Colditz GA, Rai A, Epstein AM. Cost-effectiveness and cost-benefit analyses in the medical literature: Are the methods being used correctly? *Ann Intern Med* 1992; 116:238-44.

United States Bureau of the Census (1995). *Statistical Abstract of the United States: 1995* (115th edition). Washington, D.C.

Weber BL, Giusti RM, Liu ET. Developing strategies for intervention and prevention in hereditary breast cancer. *Monogr Natl Cancer Inst* 1995; 17: 99-102.

Weeks J, O'Leary J, Fairclough D, et al. The "Q-tility index": A new tool for assessing health-related quality of life and utilities in clinical trials and clinical practice. *Proc Am Soc Clin Oncol* 1994; 13: 436.

Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med* 1977; 296: 716-21.

Weinstein M, for members of the Panel on Cost-Effectiveness in Health and Medicine. Recommendations for Conducting Cost-Effectiveness Analysis (Mandelblatt, panel member). *JAMA* 1996;276:1253-1258.

Weinstein MC, Fineberg HV, et al. *Clinical Decision Analysis*, 1980. Philadelphia: W. B. Saunders, pages 228-65.

Winchester DP, Senen S, Immerman S, Blum MA. A systematic approach to the evaluation and management of breast masses. *Cancer* 1983; 51: 2535-40.

Wolfson AD, Sinclair AJ, Bambardier C and McGeer A. Preference Measurements for Functional Status in Stroke Patients: Inter-rater and Inter-technique Comparisons. In: *Values and Long Term Care*. Kane RL, Kane RA, eds. Lexington, MA: Lexington Books, 191-214, 1992.

Wooster R, Bignell G, Lancaster J, et al. (1995). Identification of the breast cancer susceptibility gene BRCA2. *Nature,* 378, 789-92.

Yellen SB, Cella, and Leslie WT: Age and clinical decision making in oncology patients. *Journal of the National Cancer Institute* 86;1766-70, 1994.

V. APPENDICES (included in full packet following annual report text)

Appendix 1: Project 1 Survey Instruments
Appendix 2: Core 1 Cost Data Collection Instrument

Appendix 3: Project 2 Survey Instrument
Appendix 4: Novel Palliative Treatments of Metastatic Breast Cancer - Survey Instruments
Appendix 5: Core Advisory Committee Meeting Agenda
Appendix 6: Quality of Life Library Contents
Appendix 7: Core Consultants
Appendix 8: Core Publications and Grants

APPENDIX MATERIALS FOR ALL PROJECTS AND CORES

Project 1: Impact of Genetic Testing for Breast Cancer Susceptibility

Appendix 1: Eligibility criteria
Appendix 2: Estimated likelihood of identifying BRCA1/2 mutations
Appendix 3: Family history form for patient completion
Appendix 4: CARE recruitment brochure (general)
Appendix 5: CARE brochure for relatives
Appendix 6: Sample pedigrees
Appendix 7: Baseline interview
Appendix 8: CARE written educational material
Appendix 9: CARE newsletter

Project 2: A Coordinated Approach to Breast Cancer Diagnosis

Appendix 1: NIH Biosketch for Susan M. Ascher, MD

Project 3: Development of Novel Antiangiogenic Therapies in Metastatic Breast Cancer

Appendix 1: TNP-470 Pilot Trial 1
Appendix 2: Thalidomide protocol documentation

Core 1: Patient Accession Core

Appendix 1: CARE Flow of Activities
Appendix 2: Primary Care Clinic Advisory Board Meeting Minutes
Appendix 3: Key Informant Questionnaire
Appendix 4: Materials
Appendix 5: Strategic Plan

Core 2: Cancer Clinical and Economic Outcomes Evaluations Core

Appendix 1: Project 1 Survey Instruments
Appendix 2: Core 1 Cost Data Collection Instrument
Appendix 3: Project 2 Survey Instrument
Appendix 4: Novel Palliative Treatments of Metastatic Breast Cancer - Survey Instruments
Appendix 5: Core Advisory Committee Meeting Agenda
Appendix 6: Quality of Life Library Contents
Appendix 7: Core Consultants
Appendix 8: Core Publications and Grants

Project 1: Impact of Genetic Testing for Breast Cancer Susceptibility

Appendix 1: Eligibility criteria
Appendix 2: Estimated likelihood of identifying BRCA1/2 mutations
Appendix 3: Family history form for patient completion
Appendix 4: CARE recruitment brochure (general)
Appendix 5: CARE brochure for relatives
Appendix 6: Sample pedigrees
Appendix 7: Baseline interview
Appendix 8: CARE written educational material
Appendix 9: CARE newsletter

Appendix 1: Eligibility criteria

Appendix 1

Eligibility criteria for the CARE program
Georgetown University Medical Center
Revised: September 17, 1997

Genetic testing is first initiated in a family by testing an individual who has already had breast and/or ovarian cancer (preferably with the youngest age of onset in the family). Therefore, in order to be eligible for the CARE program, individuals must have a history of one or both of these cancers or must be the **relative of an individual with a documented risk-conferring mutation in BRCA1 or BRCA2.** Note the following abbreviations when interpreting the following eligibility criteria:

FDR = First Degree Relative/s (mother, daughters, sisters) SDR = Second Degree Relative/s (aunts, grandmother, nieces)

A **single affected individual** with:

-breast and ovarian primary cancers, one diagnosed $\leq$ 50, OR
-breast cancer diagnosed $\leq$ 30 years old, OR
-breast cancer diagnosed $\leq$ 45 years old and Jewish descent, OR
-ovarian cancer diagnosed $\leq$ 50 years old and Jewish descent

An **affected individual plus one FDR** with:

-breast cancer diagnosed < age 50 (in BOTH individuals), OR
-breast cancer diagnosed < age 50 (in ONE individual) and breast cancer diagnosed at any age in the other relative and Jewish descent, OR
-breast cancer (any age) in one individual and ovarian cancer (any age) in the other individual, OR
-ovarian cancer, diagnosed any age (in BOTH individuals)

An **affected individual plus at least 2 other relatives (FDR or SDR)** on the same side of the family with:

-breast cancer, at least 1 case diagnosed < age 50, OR
-breast and ovarian cancer at any age (not necessarily in the same individual), OR
-ovarian cancer, diagnosed at any age

Case by case considerations for eligibility include the following:

-Index case affected with breast or ovarian cancer and only one paternal second degree relative with breast or ovarian cancer; breast cancer case(s) must still be less than age 50 for consideration (when there is ovarian cancer in the index case and/or in the relative, these will most likely be accepted into the study)
-Index case affected with breast or ovarian cancer and only one maternal second degree relative with breast or ovarian cancer; breast cancer case(s) must still be less than age 50 for consideration (these will be more likely to be accepted into the study if the mother of the index case died at a young age and the relative was affected at a very young age)
-Male breast cancer, diagnosed at any age, with or without a family history of breast or ovarian cancer
-Ovarian cancer in non-Jewish women diagnosed less than age 45, with pathology confirming epithelial origin
-Three or more cases of breast and ovarian cancer diagnosed in women all over the age of 65

Patients should be referred to Ms. Kristen Willard at (202) 687-1750.

Appendix 2: Estimated likelihood of identifying BRCA1/2 mutations

Cancer Assessment and Risk Evaluation (CARE) Program: Eligibility Criteria and Estimated Likelihood of Identifying BRCA1 or BRCA2 Mutations

Eligibility Criterion	BRCA1 Probability	BRCA2 Probability	References
Single affected: BC and OC primary cancers, one dx'd ≤ 50	Up to 50%	Unknown	Couch et al 1997
Single affected: BC dx'd ≤ 30	12%	< 5%	Shattuck-Eidens et al 1995; Krainer et al 1997
Single affected: BC dx'd ≤ 40 and Jewish	21% (185delAG)	Up to 8% (6174delT)	FitzGerald et al 1996 Neuhausen et al 1996
Single affected: OC dx'd ≤ 50 and Jewish	37% (185delAG)	<5%	Muto et al 1996 Levy-Lahad et al 1997
Two affected FDR: 1) BC dx'd <50 in both 2) One with BC dx'd <50 and Jewish descent 3) BC dx'd any age and OC dx'd any age 4) OC dx'd any age	1) Up to 20% 2) Probably at least 13% (185delAG and 5382insC) 3) 7-55% depending on age of BC onset 4) Up to 61%	1) < 20%* 2) <13% (6174delT) * 3) < 10%* 4) <5%*	Shattuck-Eidens et al 1995; Couch et al 1997
Three affected relatives on the same side of the family (FDRs and SDRs): 1) BC, with ≥ 1 case dx'd <50 2) BC and OC dx'd any age 3) OC dx'd any age	1) Up to 40% 2) Up to 91% 3) Up to 61%*	1) < 40%* 2) < 20%* 3) < 5%*	Shattuck-Eidens et al 1995; Couch et al 1997

* Our estimate based on literature review and clinical experience

References:

-Couch FJ, DeShano ML, Blackwood MA, Calzone K, Stopfer J, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. NEJM 1997;336:1409-15.
-FitzGerald MG, MacDonald DJ, Krainer M, Hoover I, O'Neil E, et al. Germ-line BRCA1 mutations in Jewish and non-Jewish women with early onset breast cancer. NEJM 1996; 334: 143-9.
-Krainer M, Silva-Arrieta S, FitzGerald MG, Shimada A, Ishioka C, et al. Differential contributions of BRCA1 and BRCA2 to early-onset breast cancer. NEJM 1997; 336: 1416-21.
-Levy-Lahad E, Catane R, Eisenberg S, Kaufman B, Hornreich G, et al. Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer in and breast-ovarian cancer families. Am J Hum Genet 1997; 60: 1059-67.
-Muto MG, Cramer DW, Tangier J, Berkowitz R, Mok S. Frequency of the BRCA1 185delAG mutation among Jewish women with ovarian cancer and matched population controls. Cancer Research 1996; 56: 1250-52.
-Neuhausen S, Gilewski T, Norton L, Tran T, McGuire P, et al. Recurrent BRCA2 6174delT mutations in Ashkenazi Jewish women affected by breast cancer. Nat Genet 1996; 13: 126-8.
-Shattuck-Eidens D, McClure M, Simard J, Labrie F, Narod S, et al. A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene: implications for presymptomatic testing and screening. JAMA 1995; 273: 535-41.

Appendix 3: Family history form for patient completion

Appendix 3

GEORGETOWN UNIVERSITY MEDICAL CENTER

LOMBARDI CANCER CENTER
Research • Education • Treatment

CANCER GENETICS

2233 WISCONSIN AVENUE NW
SUITE 535
WASHINGTON, DC 20007-4104
TELEPHONE: (202) 687-0802
FAX: (202) 687-0820

Offices in
Washington, DC
Rockville, MD
Arlington, VA

This questionnaire is intended for women with a personal history or family history of breast and/or ovarian cancer. The information you provide will help to determine if you are eligible to participate in a genetic counseling and cancer susceptibility testing program available at the Lombardi Cancer Center. Currently, this program is being offered free of cost, through the support of a research grant from the Susan G. Komen Foundation. This program is called the CARE (Cancer Assessment and Risk Evaluation) program. If you are willing to be contacted for more information about this program, please fill out the following:

All of your responses will be kept strictly confidential.
If you have completed this questionnaire at a previous visit, it is not necessary to fill it out again.

TODAY'S DATE: _____

NAME: _____ DATE OF BIRTH: _____

ARE YOU HERE TODAY FOR A BREAST BIOPSY? YES☐ NO☐ DON'T KNOW☐

HAVE YOU EVER HAD A DIAGNOSIS OF BREAST CANCER? YES☐ NO☐
IF YES, AGE AT DIAGNOSIS _____

HAVE YOU EVER HAD A DIAGNOSIS OF OVARIAN CANCER? YES☐ NO☐
IF YES, AGE AT DIAGNOSIS _____

RACE: Black/African American ☐ Caribbean/West Indian ☐ White/Non-Hispanic ☐
Hispanic ☐ Asian/Pacific Islander ☐ Native American ☐

RELIGION: Catholic ☐ Protestant ☐ Jewish ☐ Atheist/None ☐ Other ☐

ADDRESS: _____

_____

DAY PHONE: _____ EVENING PHONE: _____

BEST TIME TO CALL: _____

TODAY'S APPOINTMENT IS WITH: _____ DEPARTMENT: _____

Once completed, please return this questionnaire to Tiffani DeMarco, M.S. at the address listed above.

Last name: _____

Family History Form

Please indicate (with a check) if any of the following relatives have had breast and/or ovarian cancer, the age at which they were diagnosed, and whether your relatives with cancer are living or deceased. *If the given individual has not had either breast or ovarian cancer, please leave all the spaces blank.* The first two rows are examples of how to complete the table.

IF YOU DO NOT HAVE A FAMILY HISTORY OF CANCER PLEASE CHECK HERE ☐

INDIVIDUAL	BREAST CANCER (check one box)		Age at first breast cancer diagnosis	OVARIAN CANCER (check)	Age at ovarian cancer diagnosis	Alive or Deceased (A or D)
	One breast	Both breasts				
MOTHER	✓		**45**			**A**
MATERNAL* GRANDMOTHER		✓	**56**	✓	**60**	**D**
MOTHER						
MATERNAL* GRANDMOTHER						
SISTER 1						
SISTER 2						
SISTER 3						
MATERNAL* AUNT 1						
MATERNAL* AUNT 2						
MATERNAL* AUNT 3						
PATERNAL** GRANDMOTHER						
PATERNAL** AUNT 1						
PATERNAL** AUNT 2						
PATERNAL** AUNT 3						
DAUGHTER 1						
DAUGHTER 2						
DAUGHTER 3						

* *Maternal* refers to individuals on your mother's side of the family

** *Paternal* refers to individuals on your father's side of the family

Last name: _____

Please use this page to identify other family members who have had breast and/or ovarian cancer. Please specify the way in which each individual is related to you. For example, "the daughter of my maternal aunt (#2 above)" or "my maternal grandmother's sister."

INDIVIDUAL	BREAST CANCER (check one box)		Age at first breast cancer diagnosis	OVARIAN CANCER (check)	Age at ovarian cancer diagnosis	Alive or Deceased (A or D)
	One breast	Both breasts				
Other 1:						
Other 2:						
Other 3:						
Other 4:						
Other 5:						

Has anyone in your family ever had colon or prostate cancer? ❒ Yes ❒ No

If yes, please complete the table below:

Relative (please specify relationship to you)	Cancer Diagnosis (C= Colon Cancer, P= Prostate Cancer)	Age at diagnosis	Alive or Deceased (A or D)

Thank you very much for taking the time to complete this questionnaire.

Appendix 4: CARE recruitment brochure (general)

Appendix 4

Who is eligible for CARE?

Since eligibility for the CARE program is subject to change as research progresses, please see the insert for the current eligibility criteria.

Participants must be at least age 18 and have at least one living family member who has had breast or ovarian cancer. While the CARE program focuses on women, male relatives may also be eligible.

To learn more about the CARE Program and to find out if you are eligible to participate, please call (202) 687-1750

Produced by the Department of External Affairs, 4/96

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

lombardi

LOMBARDI CANCER CENTER

RESEARCH • EDUCATION • TREATMENT •

do you have a family history of breast or ovarian cancer?

GEORGETOWN UNIVERSITY MEDICAL CENTER

You may have heard

or read in the news about breast and ovarian cancer susceptibility genes, such as BRCA1 and BRCA2. Here is your chance to find out more.

The **CARE** (Cancer Assessment and Risk Evaluation) Program is a genetic counseling and testing program offered by the Lombardi Cancer Center at Georgetown University Medical Center. Through the CARE Program, women receive information and counseling about their risks for breast and ovarian cancer—two cancers shown to be related to genes that are inherited, or passed down, in families.

This is a free program

that is supported by research grants from the National Institutes of Health, the Department of Defense, and the Susan G. Komen Foundation.

Why should I participate in the CARE Program?

By participating in the CARE Program, you may learn valuable information about your risk of developing breast and ovarian cancer that will help you in making decisions about your health care.

You also will be helping research efforts to learn more about the best ways to educate and counsel women who are at increased risk for breast and/or ovarian cancers. Ultimately, the goal is to reduce illness and death from these cancers.

What does the CARE Program involve?

Each participant in the CARE Program will meet with a genetic counselor for approximately 1to 2 hours and will receive:

- a detailed family history and risk factor assessment
- genetic education and counseling
- guidelines for cancer prevention and screening
- option of genetic testing for cancer susceptibility, if eligible
- information regarding cancer screening services and prevention trials

Since the CARE Program is a clinical research program, all participants are asked to complete four telephone interviews over a one-year period to evaluate the benefits of the program and develop future genetic counseling and testing programs. All information is confidential.

If you had breast cancer,

you may be eligible for CARE if:

- You were diagnosed at age 40 or younger, and are of Jewish descent
- You were diagnosed before age 50 and you also have a first-degree relative (mother, sister, daughter) who had ovarian (any age) or breast cancer (before age 50)
- You were diagnosed before age 50 and you also have a first-degree relative (mother, sister, daughter) who had breast cancer at any age and are of Jewish descent.

If you had ovarian cancer,

you may be eligible for CARE if:

- You were diagnosed at age 50 or younger, and are of Jewish descent
- You also have a first-degree relative who had ovarian cancer (any age) or breast cancer (before age 50)

If you have not had breast or ovarian cancer,

you may be eligible for CARE if:

- You have a first-degree relative (mother, sister, daughter) who had breast cancer at age 30 or younger, OR
- You have two first-degree relatives who had early-onset breast cancer (age 50 or younger) and/or ovarian cancer (any age), OR
- You have three relatives on the same side of the family with early-onset breast cancer and/or ovarian cancer

Appendix 5: CARE brochure for relatives

Appendix 5

CARE

Cancer Assessment
and Risk Evaluation

This materia
genetic cou
There is no
you learn more abou
your family. If you
genetic testing, please
through this informa

The clinical staff of CARE includes two master's-level genetic counselors and a medical director—a physician trained in medical oncology. The program's principal investigator is a behavioral scientist and clinical psychologist. These individuals work closely with other oncologists, surgeons, nurses, and psychologists at Georgetown University Medical Center to provide services and information to CARE participants.

For more information about CARE, or to find out how to enroll, please call (202) 687-1750.

What is the significance of breast cancer susceptibility genes?

It is estimated that hereditary breast cancer accounts for approximately 5 percent to 10 percent of all breast cancer cases. BReast CAncer 1 (BRCA1) and BReast CAncer 2 (BRCA2) are the two major breast cancer susceptibility genes that have been identified to date. Alterations in these genes are thought to account for the majority of inherited breast and ovarian cancers. The frequency of these altered genes in the general population is not known. One estimate suggests that BRCA1 alterations occur in about 1 of every 800 individuals.

The BRCA1 and BRCA2 genes are thought to act as "tumor suppressor" genes when they function properly. Tumor suppressor genes prevent cells in our body from growing out of control; however, alterations of these genes can change their usual function. This change can increase the chance of developing breast, ovarian, and other cancers.

Because the BRCA1 and BRCA2 genes are very large, there are many places within each gene where an alteration (mutation) can occur. Thus far, more than 100 alterations have been detected in these genes and some mutations occur much more frequently than others. A few mutations have been found with increased frequency in specific populations.

A specific alteration in one of these genes has been identified in your family. Research is under way to learn more about this and other mutations in BRCA1 and BRCA2. This research will improve our understanding of the cancer risks associated with these alterations and will provide more information about the function of these genes. Ultimately, these discoveries may lead to improved prevention, early detection, and treatment of cancer.

What are the risks associated with BRCA1 and BRCA2 alterations?

Cancer risks associated with BRCA1 and BRCA2 alterations must be evaluated in the context of your medical and family history. In general, a woman with an alteration in the BRCA1 gene has a 55 percent to 85 percent chance of developing breast cancer, and a 15 percent to 60 percent chance of developing ovarian cancer. There may also be an increased risk of prostate cancer for men, as well as an increased risk of colon cancer for men and women.

Identification of the BRCA2 gene took place more recently. We know less about the cancer risks associated with alterations in this gene. When a BRCA2 alteration is present, the risk of breast cancer is estimated to be from 55 percent to 80 percent. The risk of ovarian cancer is thought to be between 15 percent and 20 percent. BRCA2 alterations also are associated with other cancers, such as breast and prostate cancer in men, pancreatic cancer, and possibly other cancers.

Research is in progress to better define these risks. As more information becomes available, these estimates may change. It is important to remember that risk varies from individual to individual and from family to family. We cannot predict with certainty the type of cancer to which an individual is most susceptible, or the age at which cancer may develop.

What is my chance of having the BRCA1 or BRCA2 alteration which is present in my family?

The genetic counselor can discuss your individual risk based upon your position in your family tree. An individual with a BRCA1 or BRCA2 alteration has a 50 percent chance of passing it down to his or her children. This happens because eggs and sperm each carry only one copy of each gene pair. Each child of a parent with an altered gene and each full brother or sister of an individual with an altered gene has a 50 percent chance of inheriting it. Individuals also have a 50 percent chance of inheriting the functioning gene. The risk is not affected by the sex of the child or the affected parent, or by the child's birth order. It cannot be predicted based on how much a child resembles either parent.

How is genetic testing performed?

As an alteration in BRCA1 or BRCA2 has already been identified in your family, it is a simple process to test you. A small blood sample is drawn. From it, genetic material (DNA) is obtained and analyzed for the specific alteration previously identified in your relative. This testing can be completed in a relatively short period of time. It is very accurate and provides results that are clearly positive or negative for a particular alteration.

What are the pros and cons of testing?

There are potential benefits to being genetically tested. There also are potential risks and limits to the information that can be obtained. Each individual needs to consider whether the potential benefits outweigh the risks in order to decide whether or not to be tested. All individuals who decide to provide a blood sample for genetic testing must sign a consent form. The form contains additional information about the benefits, limitations, and risks of genetic testing.

Increased knowledge:

Genetic tests may provide you with more information about your risk of getting cancer. It may also provide insight as to why cancer developed in your family.

Health care decisions:

Information about cancer risk can facilitate decisions about whether certain screening tests should be considered. It may help women decide about risk-reducing surgery.

Emotional implications:

Learning the test results may produce a sense of relief. It may reduce uncertainty about cancer risk. People whose test results are negative may feel a sense of reassurance. However, those who learn their test results are positive may feel sad, angry, or anxious. Given its impact on relatives or children, this information may strain relationships. Individuals may feel guilty regarding the outcome or possible outcome of testing. Each person responds differently to information about risk. Sometimes, psychological counseling and support may be helpful.

Possible discrimination:

Genetic testing may place individuals at risk for discrimination by health, life, and disability insurers, as well as employers. Knowledge that you have a genetic predisposition to cancer may compromise your ability to obtain or maintain insurance coverage. Today, fewer than half the states restrict the extent to which health insurers may use genetic information. Almost all states allow life and disability insurers to ask questions about genetic predisposition to cancer, and then use the answers in their underwriting decisions. Recently enacted federal legislation may help protect those individuals who decide to undergo genetic testing. In August 1996, President Clinton signed The Health Insurance Portability and Accountability Act of 1996. It recognizes "genetic information" as protected medical information. It forbids those who provide health care coverage from using such information to deny access to individuals who must change health plans when they change jobs.

The act also states that, based on genetic information, a group medical plan cannot require an individual to pay a premium or contribution (to join the plan or stay in it) that is greater than that for a "similarly situated" enrollee. The term "similarly situated" means that a plan or coverage could vary benefits available to different groups of employees, such as full-time versus part-time, or employees in different geographic locations. A limitation of the act is that it does not restrict the premiums charged for individual health insurance. Such premiums need only comply with state law. These insurance reform provisions went into effect on July 1, 1997.

The Health Insurance Portability and Accountability Act of 1996 is a major step toward protecting individuals who undergo genetic tests; however, it does not address the issue of confidentiality, nor does it require an individual's permission to release genetic information. There has been no federal legislation passed regarding medical record privacy, employment, and other forms of insurance, such as life and disability. The Senate and the House are reviewing bills that would offer additional federal protection from genetic discrimination.

The staff of the CARE program will do everything possible to maintain the privacy of genetic test results. Each participant is identified by a unique number, and no information about him or her is released to third parties without that participant's consent. Our research program received a Certificate of Confidentiality from the Department of Health and Human Services. This allows CARE to withhold information about participants from any outside sources, unless an individual has given written consent.

How do I get more information?

If you are interested in participating in CARE, you are eligible to come to Georgetown University Medical Center and receive free genetic counseling and testing. Even if you are not interested in genetic counseling or testing, we would appreciate your participation in a few brief telephone interviews. If you are interested in genetic testing, but cannot travel to Georgetown, one of our research assistants can provide information about referrals in your local area. Many of these referral programs charge a fee for genetic counseling and testing.

Please feel free to contact us at (202) 687-1750 for more information.

NCI
CCC

A Comprehensive Cancer Center Designated by the National Cancer Institute

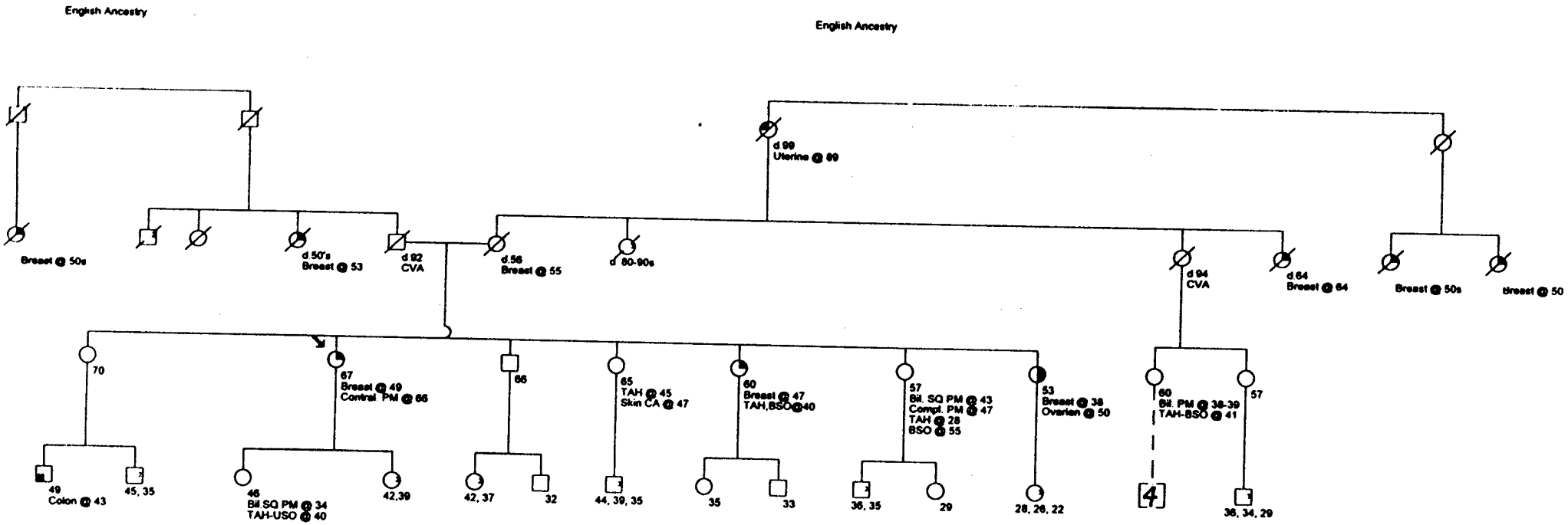
GEORGETOWN

The Art of Medicine

Produced by the Department of External Affairs 8/97

Appendix 6: Sample pedigrees

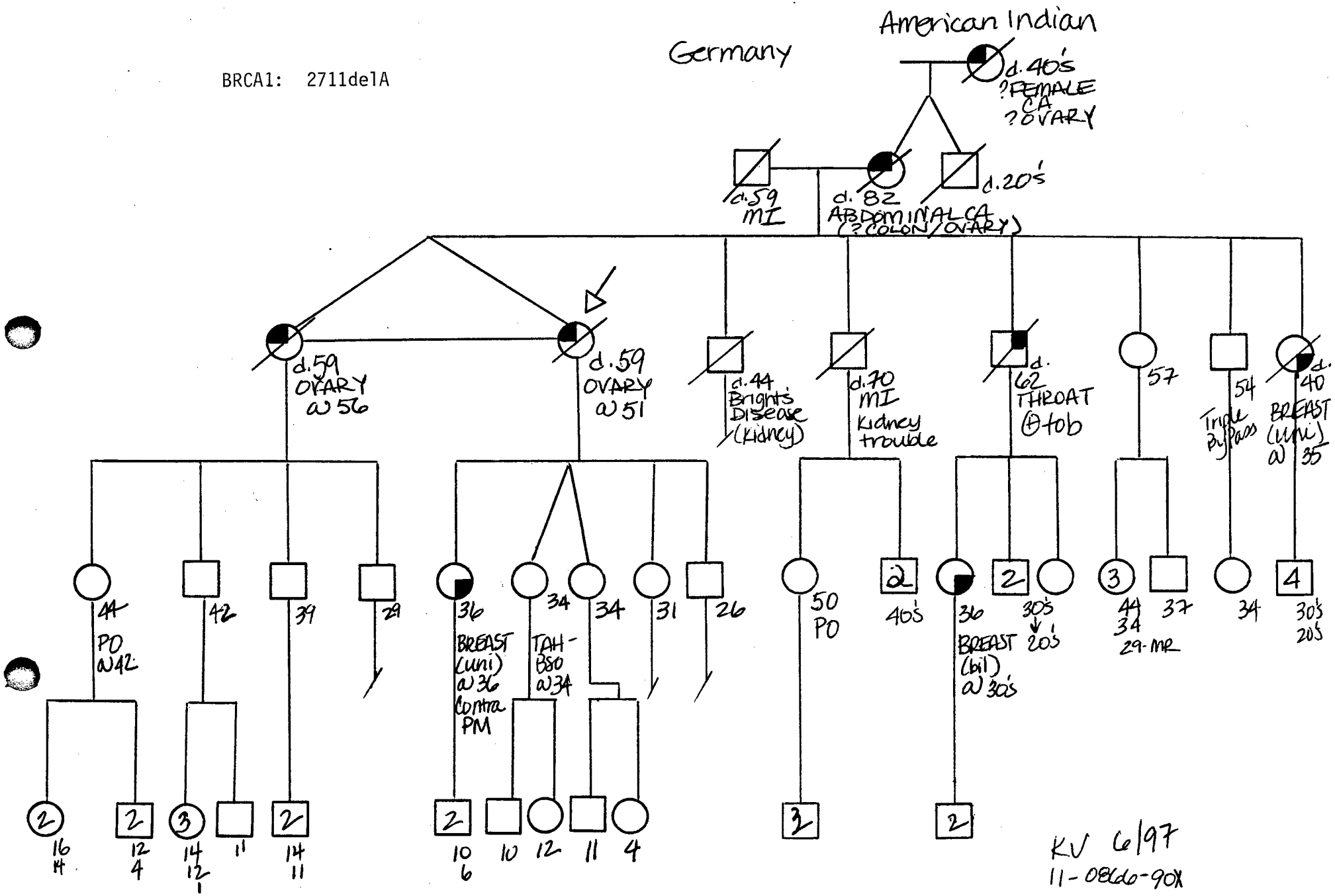
BRCA1: 185delAG



red #0664
1/97

Appendix 6

BRCA1: 2711delA



Appendix 7: Baseline interview

ID#_____

Date_____

BASELINE INTERVIEW

INTRO FOR SELF/MD/GENETIC COUNSELOR REFERRED

Hello, my name is _____ and I'm calling for the [SITE]. I understand that you may be interested in participating in our genetic education and counseling program for individuals who have a family history of breast or ovarian cancer. There is no charge for this service. As part of this program, I'd like to ask you some questions about your medical history and about your attitudes, opinions, and feelings related to breast and ovarian cancer. This information is necessary to help us to counsel you and to evaluate the effectiveness of our program. It should take about 15-20 minutes. All of the information you provide will be strictly confidential. You will also have the opportunity to participate in a free educational and counseling program.

If interested, GO to Question 1 below.

If not interested in completing the survey, add: You may be able to participate in one of our programs which does not involve completing this survey -- however, there may be a charge for these services. In order to determine whether you are eligible to participate, I would need to ask you very briefly about your family history of cancer.

If still not interested, add: Thank you.

If interested in service, but not survey, complete Question 1 only (family history) below. If high risk, refer directly to Beth Peshkin. If not high risk, refer to Comprehensive Breast Program.

INTRO FOR PATIENT (RIF) REFERRED

Hello, my name is _____ and I'm calling for the [SITE]. We received your name from_____, a patient at [SITE]. We have a new genetic education and counseling program for individuals who have a family history of breast or ovarian cancer. There is no cost for this service. I'm calling to ask if you got the letter we sent you and if you'd be willing to answer some questions about your medical history and about your attitudes, opinions, and feelings related to breast and ovarian cancer. The information in this survey is necessary to help us to counsel you and to evaluate the effectiveness of our program. It should take about 15-20 minutes. All of the information you provide will be strictly confidential. We also will invite you to participate in a free educational and counseling program.

Interested..... 1 → **If yes, continue with Question 1**
Not interested..... 2 → **(If no) May I ask why not?** _____

_____

_____

1. The first questions are about your family history of cancer. Here we are only talking about blood relatives.

1.1 Does anyone in your family have an altered breast-ovarian cancer gene?

Yes.... 1
No..... 2

1.a. Was your mother ever diagnosed with breast cancer?

Yes....1→ How old was she at diagnosis? _____; Was it bilateral (both breasts)? Yes....1 No....2
No.....2 Is she living? Yes....1 No....2

1.b. Was your mother ever diagnosed with ovarian cancer?

Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2
No.....2

1.c. Do you have any sisters?

Yes....1 → **Continue**
No.....2 → **Go to Question 1.f.**

1.d. Did any of your sisters have breast cancer?

Yes....1 → How many? _____
No.....2 → **Go to Question 1.e.**

Sister #1: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2
Sister #2: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2
Sister #3: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2

1.e. Did any of your sisters have ovarian cancer?

Yes....1 → How many? _____
No.....2 → **Go to Question 1.f.**

Sister #1: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

Sister #2: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

Sister #3: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

1.f. Do you have any daughters?

Yes....1 → **Continue**
No.....2 → **Go to Question 1.i.**

1.g. Did any of your daughters have breast cancer?

Yes....1 → How many? _____
No.....2 → **Go to Question 1.h.**

Daugh.#1: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No..,.2
Daugh.#2: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2
Daugh.#3: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2

1.h. Did any of your daughters have ovarian cancer?

Yes....1 → How many? _____
No.....2 → **Go to Question 1.i.**

Daugh.#1: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

Daugh.#2: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

Daugh.#3: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

1.i. Does/did your mother have any sisters?

Yes....1 → **Continue**
No.....2 → **Go to Question 1.l.**

1.j. Did any of your mother's sisters have breast cancer?

Yes....1 → How many? _____
No.....2 → **Go to Question 1.k.**

Maternal aunt #1: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2

Maternal aunt #2: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2

Maternal aunt #3: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2

1.k. Did any of your mother's sisters have ovarian cancer?

Yes....1 → How many? _____
No.....2 → **Go to Question 1.l.**

Maternal aunt #1: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

Maternal aunt #2: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

Maternal aunt #3: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

1.l. Does/did your father have any sisters?

Yes....1 → **Continue**
No.....2 → **Go to Question 1.o.**

1.m. Did any of your father's sisters have breast cancer?

Yes....1 → How many? _____
No.....2 → **Go to Question 1.n.**

Paternal aunt #1: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2

Paternal aunt #2: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2

Paternal aunt #3: Yes....1→ How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
Is she living? Yes....1 No....2

1.n. Did any of your father's sisters have ovarian cancer?

Yes....1 → How many? _____
No.....2 → **Go to Question 1.o.**

Paternal aunt #1: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

Paternal aunt #2: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

Paternal aunt #3: Yes....1→ How old was she at diagnosis? _____ Is she living? Yes....1 No....2

1.o. Was your mother's mother ever diagnosed with breast cancer?

Yes....1 → How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
No.....2 Is she living? Yes....1 No....2

1.p. Was your mother's mother ever diagnosed with ovarian cancer?

Yes....1 → How old was she at diagnosis? _____ Is she living? Yes....1 No....2
No.....2

1.q. Was your father's mother ever diagnosed with breast cancer?

Yes....1 → How old was she at diagnosis? _____; Was it bilateral? Yes....1 No....2
No.....2 Is she living? Yes....1 No....2

1.r. Was your father's mother ever diagnosed with ovarian cancer?

Yes....1 → How old was she at diagnosis? _____ Is she living? Yes....1 No....2
No.....2

1.r.1 Do you have any other female relatives affected with breast cancer?

Yes.....1 → How many? ___
No.....2

1.s. Do you have any male relatives affected with breast cancer?

Yes....1 ----->How many? _____
No.....2 ----->**Go to question 1.t**

Male relative #1: Relationship _____ Age at diagnosis ___ Is he living? Yes..1 No...2
Was it bilateral? Yes..1 No...2

Male relative #2: Relationship _____ Age at diagnosis ___ Is he living? Yes..1 No...2
Was it bilateral? Yes..1 No...2

Male relative #3: Relationship _____ Age at diagnosis ___ Is he living? Yes..1 No...2
Was it bilateral? Yes..1 No...2

1.t. Do you have any Jewish ancestors from central or eastern Europe?

Yes.....1
No.....2

2. Have you yourself ever had cancer?

Yes → **If high risk, go to Question 2.a. below; otherwise go to early close**
No → **Go to Question 3**

2a. What type of cancer?

Breast.....1 How old were you at first diagnosis? ___ Was it bilateral?__
Ovary.....2 How old were you at first diagnosis? ___ Was it bilateral?__
Colon.....3
Endometrium.....4
Cervical.....5
Lung.....6
Melanoma.....7
Other.....8
Prostate.....9

EARLY CLOSE (FOR LOW RISK INDIVIDUALS ONLY): This study is for individuals who have a mother, sister, or daughter with breast cancer, but (have not had any type of cancer themselves). Because you have a personal history of cancer, the study would not be appropriate for you. If you would like information about programs for which you may be eligible, you can call the Cancer Information Service (1-800-4-CANCER). Thank you very much for your time and help.

MEN SHOULD SKIP TO QUESTION 14.

3. Have you ever had a breast biopsy?

Yes..... 1
No.....2 → **Go to Question 5**

3a. If yes, what was the result?

Atypical hyperplasia..... 1
Hyperplasia..... 2
Neither (i.e., calcification, benign, fibrocystic)..... 3
Malignant..... 4
Don't know..... 9

4. How many breast biopsies have you had? _____ biopsies

5. How old were you when you had your first menstrual period? _____ years old

6. Are you still menstruating?

Yes..... 1 → **Go to Question 7**
No..... 2

6a. If no, how old were you when you had your last period?

_____ years old _____ don't know

6b. Why did your periods stop?

Natural menopause (change of life)..... 1
Hysterectomy.....2
Took medication that stopped periods..... 3
Other_____.....4

7.. Have you ever used oral contraceptives; that is, birth control pills?

Yes..... 1
No..... 2 → **Go to Question 8**
Don't know..... 9 → **Go to Question 8**

7a. If yes, what was the total number of months or years that you used oral contraceptives?

_____ months or years _____ don't know

7b. How many of these months or years of use occurred before you ever gave birth - (IF SUBJECT SAYS NEVER GAVE BIRTH, ANSWER IS SAME AS 7a).

_____ Months or years _____don't know

8. To your knowledge, have you ever been exposed to DES, an estrogen given to women to avoid miscarriage, when you were pregnant or when your mother was pregnant with you?

Yes..... 1
No..... 2
Don't know..... 9

9. Have you ever been pregnant?

Yes..... 1
No..... 2 → **Go to Question 13**

10. How many pregnancies have you had? ___ Pregnancies

Don't know..... 9

10a. Have you ever given birth?

Yes..... 1
No..... 2 → **Go to Question 13**

11. How old were you when you had your first child? _____ years old

12. How many children do you have? _____ children

12a. How old is your first child? _____ years old

Did you breast feed this child?

Yes..... 1 → For how many months? _____
No.....2

12b. How old is your second child? _____ years old

Did you breast feed this child?

Yes..... 1 → For how many months? _____
No.....2

12c. How old is your third child? _____ years old

Did you breast feed this child?

Yes..... 1 → For how many months? _____
No.....2

12d. How old is your fourth child? _____ years old

Did you breast feed this child?

Yes..... 1 → For how many months? _____
No.....2

12e. How old is your fifth child? _____ years old

Did you breast feed this child?

Yes..... 1 → For how many months? _____
No.....2

12f. How old is your sixth child? _____ years old

Did you breast feed this child?

Yes..... 1 → For how many months? _____
No.....2

12g. How old is your seventh child? _____ years old

Did you breast feed this child?

Yes..... 1 → For how many months? _____
No.....2

12h. How old is your eighth child? _____ years old

Did you breast feed this child?

Yes..... 1 → For how many months? _____
No.....2

13. Have you ever had infertility problems? This is defined as a one-year period trying to get pregnant, but not being able to. (Here we're referring to your difficulties, not your partners).

Yes..... 1→ At what age did this happen? ____ Years
No..... 2→ **Go to Question 13a**

IF YES, did you seek treatment?

Yes..... 1
No..... 2→ **Go to Question 13a**

IF YES, what type of treatment did you have?

_____

_____

_____

13a. Have you ever participated (or currently participating) in a Tamoxifen program, a study for preventing breast cancer in high risk women?

Yes..... 1
No.....2

EVERYONE

14. In your opinion, do you think there are benefits to people who participate in medical research? (By medical research, I mean studies of prevention and treatment of diseases) **[READ LIST]**

Not at all..... 1
A little..... 2
Somewhat..... 3
Very much..... 4

15. In your opinion, do you think that participants in medical research are taken advantage of or exploited? **[READ LIST]**

Not at all..... 1
A little..... 2
Somewhat..... 3
Very much..... 4

Please tell me how much you agree with the following statement. **[READ STATEMENT]** Do you agree or disagree? Do you agree/disagree somewhat or strongly?

	Strongly Disagree	Disagree	Agree	Strongly Agree
16. Even when I am feeling quite sick, there are times when I don't feel it is worth going to a doctor.....	1.....	2.....	3.....	4

MEN SKIP TO SCRIPT ON PAGE 13

The next segment of this survey is about your knowledge, attitudes, and opinions about breast and ovarian cancer.

17. In your opinion, compared to other women your age, are your chances of getting breast cancer (again)... **[READ LIST]**

Much lower.....1
A little lower..... 2
About the same..... 3
A little higher..... 4
Much higher.....5

18. How certain are you about your chances of getting breast cancer (again)? **[READ LIST]**

Not at all certain.....1
A little certain..... 2
Somewhat certain.....3
Very certain.....4

19. During the past month, how often have you thought about your own chances of getting breast cancer (again)? Would you say... **[READ LIST]**

Not at all or rarely.....1
Sometimes.....2
Often.....3
A lot.....4

20. During the past month, how often have thoughts about your chances of getting breast cancer (again) affected your mood? Would you say... **[READ LIST]**

Not at all or rarely.....1
Sometimes.....2
Often.....3
A lot.....4

21. During the past month, how often have thoughts about your chances of getting breast cancer (again) affected your ability to perform your daily activities? **[READ LIST]**

Not at all or rarely.....1
Sometimes.....2
Often.....3
A lot.....4

22. How much control do you feel you have over whether you develop breast cancer (again)? **[READ LIST]**

None at all.....1
A little.....2
A moderate amount.....3
A lot.....4

Now, I'd like to ask you about ovarian cancer.

23. In your opinion, compared to other women your age, are your chances of getting ovarian cancer (again)... **[READ LIST]**

Much lower.....1
A little lower..... 2
About the same..... 3
A little higher..... 4
Much higher.....5

24. How certain are you about your chances of getting ovarian cancer (again)? **[READ LIST]**

Not at all certain.....1
A little certain..... 2
Somewhat certain.....3
Very certain.....4

25. During the past month, how often have you thought about your own chances of getting ovarian cancer (again)? **[READ LIST]**

Not at all or rarely.....1
Sometimes.....2
Often.....3
A lot.....4

26. During the past month, how often have thoughts about your chances of getting ovarian cancer (again) affected your mood? **[READ LIST]**

Not at all or rarely.....1
Sometimes.....2
Often.....3
A lot.....4

27. During the past month, how often have thoughts about your chances of getting ovarian cancer (again) affected your ability to perform your daily activities? **[READ LIST]**

Not at all or rarely.....1
Sometimes.....2
Often.....3
A lot.....4

28. How much control do you feel you have over whether you develop ovarian cancer (again)? **[READ LIST]**

None at all.....1
A little.....2
A moderate amount.....3
A lot.....4

EVERYONE: CONTINUE

As you may already know, breast cancer tends to run in certain families. In a small number of families, many of the females develop breast cancer -- often at younger ages. Cancers of the ovaries, colon, and prostate sometimes occur more frequently in these families as well.

Scientists believe that in <u>some</u> families, persons who develop cancer have inherited an altered copy of a cancer gene called <u>BRCA1 or BRCA2</u>. This gene is passed down from generation to generation in these families. Some family members will inherit the gene and others will not. Both men and women have an equal chance of inheriting this gene.

It may soon be possible to use a blood test to determine which members of your family may have inherited an altered breast-ovarian cancer gene. A woman who has inherited an altered copy

of this gene would have a very high risk of developing breast or ovarian cancer in her lifetime. A woman who hasn't inherited an altered copy still would have the general population risk of developing breast or ovarian cancer.

29. The next questions are to find out how much you may already know about genes for cancer. Please tell me whether you think each item is **True** or **False**, or if you **Don't Know**. This is not a test. This information will help us to evaluate our education and counseling programs.

		True	False	Don't Know
a)	About one-half of all cases of breast cancer in the United States occur in women who inherited an altered breast-ovarian cancer gene	1	2	9
b)	A father can pass down an altered breast-ovarian cancer gene to his daughter	1	2	9
c)	All women who have an altered breast-ovarian cancer gene will get breast cancer	1	2	9
d)	A woman who does not have an altered gene can still get breast or ovarian cancer	1	2	9
e)	A woman who has an altered gene has a higher risk of ovarian cancer	1	2	9
f)	About one in ten women have an altered breast-ovarian cancer gene	1	2	9
g)	Having one's ovaries removed will definitely prevent ovarian cancer	1	2	9
h)	Early onset breast cancer is less likely to be due to an altered gene than late onset breast cancer	1	2	9
i)	A woman who has a sister with an altered breast-ovarian cancer gene has a 50% chance (1 in 2) of also having an altered gene	1	2	9
j)	Tests for ovarian cancer often do not detect a tumor until after it has spread	1	2	9
k)	A woman who has her breasts removed can still get breast cancer	1	2	9

30. I'm going to read a short list of reasons some people give for wanting genetic testing for breast-ovarian cancer risk. Please tell me how important each reason is for you. **[READ STATEMENT]** Would you say this is...not at all important, somewhat important, or very important?

		Not at all Important	Somewhat Important	Very Important	
a)	To learn about my children's risk	1	2	3	NA
b)	To make a decision about surgery to have my breasts or ovaries removed	1	2	3	NA
c)	To know if I need to get cancer screening tests more often	1	2	3	
d)	To reduce the uncertainty about my risk	1	2	3	
e)	To make decisions about having (more) children	1	2	3	NA
f)	To be reassured	1	2	3	
g)	To know if I need to take certain steps to prevent cancer	1	2	3	

31. Which of these reasons would be your most important reason for wanting to be tested? **[READ LIST]**

To learn about my children's risk.....1

To make a decision about surgery to have my breasts or ovaries removed.....2.....NA

To know if I need to get cancer screening tests more often.....3

To reduce uncertainty.....4

To make decisions about having (more) children.....5

To be reassured.....6

To know if I need to take certain steps to prevent cancer.....7

None.....8

Other_____.....9

32. Now, I'm going to read a list of reasons some people give for not wanting genetic testing for breast-ovarian cancer risk. Please tell me how important each reason is for you. **[READ STATEMENT]** Would you say this is...not at all important, somewhat important, or very important?

		Not at all Important	Somewhat Important	Very Important
a)	I am concerned about the effect it would have on my family	1	2	3
b)	I do not trust the medical community	1	2	3
c)	I do not believe that there is anything I could do to prevent getting cancer	1	2	3
d)	I am concerned that I could not handle it emotionally	1	2	3
e)	I would worry about losing my insurance	1	2	3
f)	I would worry that the results might not stay confidential	1	2	3
g)	If I tested positive, I would feel labeled or singled out	1	2	3

33. Which of these reasons would be your most important reason for not wanting to be tested? **[READ LIST]**

Concern about the effect on your family.....1
Do not trust modern medicine.....2
Do not believe there is anything I can do to prevent getting cancer.... 3
Concern about your handling it emotionally..... 4
Worry about losing your insurance.....5
Worry results not confidential..... 6
If positive, would feel labeled/singled out..... 7
None.....8
Other_____.....9

34. At this time, which of the following statements describes you best? Would you say... **[READ LIST]**

You are not considering genetic testing for breast-ovarian cancer risk..... 1

You are considering genetic testing for breast-ovarian cancer risk..... 2

You probably will have genetic testing for breast-ovarian cancer risk..... 3

You definitely will have genetic testing for breast-ovarian cancer risk..... 4

Haven't thought about it.....5

35. In your opinion, how likely is it that you have an altered breast-ovarian cancer gene? **[READ LIST]**

Not at all likely..... 1
Somewhat likely..... 2
Very likely..... 3
Definitely..... 4

36. Before this interview, how much had you read or heard about genetic testing...

		Almost Nothing	A Little Bit	A Fair Amount	A Lot
a.	for inherited disease?	1	2	3	4
b.	for cancer?	1	2	3	4

37. I'm going to read a list of comments made by some people who have cancer in their family. Please tell me how frequently these comments were true for you **during the past seven days**. **[READ STATEMENT]** Would you say this occurred...not at all, rarely, sometimes, or often?

		Not at All	Rarely	Some-times	Often
1)	I thought about it when I didn't mean to	0	1	3	5
2)	I avoided letting myself get upset when I thought about it or was reminded of it	0	1	3	5
3)	I had tried to remove it from memory	0	1	3	5
4)	I had trouble concentrating	0	1	3	5
5)	Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart	0	1	3	5
6)	I had trouble falling asleep or staying sleep, because pictures or thoughts about it came into my mind	0	1	3	5
7)	I had waves of strong feelings about it	0	1	3	5
8)	I had dreams about it	0	1	3	5
9)	I felt watchful and on guard	0	1	3	5
10)	I stayed away from reminders of it	0	1	3	5
11)	I felt as if it hadn't happened or it wasn't real	0	1	3	5
12)	I tried not to talk about it	0	1	3	5
13)	Pictures about it popped into my mind	0	1	3	5
14)	I was jumpy and easily startled	0	1	3	5
15)	Other things kept making me think about it	0	1	3	5
16)	I felt irritable and angry	0	1	3	5
17)	I was aware that I still had a lot of feelings				

about it, but I didn't deal with them..... 0.....1..... 3..... 5

18) I tried not to think about it.....0.....1..... 3..... 5

19) Any reminder brought back feelings about it..... 0.....1..... 3..... 5

20) My feelings about it were kind of numb..... 0.....1..... 3..... 5

21) I found myself acting or feeling like I was back at that time.....0..... 1.....3..... 5

MEN: SKIP TO QUESTION 44d

The next questions are about your health behaviors.

38. Have you had your breast removed?

Yes..... 1 Date: _____/_____
month year

No..... 2 → **Go to Question 39**

38a. **IF YES**, was it for prevention or treatment?

Prevention..... 1
Treatment..... 2

38b. **IF YES,** did you have one or both breasts removed?

One..... 1
Both..... 2 → **Go to Question 42**

39. How many times did you examine your own breasts in the past 3 months?

_____ times

40. Have you ever had a mammogram?

Yes..... 1
No.....2 → **Go to Question 41**

40a. **IF YES**, how old were you when you had your first mammogram?

_____ years old

40b. When was your last mammogram?

_____/_____
month year

40c. How many mammograms have you had in your lifetime?

_____mammograms

41. When was your last breast exam by a doctor or nurse?

_____/_____
month year

42. Have you had your uterus removed?

Yes..... 1 → What age? _____
No.....2

43. Have you had your ovaries removed?

Yes..... 1 → Date: _____/_____
month year

No.....2 → **Go to Question 44**

43a. **IF YES**, was it for prevention or treatment?

Prevention..... 1
Treatment..... 2

43b. Was it your right ovary, left ovary, or both?

One.....2
Both.....3 → **Go to Question 45**

44. Have you had any of the following tests to screen for ovarian cancer?

44a. CA-125 (a blood test)

Yes.....1
No.....2
Don't know or never heard of it..... 9

When was the last time you had this? _____/_____
month year

44b. Pelvic ultrasound for screening purposes, not pregnancy. **Pelvic ultrasound** (sound waves are projected onto the abdomen and an image is displayed -- your bladder has to be full).

Yes.....1
No.....2
Don't know or never heard of it..... 9

When was the last time you had this? _____/_____
month year

44c. Transvaginal ultrasound for screening purposes, not pregnancy. **Transvaginal ultrasound** (a probe is inserted into the vagina to image the ovaries -- your bladder does not have to be full).

Yes.....1
No.....2 → **go to question 45**
Don't know or never heard of it..... 9 → **go to question 45**

When was the last time you had this? _____/_____
month year

Did this test include Doppler flow color imaging?

Yes.....1 → **go to question 45**
No.....2 → **go to question 45**
Don't know or never heard of it..... 9 → **go to question 45**

FOR MEN ONLY

The next two questions are about cancer screening.

44d. Have you had any of the following tests to screen for prostate cancer?

Prostate specific antigen (PSA) (a blood test)

Yes.....1
No.....2
Don't know or never heard of it.....3

When was the last time you had this? _____/_____
month year

44e. Digital rectal examination (this is an exam where the doctor feels the prostate through the rectum).

Yes.....1
No.....2
Don't know or never heard of it..... 3

When was the last time you had this? _____/_____
month year

EVERYONE

45. Have you or your spouse ever used genetic testing or counseling before?

Yes.....1
No.....2

IF YES, did you or your spouse have.... **[READ LIST]**

	Yes	No
a) MSAFP (maternal serum alpha fetoprotein).....	1	2
b) CVS (chorionic villous sampling).....	1	2
c) Amniocentesis.....	1	2
d) Cancer risk assessment based on family history.....	1	2
e) Other (**PROBE:** Such as sickle cell or Tay-Sachs screening)_____.....	1	2

The last questions are about your background.

46. What is the date of your birth? _____/_____/_____
month day year

47. What is your race or ethnic background? **[READ LIST]**

Black or African American..... 1
Caribbean or West Indian..... 2
White/non-Hispanic..... 3
Hispanic..... 4
Asian or Pacific Islander..... 5
Native American..... 6
Other..._____ 9

48. Which of the following describes your current situation? **[READ LIST]**

Single or never married..... 1
Married, or living as married..... 2
Divorced or separated..... 3
Widowed..... 4

49. How many years of school have you completed? **[READ LIST]**

8 or less years..... 1
Some high school..... 2
High school graduate, or GED..... 3
Some college..... 4
College graduate or beyond..... 5

50. What is your religious background? **[DO <u>NOT</u> READ LIST]**

Catholic.....1
Protestant.....2
Jewish..... 3
Atheist/None.....4
Other_____..... 5

51. How strong would you say your religious or spiritual faith is? **[READ LIST]**

Not very strong..... 1
A little strong..... 2
Moderately strong.....3
Very strong.....4

52. How comforting to you are your religious or spiritual beliefs? **[READ LIST]**

Not at all comforting.....1
A little comforting.....2
Moderately comforting.....3
Very comforting.....4

53. Are you currently employed for salary or wages?

Not employed.....1
Full-time employed..... 2
Part-time employed..... 3
Retired.....4

54. What was your household income before taxes last year? **[READ LIST]**

less than $20,000..... 1
$20,001 - $35,000.....2
$35,001 - $50,000.....3
$50,001 - $75,000.....4
greater than $75,000.....5

55. Do you have health insurance?

Yes.....1
No.....2

IF YES, what type? **[READ LIST]**

Fee for service (such as Blue Cross/Blue Shield)..... 1
Health Maintenance Organization, HMO or other prepaid plan..... 2
PPO or Point of Service.....3
Military/Champus.....4
Medicaid.....5
Medicare.....6
Other _____.....9

56. Is there one particular clinic, health center, or doctor's office that you usually go to if you are sick or need health advice?

Yes..... 1
No..... 2

INVITATION FOR INDIVIDUALS AT HIGH RISK

Now I'd like to tell you about a program for individuals with a family history of breast or ovarian cancer.

[FOR THOSE INDIVIDUALS NOT IN THE AREA] I realize that you live outside of the area, but if you would ever be coming to this area and would be interested in this program, we may be able to arrange an appointment for you. Would you be interested in hearing about the program?

[PROGRAM DESCRIPTION] Because of your family history of cancer, you would be eligible to participate in our genetic counseling program. This involves 1 or 2 (or more) meetings (about 1 ½ - 2 hours duration) with a genetic counselor. She will review your family history with you in detail, tell you about approaches for cancer risk assessment, and discuss options for genetic testing and cancer prevention. There is no charge for this service. Do you think you might be interested in seeing our genetic counselor?

[IF HE/SHE WOULD LIKE MORE INFORMATION BEFORE SCHEDULING, TELL HIM/HER THAT BETH WILL CALL HIM/HER WITHIN THE NEXT COUPLE OF DAYS.]

ACCEPTS..... 1

With your permission, I will give your name to one of our genetic counselors, Beth Peshkin or Tiffani DeMarco. One of them will call you within the next couple of weeks to schedule an appointment and give you more details about the visits. We will also mail directions to you.

When is the best time to call?

Best time:_____

If we are unable to reach you, may we leave a message at home?_____ at work?_____

How did you hear about our program?_____

_____

_____

Thank you very much for your time and help in completing the survey.

DECLINES..... 2

(CARE ONLY)

We would still like to contact you for three 15-minute telephone interviews over the next 12 months. This is an important part of our study which will help us learn more about the effects of genetic testing on women's lives. Ultimately, this will help us to develop better education and counseling programs for women like yourself who have a family history of cancer.

INTERESTED..... 1 **NOT INTERESTED..... 2**

If no, may I ask why not?_____

Appendix 8: CARE written educational material

lombardi

Appendix 8

care

Cancer Assessment and Risk Evaluation

information packet

LOMBARDI
CANCER
CENTER

RESEARCH •
EDUCATION •
TREATMENT •

GEORGETOWN
UNIVERSITY
MEDICAL CENTER

CARE Program Overview

The CARE (Cancer Assessment and Risk Evaluation) Program is a genetic counseling and testing program offered by the Lombardi Cancer Center at Georgetown University Medical Center. This is a free program that is supported by research grants from the National Institutes of Health, the Department of Defense, and the Susan G. Komen Foundation.

Participation in CARE

Through the CARE Program, each participant meets with a genetic counselor to discuss:

- *a detailed family history and risk factor assessment*
- *the genetics and inheritance of breast and ovarian cancer*
- *personalized guidelines for cancer prevention and screening*
- *the options available for genetic testing for cancer susceptibility, including the pros and cons of testing (genetic testing is offered to all eligible individuals)*

The CARE program is a clinical research program. Therefore, all participants are asked to complete telephone and in-person interviews and questionnaires both before and after participation. These assessments are important to evaluate the benefits of the program, and will help us learn more about how people make decisions about genetic testing and about the impact of these decisions on their lives.

CARE Staff

The clinical staff of the CARE program includes two master's level genetic counselors and a medical director—a physician trained in medical oncology. The principal investigator of the CARE program is a behavioral scientist and clinical psychologist. These individuals work closely with other oncologists, surgeons, nurses, and psychologists at Georgetown University Medical Center to provide services and information to CARE participants.

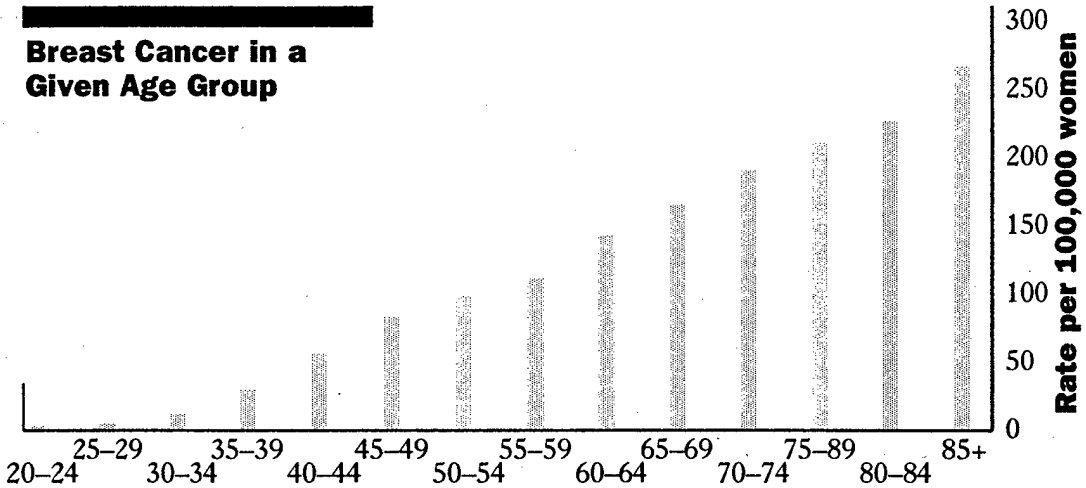
Care *info sheet*

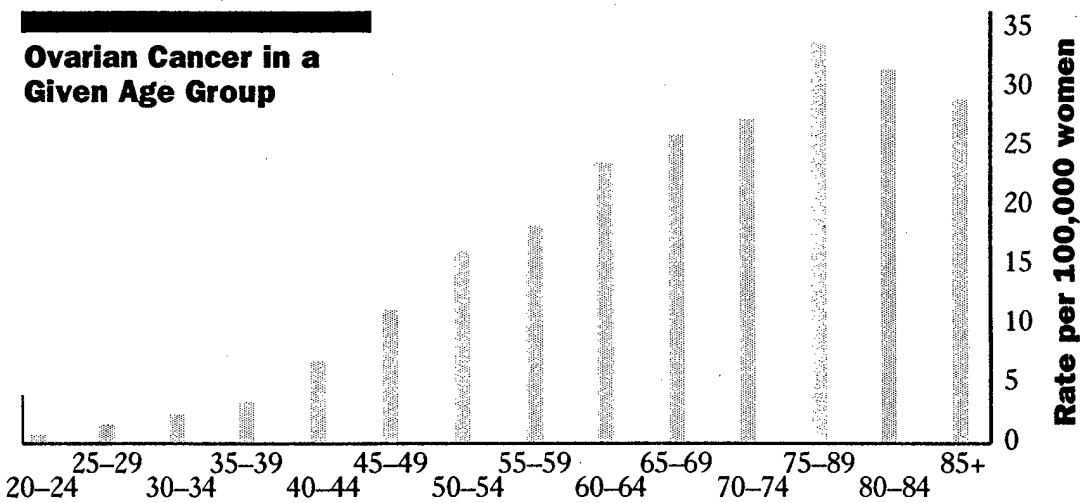
Major Risk Factors for Breast and Ovarian Cancer

All women have a risk of developing breast and ovarian cancer over their lifetimes. Breast cancer is a common disease, with over 180,000 women diagnosed every year in the United States. Ovarian cancer is a much rarer disease, which is newly diagnosed in about 24,000 women annually.

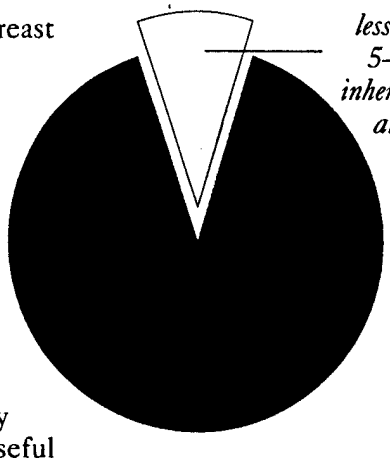
The cause of these diseases cannot be pinpointed to a single factor. Breast and ovarian cancers result from a combination of genetic (inherited) and environmental (non-inherited) factors. Key risk factors for breast and ovarian cancer are summarized below:

Age: A woman's age is the most significant risk factor for getting breast or ovarian cancer. The older a woman is, the higher her risk of developing breast or ovarian cancer. At least three-fourths of breast and ovarian cancers are diagnosed in women over the age of 50. However, women with an inherited predisposition to breast and ovarian cancer face an increased risk of developing these cancers at younger ages, such as in their 30s and 40s.





Family history: The risk of developing breast or ovarian cancer is higher among women who have one or more close relatives with these cancers. The risk may be further increased if the cancers were diagnosed at a young age, especially before menopause, or if breast cancer occurred in both breasts. Although many women with breast cancer have a close relative with this disease, only about 5–10% of women are thought to have inherited a cancer susceptibility gene, such as the BRCA1 or BRCA2 gene. Because ovarian cancer is much rarer, familial clusters are less common. A family tree constructed by the genetic counselor is a useful tool to help determine whether an individual's family history is suggestive of an inherited pattern of cancer predisposition.



Biopsy history: Most breast lumps, often called "fibrocystic disease," are benign (not cancerous). However, a breast biopsy that shows the growth of altered cells (known as atypical hyperplasia) is associated with an increased risk of developing breast cancer. This risk is further increased if a woman has a close relative with breast cancer.

Prior cancer history: Any woman who has a prior history of breast cancer has an increased risk of developing a second breast cancer (for example, in her opposite breast after a mastectomy). Women with a prior history of breast cancer also have a slight increased risk for ovarian cancer. These risks are significantly higher if a woman is found to have an alteration in a gene such as BRCA1.

Care *info sheet*

Other Risk Factors for Breast and Ovarian Cancer

In addition to a woman's age, history of breast biopsies or cancer, and family history, other factors may contribute to a woman's risk for developing breast or ovarian cancer. It is important to understand that for women with an inherited predisposition to breast or ovarian cancer, it is not known to what extent the risk factors listed below may affect risk. Studies are underway to address these issues.

Reproductive factors:

Hormonal changes related to menstruation and pregnancy may increase a woman's risk for breast cancer. These include having menstrual periods before age 12, menopause after age 55, never having children, or giving birth to a first child after age 30. A woman who has never given birth also has a somewhat increased risk for ovarian cancer.

Hormone use:

The use of birth control pills (BCPs) is not associated with a significantly elevated risk of breast cancer, although long-term use of BCPs in women under age 25 may be associated with a slight increase in the risk of developing breast cancer at a young age. However, even short-term (i.e., 6 month) use of BCPs may reduce the risk of ovarian cancer. The effect of BCPs in women with a family history of cancer suggestive of an inherited predisposition to breast or ovarian cancer is unknown. Some studies have demonstrated that long-term hormone replacement therapy (HRT), with estrogen alone or estrogen and progesterone, slightly increases breast cancer risk. It is important to remember, however, that estrogen replacement therapy may also provide other health benefits such as relief of menopausal symptoms, and protection from cardiac and bone disease (i.e., osteoporosis).

Other factors:

Based on current information, it is not clear whether high amounts of fat in the diet increase the chance of developing breast cancer; however, reducing fat in the diet can reduce the risk of other diseases and cancers. Alcohol consumption is also associated with a slight increase in breast cancer risk, and appears to be related to the amount consumed over a period of years.

Care *info sheet*

Inheritance of Cancer Susceptibility

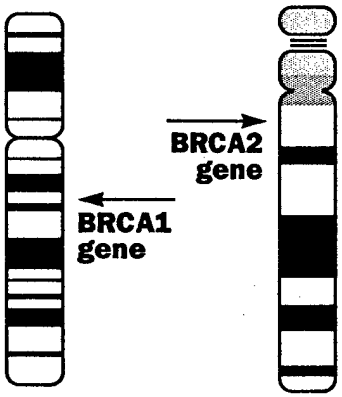
In order to better understand how an individual may inherit a susceptibility to cancer, it is helpful to know some basic concepts in genetics.

Chromosomes:

Chromosomes are found in the nucleus or control center of a human cell and are the structures on which genes are located. There are 46 individual chromosomes, or 23 different pairs, in each cell. The chromosomes are passed down, or inherited, randomly from parent to child; 23 chromosomes are passed down from the mother and 23 chromosomes are passed down from the father. Since our chromosomes are found in pairs, the genes they contain are also found in pairs.

Genes:

There are approximately 50,000 to 100,000 genes in a human cell. Genes are the blueprints or instructions that control the growth, development, and normal function of the body. Only a small proportion of our genes is associated with cancer susceptibility. When genes are working properly, our bodies are able to develop and function smoothly. However, when a gene is altered (e.g., by the addition, deletion, or rearrangement of genetic material), a normal cell function, such as cell growth, may be impaired or changed. Thus, in some instances, altered genes may result in a deformity or the development of disease. An altered gene may also result in very subtle effects. In fact, it is estimated that each individual has between 4 to 8 altered genes that have no harmful effects.



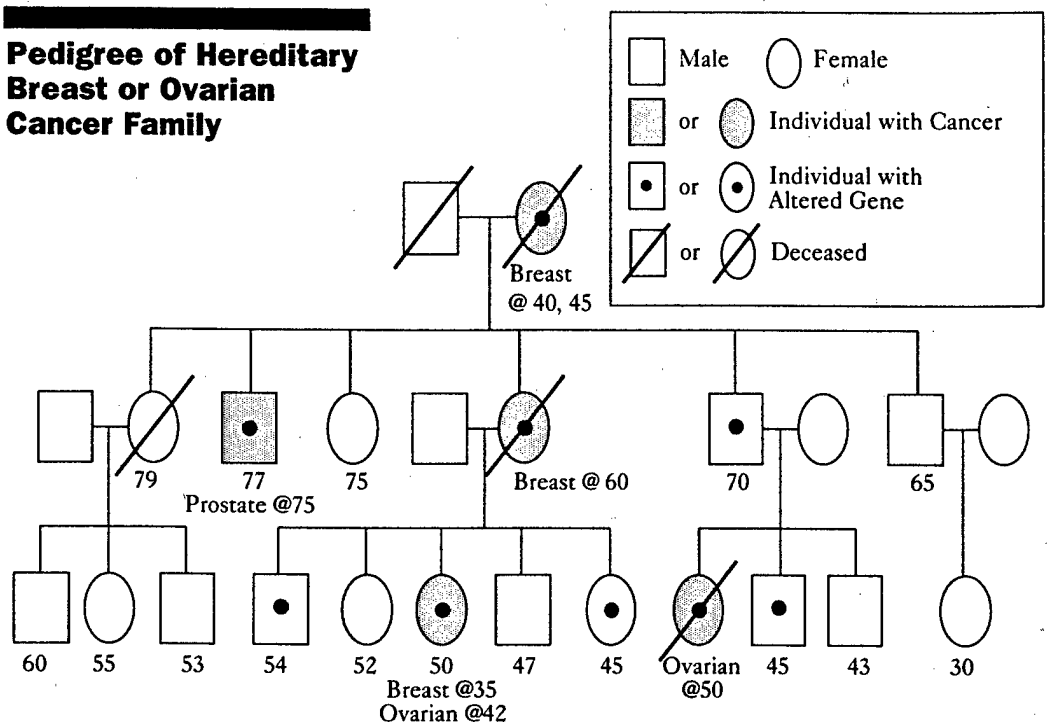
17 Chromosome 13

Dominant Inheritance:

The way that cancer susceptibility may be passed down in families is by dominant inheritance. People have two copies of every gene (one copy from each parent). Both copies of a gene pair control the same function but may vary in form from each other, since each copy is received from a different parent. An alteration or change in one copy of a gene pair can affect how the body functions even though the other copy of that gene may not be altered. In this situation, the altered gene has a dominant effect on a specific body function. Alterations in BRCA1 and BRCA2 are inherited in a dominant fashion.

In large families, this inheritance pattern may be observed clearly because there are multiple individuals in several generations affected with breast and/or ovarian cancer, often at young ages. The family tree on the following page depicts dominant inheritance of a cancer susceptibility gene, showing individuals who have inherited the altered gene, and whether they have developed cancer.

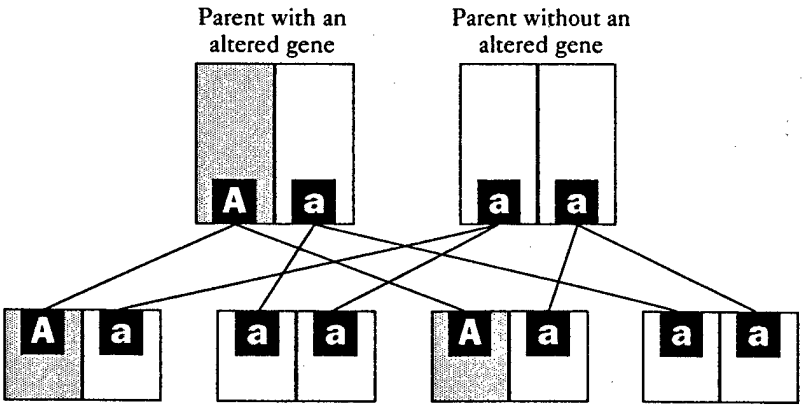
Pedigree of Hereditary Breast or Ovarian Cancer Family



An individual with a BRCA1 or BRCA2 alteration has a 50% chance of passing down that alteration to his or her children. This happens because eggs and sperm each carry only one copy of each gene pair. Thus, each child of a parent with an altered gene has a 50% chance of inheriting the altered gene and a 50% chance of inheriting the functioning gene (see below). The risk is not affected by the sex of the child or the affected parent, or by the child's birth order, and cannot be predicted based on how much a child may resemble one or the other parent.

Inheritance of a Dominant Breast Cancer Susceptibility Gene

A = Altered copy of breast cancer susceptibility gene
a = Working copy of breast cancer susceptibility gene



50% chance for each child to inherit the altered copy of the gene

Care *info sheet*

Breast Cancer Susceptibility Genes

BReast CAncer-1 (BRCA1) and BReast CAncer-2 (BRCA2) are the two major breast cancer susceptibility genes that have been identified to date. Alterations in these genes are thought to account for the majority of inherited breast and ovarian cancers. The frequency of these altered genes in the general population is not known, but one estimate suggests that BRCA1 alterations occur in up to 1 of every 800 individuals in the general population and BRCA2 alterations appear to be even more rare.

The BRCA1 and BRCA2 genes are thought to act as "tumor suppressor" genes when they are functioning properly. Tumor suppressor genes prevent cells in our body from growing out of control. However, alterations of these genes can change their usual function. This change in function can increase a person's chance of developing breast, ovarian, and some other cancers.

Hundreds of alterations have been detected in these genes. The BRCA1 and BRCA2 genes are very large. Therefore, there are many places within each gene where an alteration (mutation) can occur. However, some mutations occur much more frequently than others.

A few mutations have been found with increased frequency in specific populations. For example, a study of over 5000 Ashkenazi (Central or Eastern European) Jewish individuals in the Washington DC area revealed that about 1 in 44, or 2.3%, of the participants carried one of three alterations in the BRCA1 or BRCA2 genes. Specifically, the alterations are referred to as 185delAG and 5382insC in the BRCA1 gene and 6174delT in the BRCA2 gene. The notion refers to the place in the gene where some material was *del*eted or *ins*erted. Preliminary studies suggest that the 185delAG alteration may account for a significant proportion of breast and ovarian cancer in young Jewish women, especially breast cancer in women diagnosed at or before age 40, and ovarian cancer in women diagnosed less than age 50. Many of these women may not have a strong family history of breast/ovarian cancer. While these mutations occur mostly in Jewish families, they have also been observed in families with no known Jewish ancestry.

Research is underway to identify and characterize mutations in BRCA1 and BRCA2. This research will lead to more rapid and efficient means of genetic testing, an improved understanding of the cancer risks associated with these alterations, and more information about the function of these genes. Ultimately, these discoveries may lead to improved prevention, early detection, and treatment of cancer.

Care *info sheet*

Estimated Cancer Risks Associated with BRCA1 and BRCA2 Alterations

The risks for cancer associated with BRCA1 or BRCA2 alterations, summarized below, are based on several disease-conferring mutations. As the BRCA2 gene was identified more recently than the BRCA1 gene, there is less information about the cancer risks associated with BRCA2 alterations.

The available risks are cumulative (lifetime) and are only estimates, derived in part from studies of large families in which multiple women developed breast and ovarian cancer. However, some of the risks are derived from studies in which individuals who were tested were not selected because of a strong family history of breast or ovarian cancer. It is therefore important to note that as additional families are studied, these risks may be modified. However, it is unclear by how much these cancer risks may change.

The table on the next page summarizes estimated lifetime risks for different cancers for individuals with a BRCA1 or BRCA2 alteration as compared to the general population.

As more information becomes available, these estimates may be modified and better defined. It is also important to remember that risk varies from individual to individual and from family to family, so it is not possible to predict with certainty the type of cancer to which an individual is most susceptible or the age at which cancer may develop.

Estimated Cancer Risks Associated with BRCA1 and BRCA2 Alterations

Updated July 1997

Type of Cancer	Estimated lifetime risk in BRCA1 mutation carriers	Estimated lifetime risk in BRCA2 mutation carriers	Lifetime risk in general population
Breast cancer (female)[1]	55%-85%	55%-80%	12%
2nd breast cancer (in opposite breast)[1]	Up to 65%	Probably elevated over general population	0.5-1% a year (up to about 25%)
Ovarian cancer [1]	15%-60%	15%-20%	1.4%
Ovarian cancer after breast cancer [1]	Up to 30%-55%	Probably elevated over general population	2-3% (about twice the average risk)
Colon cancer[2]	Possible 4-fold increased risk	Possible increased risk	About 6%
Prostate cancer[3]	Increased risk, possibly up to 3-fold	Possible increased risk	Up to 19%, but includes cancers that are not clinically evident
Male breast cancer	A few reported cases	About 6%	Extremely rare
Pancreatic cancer[4]	Not increased	Associations noted	Less than 1%

[1] Early ages of onset for breast and ovarian cancer have been reported to occur frequently in women with BRCA1 or BRCA2 alterations. Whereas women in the general population often develop breast or ovarian cancer after age 50, women with BRCA1 or BRCA2 alterations have an increased risk of developing breast cancer before age 50 and throughout their lifetimes.

[2] When colon cancer has been reported in individuals with a BRCA1 or BRCA2 alteration, the ages of onset do not appear to be significantly younger than those found in the general population. The peak incidence of colon cancer occurs in men and women over age 60.

[3] Although early ages of onset for prostate cancer has been reported occasionally, in general, the ages at diagnosis do not appear to differ significantly from those noted in the general population. Prostate cancer occurs most often in men over age 60.

[4] Early ages of onset have been reported in association with pancreatic cancer; however, additional research is needed to confirm these findings. The median age of diagnosis for pancreatic cancer is age 70.

Care *info sheet*

Cancer Screening

At present, there are no long term studies that have demonstrated the best methods to screen for or prevent cancer in an individual with an alteration in the BRCA1 or BRCA2 gene. Participants in the CARE program receive individualized guidelines for cancer risk management that should be discussed with personal physicians. The following summarizes the general approaches that are now suggested.

Breast Cancer Screening:

Monitoring for breast cancer includes:
- *monthly breast self-examination*
- *frequent clinician breast exams*
- *mammography*

Women at increased risk for breast cancer may choose to undergo exams at a younger age and more frequently than women in the general population.

Ovarian Cancer Screening:

Women in the general population do not undergo routine screening to detect ovarian cancer. An annual gynecological exam, which should be a part of every woman's care, includes a Pap smear, a test used to detect cancer of the cervix, and a pelvic exam. A pelvic exam is important for detecting some problems, but it is not a sensitive method to detect ovarian cancer. Therefore, for women at increased risk of ovarian cancer, screening involves two tests in addition to pelvic exams: a CA-125 blood test and a pelvic ultrasound with color Doppler enhancement. Although these additional screening tests are available, they have not been proven to detect ovarian cancer in its early stages, when treatment is most effective. In other words, these tests can be abnormal even when no cancer is present, or can be normal when cancer is present.

Colon Screening:

All individuals (men and women) are encouraged to undergo routine screening for colon cancer beginning at age 50. Such exams include digital rectal exams and fecal (stool) blood test annually, in addition to sigmoidoscopy (an exam of the lower colon) every 3-5 years. If you have other medical conditions which might increase your risk for colon cancer, a family history of colon cancer, or an alteration in the BRCA1 or BRCA2 gene (which may also increase the risk of colon cancer), then a colonoscopy could be considered. A colonoscopy is a more extensive exam of the whole colon and enables the physician to remove polyps (growths) at the time of the exam. Your physician can help determine which procedure(s) is right for you.

Prostate Screening:

Men should have regular screening for prostate cancer, beginning at age 50, or earlier if certain risk factors exist, such as a family history of prostate cancer. Screening tests for prostate cancer include a PSA (prostate specific antigen) blood test and a digital rectal exam.

Prevention for Breast and Ovarian Cancer

Prophylactic Surgery:

Some women at increased risk for breast cancer may consider having their breast(s) removed preventively, a procedure known as prophylactic mastectomy. This procedure involves the removal of the entire breast, including the skin overlying the breast and the nipple. However, because some breast tissue remains after this surgery, there is still a small chance for a woman to develop breast cancer after having prophylactic mastectomy.

Due to the limitations of ovarian screening, women at high risk for ovarian cancer may consider having their ovaries removed, especially after childbearing is completed. This procedure is known as prophylactic oophorectomy. While this surgery significantly reduces the risk of ovarian cancer, there is still a small chance of developing an ovarian-like cancer after the ovaries are removed. Women who have had this surgery generally do not undergo screening tests for ovarian cancer, but are closely followed by their physicians.

It is important to remember that there is no right or wrong decision about getting prophylactic surgery. We know that women who undergo preventive surgery still have residual risks for cancer, and it is possible that women with an inherited susceptibility to breast or ovarian cancer may face a higher remaining risk than women without a genetic predisposition to cancer. There are many other factors to be considered before undergoing surgery, such as the effectiveness of currently available screening procedures, the type and extent of surgery that would be performed, the emotional impact of surgery, other medical implications, and financial costs. Before deciding whether to have surgery, all of these issues should be discussed in more detail with your physicians.

Chemoprevention:

Some women may be eligible to participate in studies evaluating the effectiveness of a medicine, nutritional supplement, or other substance to reduce cancer risk. For example, researchers are evaluating whether Tamoxifen, a drug used to treat breast cancer, may reduce the risk of breast cancer in healthy high risk women. As with any drug, there are possible side effects from Tamoxifen. Results pooled from several collaborating centers are expected to take a few years to obtain. It is also not known whether Tamoxifen reduces the risk of breast cancer in women with a genetic susceptibility to breast cancer. The National Institutes of Health has begun a study to determine whether a combination of Tamoxifen and a vitamin A derivative reduces the risk of breast cancer in high-risk women who have no prior history of cancer. This study is not randomized; thus all participants are guaranteed to receive the medications. Additional information about this study may be obtained through the CARE program. Other chemoprevention studies are expected to become available in the future.

Other Screening and Prevention Issues

Hormone Use:

As with every important medical decision, the relative pros and cons of using birth control pills (BCPs) or hormone replacement therapy (HRT) must be weighed very carefully. There are no data on the effects of these medications in women with a genetic susceptibility to cancer. It is therefore a good idea to consider with physicians a range of options that may provide benefits similar to those provided by taking BCPs or HRT. For example, it is important to consider what other forms of birth control may be acceptable; what non-hormonal methods are available to reduce the symptoms of menopause; what other medications or interventions may provide similar health benefits to HRT in reducing risk of heart disease and osteoporosis. Each woman must make a informed decision with which she and her doctor are comfortable.

Risk Avoidance:

All individuals are encouraged to minimize their intake of alcohol and dietary fat, refrain from tobacco smoking, and minimize sun exposure. While these measures may not reduce the risk of breast or ovarian cancer, they do have proven benefits in maintaining general good health and in reducing the risk of other cancers.

Care *info sheet*

The Process of Genetic Testing

The process of genetic testing is different from most other medical tests. A genetic test for cancer susceptibility is not diagnostic; that is, it does not reveal the presence or absence of cancer, but whether an individual has an inherited tendency or predisposition to cancer. Also, the methods used in performing genetic analysis are very complex and time consuming. Unlike most routine lab work, results from genetic testing may take several weeks or months to obtain and sometimes results may be difficult to interpret. Another difference is that most of the risks associated with genetic testing are not physical risks, but involve risks associated with how one may feel or how others, including family members, may react after learning about a genetic test result. For this reason, education and counseling before and after testing are offered as part of the CARE program.

A small blood sample is needed in order to perform genetic testing. Genetic material (DNA) is then obtained from your blood and analyzed for alterations (mutations). For a family in which a mutation has not been previously found, it is helpful to first test a blood sample from a woman with breast and/or ovarian cancer who was diagnosed at a young age. Scientists have a number of ways of looking for genetic mutations. In some instances, testing is performed in steps, whereby common mutations in a gene are looked for first. If these are ruled out, then more complete analysis of the gene is usually undertaken. The most complex type of genetic analysis is called sequencing, which means that the "chemical alphabet" of an individual's DNA is obtained and compared to DNA that is known to be "normal." The process of sequencing is comparable to looking for a single spelling mistake in a several thousand page book—a very difficult and time consuming process. Alterations include those in which some genetic material is missing, substituted, or inserted. In very rare instances, an alteration may be identified that is of questionable clinical significance (in other words, the alteration may represent a normal variation in DNA as opposed to an alteration known to be associated with increased cancer risks). Interpretation of such results is handled on a case by case basis.

Once a clinically significant alteration in the BRCA1 or BRCA2 gene has been identified in a close relative, it is easier to test other individuals in the family. Because the specific alteration in the gene is known, other individuals in the family are usually tested only for the presence or absence of that mutation. This testing can be completed in a relatively short period of time and is very accurate, providing results that are clearly positive or negative for a particular alteration.

If an alteration is not identified in a family member who has had cancer, relatives are usually not tested. This is because testing would not be expected to provide further information about their cancer risks. For example, it may be determined that the first woman to be tested within a family who has a prior history of breast cancer does not have a BRCA1 or BRCA2 alteration. This test result may be due to one of the following possibilities:

- Current methods may not be sensitive enough to detect a mutation in the BRCA1 or BRCA2 gene (e.g., the mutation may be in a part of the gene that is difficult to analyze).
- A mutation is present in a different cancer susceptibility gene for which testing was not performed.
- The individual(s) tested does not have an inherited susceptibility to cancer due to an alteration in a single gene such as BRCA1 or BRCA2.

Genetic Testing: Pro and Cons

There are potential benefits to having genetic testing, as well as potential risks of testing and limitations to the information that is obtained. Each individual needs to consider whether the potential benefits outweigh the potential risks in order to make his or her own decision about whether or not to be tested. All individuals who decide to provide a blood sample for genetic testing must sign a consent form which contains additional information about the benefits, limitations, and risks of genetic testing. Some of the major points are highlighted below.

PROS:

There are potential benefits of testing which may lead some individuals to decide to have testing for alterations in cancer susceptibility genes.

Increased knowledge: Genetic testing may provide individuals with more information about their risk for getting cancer and provide insight as to why cancer developed in themselves or their family.

Health care decisions: Information about cancer risk can facilitate decisions about whether certain screening tests should be considered and may help women decide about prophylactic surgery.

Information for other relatives: Testing may provide information about cancer risk for children, siblings, and other family members.

Emotional benefits: Learning the results of testing may produce a sense of psychological relief because uncertainty about cancer risk may be reduced.

Contribution to research: Participation in genetic counseling and testing programs will help further understanding about inherited cancer.

CONS:

There are limitations and potential risks of testing which may lead some individuals to decide they do not wish to have testing.

Difficulties in test result interpretation: Because genetic testing for BRCA1 and BRCA2 alterations is investigational, it is possible that test results will be uninformative or difficult to interpret. Genetic testing does not provide a definitive answer about an individual's risk for getting cancer.

Length of time to receive results: There is a possibility that test results will take a long time to acquire. Such a delay may make it more difficult to make decisions about cancer prevention and screening.

Discrimination: Genetic testing may place individuals at risk for discrimination by health, life, and disability insurers, as well as employers. Knowledge that you have a genetic predisposition to cancer may compromise your ability to obtain or maintain insurance coverage. At the present time, fewer than half of the states have laws restricting the extent to which genetic information may be used by health insurers. Almost all states allow life and disability insurers to ask questions about genetic predisposition to cancer and use the answers in their underwriting decisions. However, recently enacted federal legislation may help to protect those individuals who decide to undergo genetic testing. In August 1996, President Clinton signed The Health Insurance Portability and Accountability Act of 1996, which recognizes "genetic information" as protected medical information, and forbids those who provide health care coverage from using such information to deny access to individuals who must change health plans when they change jobs.

The Act also states that, based on genetic information, a group medical plan cannot require an individual to pay a premium or contribution (to get into the plan or to stay in the plan) that is greater than that for a "similarly situated" individual enrolled in that plan. The term "similarly situated" means that a plan or coverage would be permitted to vary benefits available to different groups of employees, such as full-time vs part-time or employees in different geographic locations. A limitation of the Act is that the premiums charged for individual health insurance are not restricted by the Act, and need only comply with state law. These insurance reform provisions of the Act went into effect on July 1, 1997.

The Health Insurance Portability and Accountability Act of 1996 is a major step toward gaining protection for individuals who undergo genetic testing. However, it does not address the issue of confidentiality and does not require the individual's permission to release genetic information. Although there has been no federal legislation passed regarding the areas of medical record privacy, employment, and other forms of insurance, such as life and disability, both the Senate and the House are reviewing bills that would offer additional federal protection from genetic discrimination.

The staff of the CARE program will do everything possible to protect the privacy of genetic testing results for participants in the CARE program. Each individual is identified by a unique ID number and no information about a participant of the program is released to third parties without the consent of that individual. Likewise, our research program has been issued a Certificate of Confidentiality from the Department of Health and Human Services, which allows the CARE program to withhold information about CARE participants from any outside sources, unless that individual has given written consent.

Emotional implications: Individuals who learn their test results may feel sad, angry, or anxious. Particularly when the impact on relatives or children is considered, relationships may become strained and individuals may feel guilty regarding the outcome or possible outcome of testing. Each person responds differently to information about risk and in some circumstances, psychological counseling and support may be helpful.

Family information: The correct interpretation of the test results is based on the family history provided by each participant. In gathering this information and pursuing genetic testing, it is possible that you may learn unanticipated information, such as information regarding adoption or non-paternity (i.e., that someone is not the biological father of a child).

Resources

any resources for information and support are available at Georgetown University Medical Center and in the surrounding community, as listed below:

Physicians/Professional Services at GUMC:

Lombardi Cancer Center's Comprehensive Breast Center (202) 687-2122

Offers women the keystones of breast health: instruction in monthly breast self-examination, breast examinations by a health care professional, and regular mammograms.

Lombardi Cancer Center Helplink (202) 784-4000

Cancer Information and Referral
A toll-free hotline with a registered nurse, who is certified in oncology, and will answer questions about cancer screening, diagnosis, and treatment.

Other referrals to specific physicians, nutritionists, or psychologists are provided upon request.

Other Organizations:

American Cancer Society 1-800-ACS-2345

Web page: http://www.cancer.org
A nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives from cancer, and diminishing suffering from cancer through research, education, and service.

National Alliance of Breast Cancer Organizations (212) 719-0154

Web page: http://www.nabco.org
A network of breast cancer organizations that provides information, assistance, and referrals to anyone with questions about breast cancer, and acts as a voice for the interests and concerns of breast cancer survivors and women at risk.

National Breast Cancer Coalition (202) 296-7477

Web page: http://www.natlbcc.org
A national advocacy group concerned with furthering research about breast cancer. The group is also involved in lobbying efforts for issues such as legislation to protect against genetic discrimination.

National Cancer Institute's Cancer Information Service 1-800-4CANCER

Web page: http://www.nci.nih.gov
A nationwide telephone service for cancer patients and their families, the public, and health care professionals providing up-to-date and understandable information about cancer screening, diagnosis, and treatment. Many publications are available free of charge.

Gilda's Club (212) 647-9700

Web page: http://www.jocularity.com/gilda1.html
Education and support for people with cancer and their families.

Y-ME National Breast Cancer Organization 1-800-221-2141

Web page: http://www.yme.org
National support hotline for breast cancer survivors. A large, comprehensive breast cancer support program founded in 1978 by two breast cancer patients.

Books/Publications:

Krause, C. **How Healthy is Your Family Tree? A Complete Guide to Tracing Your Family's Medical and Behavioral History.** New York: Simon and Schuster. 1995. A helpful guide to gaining vital information about your family history.

What You Need to Know Series: Breast, Ovarian, Colon, and Prostate Cancer. Free publications from the National Cancer Institute's Cancer Information Service explaining the symptoms, diagnosis, and treatment of these cancers.

Understanding Genetic Testing. Free booklet by the National Cancer Institute providing information about gene testing. This booklet also provides answers to frequently asked questions about the potential risks and benefits of genetic testing.

Web Sites:

Breast Cancer Information Clearinghouse
http://nysernet.org/bcic
The purpose of this webserver is to provide information for breast cancer patients and their families. It is maintained as a partnership of organizations which provides information about cancer to the public.

The Breast Gene and BRCA123 Information Directory
http://www.ncgr.org/gpi/bc_pg_front.html
The National Center for Genome Resources' Genetic and Public Issues Program has complied this page to help people understand recent developments in genetic testing related to breast cancer.

Cancer Net
http://cancernet.nci.nih.gov
A service of the National Cancer Institute's International Cancer Information Center which provides current information on cancer.

Oncolink
http://www.oncolink.upenn.edu
A multimedia cancer information resource developed and maintained by the University of Pennsylvania Cancer Center.

The Gene Letter
http://www.geneletter.org
The U.S. Department of Energy has awarded the Shriver Center a 2 year grant to develop and generate an electronic newsletter about genetics and public policy. The major purpose of the Gene Letter is to inform consumers and professionals about advances in genetics and to encourage discourse about emerging policy dilemmas.

Legislative information on the Internet
A service of the Congress through its library
http://www.thomas.loc.gov

GEORGETOWN

The Art of Medicine

NCI CCC

A Comprehensive Cancer Center Designated by the National Cancer Institute

Appendix 9: CARE newsletter

Appendix 9

GEORGETOWN UNIVERSITY MEDICAL CENTER

LOMBARDI CANCER CENTER
Research • Education • Treatment

CANCER GENETICS

2233 WISCONSIN AVENUE NW
SUITE 535
WASHINGTON, DC 20007-4104
TELEPHONE: (202) 687-0802
FAX: (202) 687-0820

Offices in
Washington, DC
Rockville, MD
Arlington, VA

CARE NEWSLETTER

VOLUME 2, NUMBER 1
Spring/Summer 1997

RESEARCH UPDATE

The May 15, 1997 edition of the *New England Journal of Medicine* contained several important articles about hereditary breast and ovarian cancer. Two of these articles are summarized in this newsletter. First, Dr. Jeffrey Struewing and his team from the National Institutes of Health reported the results of their study of genetic testing offered to over 5,000 Ashkenazi (Central or Eastern European) Jews in the Washington, DC area. These men and women were invited to receive genetic testing for three alterations in the BRCA1 and BRCA2 genes. Because identifying information was removed from the samples, participants were not able to receive their genetic test results. The goals of the study were twofold: 1) to determine how many Jewish individuals have one of three alterations in the BRCA1 and BRCA2 gene that have been found to occur with increased frequency in this population (specifically, the 185delAG and 5382insC alteration in BRCA1 and 6174delT in BRCA2); and 2) to determine the cancer risks in those who carry an alteration.

The study found that about 1 in 44, or 2.3% of the participants carried one of the three BRCA1 or BRCA2 alterations, although only one-fourth of the volunteers had a history of breast or ovarian cancer themselves or in a close relative. Another interesting finding was that the risks of cancer associated with the three alterations did not appear to be significantly different from one another. There had been reports, for example, that the 6174delT alteration was associated with a lower breast cancer risk than other BRCA2 alterations and that the ovarian cancer risk associated with BRCA2 was different (i.e., lower) than that observed for BRCA1 alterations. The investigators determined that the average risk of breast cancer by age 70 for alteration carriers was 56%–much higher than for non-carriers, but below previous estimates of up to 85%. By age 70, the average risk of ovarian cancer associated with these alterations was 16%, which is higher than the general population risk of about 1.5% but is well below the 40-60% risk quoted for BRCA1 (the risk of ovarian cancer for BRCA2 has been previously reported as 5-20%). In addition, the average lifetime risk of prostate cancer was 16%, which was much higher than for non-carriers; however, the risk of colon cancer in men and women did not appear to be elevated over the general population.

While these findings are significant, it is important to consider some of the limitations of this study. For example, as the family histories of the participants were not verified by review of medical records, it is possible that some of the information provided may not have been accurate. In addition, the population studied was not selected because of a strong family history. Therefore, in certain high-risk families, the

cancer risks may be higher than those quoted in this study. In fact, the risk of cancer for an individual carrier may be higher or lower than the estimated "average" risks based on a number of factors, including family history. For example, cancer risks associated with BRCA1 or BRCA2 alterations may be higher in families in which many individuals have developed breast and ovarian cancer. Additional research will be needed to identify other specific factors that influence an individual's risk. It is also not clear whether the cancer risks conferred by these three alterations will be the same for other BRCA1 or BRCA2 alterations, or for non-Jewish persons. In any case, it is clear that the breast and ovarian cancer risks identified in this study, while lower than what was predicted, are still much higher than what is noted in the general population. Therefore, it is critical that an individual's risk be assessed within the context of his or her medical and family history to determine how a genetic test result may affect medical management decisions. Further research is ongoing to study the impact environmental factors have on risk, as well as the level of effectiveness of different measures for early detection and prevention.

In another article, researchers at the University of Pennsylvania reported that among 169 women with breast cancer and a family history of breast and/or ovarian cancer, only 27, or 16%, had an alteration in the BRCA1 gene. This percentage is lower than the 45% predicted; however, it is important to bear in mind that as additional individuals undergo testing, this estimate may change. In Georgetown University Medical Center's CARE (Cancer Assessment and Risk Evaluation) Program, we have also noted that several women from high-risk families have tested negative for alterations in the BRCA1 <u>and</u> BRCA2 genes. Together, these findings suggest that there is likely to be another significant, as yet unidentified, breast cancer gene that contributes to hereditary breast cancer. However, in a small number of cases, it is also possible that an alteration exists in the BRCA1 or BRCA2 gene that was not able to be detected by current testing methods. In some families, it is likely that alterations in a single gene will not be able to account for the family history of cancer. Ultimately, additional studies looking at the frequency BRCA1 or BRCA2 alterations will help us to provide better counseling to an individual about the likelihood that an alteration may be identified in his or her family and can help individuals make more informed decisions about testing.

In other research developments, preliminary data from the Mayo Foundation suggest that prophylactic mastectomy (preventive removal of the breasts) significantly reduces the risk of breast cancer in high-risk women. This study is among the first to categorize women's risk based on their family history. Although genetic testing was not part of the study, it is certainly possible that some of the women in this high risk group who opted for surgery did come from families who have a BRCA1 or BRCA2 alteration. Of women who had a very strong family history and who had their breasts removed, 28 were expected to develop breast cancer over the course of the study (about 30 years); however, only two women developed breast cancer. This represents a significant, but not total, reduction in breast cancer risk.

In general, it is important for any woman who is considering preventive surgery to consider her options very carefully and in the context of what is known and what is not known in the present day. Women choose surgery for many reasons, including their own medical history, their family history, and genetic testing results. However, these reasons are also weighed in combination with a woman's anxiety about developing cancer versus the potential limitations of the surgery. There is no right or wrong answer about the decision as to whether surgery should be pursued–it is indeed a very personal choice.

Other than prophylactic surgery, another option for risk reduction in high risk women is participation in what is referred to as a "chemoprevention trial." Many of you are aware that the largest study of chemoprevention for breast cancer involved a drug called "Tamoxifen." This medication, which is used to treat women with breast cancer, was also being evaluated for its protective effects in healthy high risk women. This trial, which was available at Georgetown, closed as of May 1997. Results are expected to take

several years to obtain. However, the National Institutes of Health has begun a study to determine whether a combination of Tamoxifen and a vitamin A derivative reduces the risk of breast cancer in high-risk women who have no prior history of cancer. This study is not randomized; thus, all participants are guaranteed to obtain the medications. There are strict eligibility criteria for entry into this study, but if you have an alteration in the BRCA1 or BRCA2 gene you may be eligible for participation. For more information about this trial, you may call Ms. Beverly Meadows, toll free, at 1-888-624-1937.

LEGISLATIVE NEWS

With the current media attention given to cancer susceptibility testing for BRCA1 and BRCA2, there has been an increasing concern about the impact of genetic testing on an individual's insurability. The possibility of discrimination may make one apprehensive about the prospect of genetic testing and may even be a deterrent to having testing. These concerns were addressed in a recently published study by Lapham et al. at Georgetown University, in which 332 members of genetic support groups shared their experiences with genetic discrimination. The study reported that 25% of respondents believed they were refused life insurance, 22% believed they were refused health insurance, and 13% believed they were denied or let go from a job as a result of genetic testing. Although this study was not specifically looking at genetic testing for cancer susceptibility, it illustrates that it may be possible for discrimination to occur as a result of genetic testing.

It is important to be aware that undergoing genetic testing may place one at risk for discrimination by employers, as well as by health, life and disability insurers. Despite the fact that fewer than half of the states have laws restricting the extent to which genetic information may be used by health insurers, in 33 states, there are approximately 70 bills currently under consideration that would limit access to and use of genetic information by employers and insurers. And even though almost all states allow life and disability insurers to ask questions about genetic predisposition to cancer and use the answers in their underwriting decisions, recently enacted federal legislation may help to protect those individuals who choose to have genetic testing.

In August 1996, President Clinton signed the Health Insurance Portability and Accountability Act of 1996 into federal law. Also known as the Kennedy/Kassebaum Health Insurance Act (in honor of its two primary sponsors), this law recognizes "genetic information" as protected medical information and forbids those who provide health care coverage from using such information to deny access to individuals who must change health plans when they change jobs or move to a different state. The Act also states that, based on genetic information, a group medical plan cannot require an individual to pay a premium or contribution (to get into the plan or to stay in the plan) that is greater than that for a similarly situated individual enrolled in that plan. One limitation of the Act is that the premiums charged for individual health insurance are not restricted by the Act, and need only comply with state law. These insurance reform provisions of the Act are effective as of July 1, 1997.

The Health Insurance Portability and Accountability Act of 1996 is a major step toward gaining protection for individuals who undergo genetic testing and sets the first standard for prevention of genetic discrimination by Congress. Nonetheless, it does not address the issue of confidentiality and does not require the individual's permission to release genetic information. Although there has been no federal legislation passed regarding the areas of medical record privacy, employment, and other forms of insurance, such as life and disability, both the Senate and the House are reviewing bills that would offer additional federal protection from genetic discrimination. The most recent of these bills, the Genetic Confidentiality and

Nondiscrimination Act of 1997, was introduced to the Senate on March 11, 1997 by Senator Pete Domenici of New Mexico. The main purposes of this Act include defining the circumstances under which genetic information may be created, stored, analyzed, or disclosed; defining the rights of individuals and persons with respect to genetic information; identifying the responsibilities of others with respect to genetic information; protecting individuals and families from genetic discrimination; establishing uniform rules that protect individual genetic privacy; and establishing effective mechanisms to enforce the rights and responsibilities outlined in the Act.

As there are few laws currently in place to protect individuals from genetic discrimination, we have taken some further precautions to try to ensure confidentiality of study participants. In order to maintain the privacy of genetic testing results for participants in the CARE program, each individual is identified by a unique ID number and no information about a participant of the program is released to third parties without the consent of that individual. Our research program has also been issued a Certificate of Confidentiality from the Department of Health and Human Services. The Certificate allows the CARE program to withhold information about CARE participants from any outside sources, even under subpoena, unless that individual has given us written consent to release such information. It is evident that more federal and state legislation is needed to protect our society from genetic discrimination; however, given the deficiency of legal protection at present, the staff of the CARE program will do everything possible to maintain the privacy and confidentiality of all participants.

To find out more or to become more involved in legislative issues, the following resources are available:

Legislative information on the Internet
A service of the Congress through its library
http://www.thomas.loc.gov/

The National Breast Cancer Coalition
1707 L Street, NW, Suite 1060
Washington, D.C. 20036
(202) 296-7477 voice
(202) 265-6854 fax
http://www.natlbcc.org/

Newsletter Staff:

Beth N. Peshkin, MS, CGC
Senior Genetic Counselor
Jeri Reutenauer, MS
Genetic Counselor
Claudine Isaacs, MDCM
CARE Medical Director

Caryn Lerman, PhD
Director, Cancer Genetics Program
Kristen Willard, BA
Data Specialist
Marnie Reed, BA
Research Associate

Project 2: A Coordinated Approach to Breast Cancer Diagnosis

Appendix 1: NIH Biosketch for Susan M. Ascher, MD

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Susan M. Ascher, M.D.	Associate Professor of Radiology

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Union College, Schenectany, New York, NY	BS	1977-1981	Chemistry/Art History
St. Lukes-Roosevelt Medical Center, New York, NY	Intern	1986-1987	Internal Medicine
Yale-New Haven Hospital, New Haven, CT	Resident	1987-1990	Diagnostic Radiology
Georgetown University Hospital, Washington, D.C.	Fellow	1990-1991	Abdominal Imaging

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

Professional Experience:

1991 - 1996	Assistant Professor of Radiology, Georgetown University Medical Center
1996-Present	Associate Professor of Radiology
1991-1996	Associate Director, Body MRI, Georgetown University Medical Center , Washington, D.C.
1997-Present	Director, Body MRI, Georgetown University Medical Center , Washington, D.C.
1992-Present	Siemens Body MRI Research Group (Head, Pelvic Section)

Publications:

Zeman RK, Silverman PM, Cooper C, Weltman DI, Ascher SM, Patt RH. Helical (Spiral) Computed Tomography: Implications for Imaging of the Abdomen. Gastroenterology Clinics of North America. 1995; 24:1-25

Ascher SM, Agrawal R, Bis KG, Brown ED Maximovich A, Markham SM, Patt RH, Semelka RC. Endometriosis: Appearance and Detection with Conventional, Fat Suppressed, and Contrast Enhanced Fat Suppressed, Spin Echo Techniques. Journal of of Magnetic Resonance Imaging. 1995; 5:251-257

Zeman RK, Silverman PM, Ascher SM, Patt RH, Cooper C, Al-Kawas F. Helical CT of the Pancreas and Biliary Tract. Radiologic Clinics of North America. 1995; 33:887-902

Hines JF, Tucker A, Grendys EC, Ascher SM, Barter JF. Case Report: Spontaneous Preoperative Internal Jugular and Subclavian Vein Thrombosis Associated with an Early-Stage Synchronous Ovarian/Endometrial Malignancy. Gynecologic Oncology 1995; 56:298-301

Ascher, M.D., Susan M., Biographical Sketch, Page 2
<Publications, Continued>

Schlund JF, Kenney PJ, Brown ED, Ascher SM, Brown JJ, Semelka RC. Adrenocortical Carcinoma: MR Imaging Appearance with Current Techniques. Journal of Magnetic Resonance Imaging 1995; 5:171-174

Arnold LL, Ascher SM, Schruefer JJ, Simon JA. The Nonsurgical Diagnosis of Adenomyosis. Obstet gynecol 1995; 86:461-465

Zeman RK, Berman PM, Silverman PM, Cooper C, Garra BS, Patt RH, Ascher SM. Biliary Tract: Three-Dimensional Helical CT Without Cholangiographic Contrast Material. Radiology 1995; 196:865-867

Ascher SM, Johnson JC, Barnes W, Bae CJ, Patt RH, Zeman RK. Spin Echo and Dynamic Contrast Enhanced Gradient Echo Imaging of the Uterus with Histopathologic Correlation in Postmenopausal Women Receiving Tamoxifen Therapy. Radiology 1996; 200:106-110

Semelka RC, John G, Kelekis NL, Burdeny DA, Ascher SM. Small bowel neoplastic disease: Demonstration by MRI. J of Magn Reson Imaging 1996; 6:855-860

Semelka RC, Hricak H, Kim B, Forstner R, Bis KG, Ascher SM, Reinhold C. Pelvic Fistulas: A Multi-Institutional Study Examining Appearances on T1, T2 and Intravenous Gadolinium Enhanced T1 Weighted MR Images. Abdominal Imaging 1997; 22:91-95

Semelka RC, Kelekis NL, John G, Ascher SM, Burdeny D, Siegelman ES. Ampullary Carcinoma: Demonstration by Current MR Techniques. JMRI 1997; 7:153-156

Burdeny DA, Semelka RC, Kelekis NL, Reinhold C, Ascher SM. Small (<1.5 cm) Angiomyolipomas of the Kidney: Characterization by the Combined Use of In-Phase and Fat-Attenuated MR Techniques. Magnetic Redsonance Imaging 1997; 15:141-145

Presentations:

Khana A, Patt RH, Rajan SS, Ascher SM, et al. High Resolution 3-D Dynamic Breast MR: Findings in 28 Suspicious Lesions. Presented at the Southern Medical Association 87th Annual Meeting, October 28-31, 1995.

Patt RH, Rajan SS, Ascher SM, et al. Optimization of Techniques for Dynamic MR Imaging of the Breast. Scientific Exhibit at the Radiological Society of North America Annual Meeting, November 27-December 3, 1993. Chicago, IL.

Project 3: Development of Novel Antiangiogenic Therapies in Metastatic Breast Cancer

Appendix 1: TNP-470 Pilot Trial 1
Appendix 2: Thalidomide protocol documentation

Appendix 1: TNP-470 Pilot Trial 1

GEORGETOWN UNIVERSITY Date: June 23, 1997

To: **Dr. Michael Hawkins**
Hematology/Oncology

From: **Elisabeth O. Crigler** loc
Executive Officer
Institutional Review Board

Subject: **Action on your protocol entitled: "A Phase I Study of 120-Hour Continuous Infusion of TNP-470 in Patients with Advanced Cancer" (97-150)**

Your above referenced protocol and consent form were approved by the Institutional Review Board at its meeting of May 15, 1997 contingent upon the receipt and approval of a revised consent form.

Your revised consent form has been approved, and you are now authorized to commence your project. However, for those investigators whose project is funded by an outside sponsor, sponsor grant or contract agreements must be reviewed and approved by the Office of the Dean of Research and Graduate Education and the Office of Sponsored Programs before the project may commence.

Promptly report any unexpected or otherwise significant adverse effects encountered in the course of this study to the Institutional Review Board within 72 hours. This includes information obtained from sources outside Georgetown that reveals previously unknown risks from the procedures, drugs or devices used in this study.

Please refer to this date and the protocol number listed above when making inquiries concerning this study.

RECEIVED
JUN 24 1997
PROTOCOL OFFICE

C41997-009

A PHASE I STUDY OF 120-HOUR CONTINUOUS INFUSION OF TNP-470 IN PATIENTS WITH ADVANCED CANCER

Study Chairman:
Michael J. Hawkins, M.D.
Director, Developmental Therapeutics Program
Associate Professor of Medicine and Pharmacology

Co-Investigators:
John Marshall, M.D.
William Dahut, M.D.
Naiyer Rizvi, M.D.

Clinical Research Fellow
Pankaj Bhargava, M.D.

Biostatistics
Edmund Gehan, Ph.D.

RECEIVED
MAR 27 1997
PROTOCOL OFFICE

Lombardi Cancer Center
Georgetown University Medical Center
3800 Reservoir Road NW
Washington, D.C. 20007

March 21, 1997

☐ Approved DATE: 4/9/97
☒ Approved w / modifications

☐ Disapproved

Chair. Clinical Research Committee

PROTOCOL SUMMARY

Eligibility Criteria:

Age ≥ 18
Histologically proven malignancy
No effective alternate therapy
ECOG performance status 0, 1, or 2
Normal hematologic, hepatic and renal function
Signed informed consent
Recovered from side-effects of previous therapies

Ineligibility Criteria:

Recent major surgery (≤ 21 days)
Frequent vomiting/poor alimentation
Recent history of weight loss (> 10% of current body weight)
Pregnant or lactating

Evaluations:

Pretreatment:

History and Physical Exam
Height and Weight
Performance Status
CBC, diff, platelet count
Serum Electrolytes,Chemistry Survey, SGPT
Urinalysis
Stool guiac
EKG
Ophthalmologic Examination
CT scan of the brain
Pregnancy Test (in women with child bearing potential)
Tumor assessment (in patients with measurable or evaluable disease)

While on study:

Days 1 and 5: TNP-470 pharmacokinetics
Days 1 and 5: 24 hour urine collections for TNP-470 levels
Days 8, 15 and 22 then q 2 weeks if no abnormalities on day 22:
- Weight
- Performance Status
- CBC, diff, platelet count
- Serum electrolytes
- Chemistry Survey

Treatment:

TNP-470 by continuous I.V. infusion (over 120 hours) once every 3 weeks. In the absence of toxicity, may be given once every 2 weeks.

Treatment continues until:

Rapid progression (≥ 50%) of measurable disease in first month → off study
Any progression (≥ 25%, new mets) after 1st month → off study

TABLE OF CONTENTS

		Page
1.	BACKGROUND	1
2.	OBJECTIVES	9
3.	PATIENT ELIGIBILITY	9
4.	STUDY PARAMETERS	11
5.	PHARMACEUTICAL DATA	11
6.	TREATMENT PLAN	14
7.	PHARMACOKINETICS	15
8.	TREATMENT MODIFICATIONS AND MANAGEMENT OF TOXICITY	16
9.	TOXICITY MONITORING AND ADVERSE EXPERIENCE REPORTING	17
10.	CRITERIA FOR TERMINATING TREATMENT	19
11.	STATISTICAL CONSIDERATIONS	19
12.	RESPONSE ASSESSMENT	20
13.	DATA REPORTING	21
14.	REFERENCES	22
APPENDIX A:	CONSENT FORM	A-i
APPENDIX B:	NCI COMMON TOXICITY CRITERIA	B-1

A STUDY OF TNP-470 IN PATIENTS WITH ADVANCED CANCER

1. BACKGROUND AND RATIONALE

1.1 Tumor induced angiogenesis. One unique property makes endothelial cell proliferation a promising target for the chemotherapy of malignant growth: In the adult the only physiologic conditions which require endothelial cell proliferation are wound healing and the reproductive cycle (**1,2,3**). Endothelial cell proliferation in a growing primary tumor can thus be targeted with high selectivity. Animal studies have given the best insight into the selective tumor-induced endothelial cell proliferation *in vivo*. In rats bearing experimental tumors, up to 80% of endothelial cells in the tumors incorporated ^{3}H-thymidine *in vivo*. Less than 5% of endothelial cells in normal tissues of the same animals showed uptake of the radiolabel (2,3,**4**). This selective endothelial cell proliferation in tumors should make selective inhibitors very effective anti-cancer drugs with only few systemic effects on the host (for a review see references **5** and **6**).

Polypeptide growth factors released from tumor cells are believed to trigger host endothelial responses and induce neoangiogenesis in the progressing tumor (1,7,**8**). It has been shown in numerous studies with different approaches, that a solid tumor can not grow beyond two millimeters in diameter without recruiting new blood vessels (**9**). The clinical significance of tumor angiogenesis and its close relation to overall prognosis and metastasis has been demostrated in a recent study in breast cancer patients (**10**). This study showed that the number of stained microvessels in a given specimen was directly proportionate to metastatic progression of the respective tumor. Furthermore, local progression from normal tissue to carcinoma in situ and finally invasive tumors was reflected in an increase in stainable microvessels. This corroborates our *in vitro* findings with cancer cell lines and in tumor models (**11**).

The endothelial cell proliferation in tumors is thought to be induced by polypeptide growth factors (1,18, 20, 7). Amongst these, heparin-binding growth factors (HBGFs) from the FGF-family have been shown to be the most efficacious endothelial stimulators *in vitro* as well as inducers of angiogenesis *in vivo* (9,**12,13,14**). In addition, we have recently shown that a novel HBGF, pleiotrophin (*PTN*) is an endothelial cell stimulating factor expressed at high levels in cell lines from human melanoma, breast cancer and prostate cancer (**15**). This gene is unrelated to the FGF-family and was originally shown to be a developmentally regulated, heparin-binding, neurite growth factor (**16,17**).

1.2 TNP-470

1.2.1 Pharmacology. TNP-470, an angiogenesis inhibitor, is a synthetic analogue of fumagillin, a natural product secreted by the fungus *Aspergillus fumigatus* fresenius. Studies demonstrating fumagillin's angioinhibitory activity were initiated in the laboratory of Judah Folkman, M.D., following observations of morphological changes in endothelial cell cultures inadvertently contaminated by this fungus. The results of these studies confirmed that fumagillin inhibited endothelial cell proliferation *in vitro* as well as angiogenesis and tumor growth *in vivo*. However, severe weight loss in laboratory animals following prolonged administration of fumagillin precluded its further development. A collaborative agreement between Harvard University and Takeda Chemical Industries, Ltd. resulted in the synthesis

by Takeda scientists of a series of less toxic analogues, termed angioinhibins. Of these, [*O*-(chloroacetyl carbamoyl)] fumagillol or AGM-1470, now referred to as TNP-470, was among the most potent identified.(**18**)

Under stable conditions, endothelial cells, which form the innermost layer of the vasculature, are in a quiescent state; i.e., in the G_0 phase of the cell cycle. However, endothelial cells are capable of responding to growth factors (e.g., bFGF, PD-ECGF, VEGF, TGFα and TNFα) in their microenvironment, resulting in the formation of new blood vessels. This process, angiogenesis or neovascularization, is a necessary component of wound healing, development, and reproduction. Angiogenesis also plays a critical role in pathological processes, e.g., tumor growth (primary and metastases), and it is this aspect of angiogenesis that the design of this clinical trial addresses.

In vitro, TNP-470 inhibits endothelial cell proliferation, migration and capillary tube formation in response to bFGF at doses far less than those required for inhibition of these activities in tumor cells. Specifically, TNP-470 reversibly inhibits endothelial cell proliferation in response to bFGF with an IC_{50} in the picogram range, while cytotoxicity is not observed until the dose of TNP-470 exceeds 10 μg/mL.(18, 19, 20)(**19,20**) *In vitro*, most tumor cell lines respond only to doses of TNP-470 in the microgram range or greater.(18, 19, 20) Several human glioblastoma cell lines are exceptions, however, demonstrating an IC_{50} that approximates that of endothelial cells.(**21**)

In vivo, TNP-470 inhibits angiogenesis in response to exogenous bFGF in several model systems, including embryonic chick chorioallantoic membrane (CAM), rat dorsal air sac, rat and rabbit corneal micropocket assays, and surgically implanted sponges.(19) Administration of TNP-470 (sc, ip, iv or ia) results in decreases in tumor vascularity, growth of primary tumor, and numbers/size of metastases, as well as increased survival in a variety of rodent (homograft and xenograft) systems. (**22,23,24**) Of special interest is the observation that TNP-470 demonstrates anti-tumor activity against several human tumors (colon, prostate, breast, glioblastoma, and fibrosarcoma) implanted in nude mice.(18, 19, 20) Further, synergism is observed when TNP-470 is co-administered with minocycline and/or cytotoxic therapies.(**25,26**)

The observation of *in vivo* antitumor activity (i.e., reduction in growth of primary tumor, decreased numbers/size of metastases, and decreased vascularity) in the absence of similar *in vitro* activity suggests that TNP-470 directly exerts its influence on endothelial cells, not on tumor cells. This is in agreement with the hypothesis proposed by Folkman that tumor growth beyond a minimal diameter of 1 to 2 mm is angiogenesis-dependent, requiring the ingrowth of newly formed capillaries into the tumor.(**27**)

Studies of TNP-470's molecular mechanism of action are ongoing, and the findings that follow are preliminary. Time course studies suggest that TNP-470 affects processes that occur late in G_1, but prior to the transition to S phase, and that the

degree of inhibition is related to the length of exposure to TNP. Differential sensitivity to TNP is observed among normal endothelial cells, depending on their anatomical source, and transformed endothelial cells appear resistant to TNP-470's antiproliferative effects.(**28**) TNP does not interact directly with DNA, and does not inhibit expression of early response genes. Within G_1, TNP-470 has been shown to inhibit expression of specific cyclins, activation of cyclin-dependent kinases, and phosphorylation of RB protein.(**29,30**)

1.2.2 **Metabolism.** Initial metabolism studies with TNP-470 indicate the compound is rapidly and extensively metabolized. Although numerous metabolites have been observed, only two have been characterized. Metabolite AGM-1883 (M-IV) is formed following cleavage of the chloroacetyl moiety of TNP-470, which is then further metabolized by hydrolysis of the epoxide rings to metabolite M-II. Radiolabeled metabolism studies in which [^{3}H]TNP-470 was administered intravenously (iv) (5 mg/kg) to rats and dogs resulted in apparent half-lives based on total radioactivity levels of 0.4 and 48 hours in the rat and 1.1, 6.7, and 77 hours in the dog. Total radioactivity $AUC_{(0\text{-}168\ h)}$ values from these studies averaged 18.5 μeq•h/mL for the rat and 22.5 μeq•h/mL for the dog. Analysis of both rat and dog plasma extracts by HPLC with radioactive detection showed that the majority (>90%) of the radioactivity was present as uncharacterized components, with only trace amounts of unchanged TNP-470 detectable. In the rat, the major route of excretion was via the feces, with 67% of the administered radioactivity recovered in the feces during the 6 days following administration of [^{3}H]TNP-470. Nearly all of the remaining radioactivity (31%) was eliminated with the urine. In the dog, renal excretion was much more significant, with 73% of the administered radioactivity eliminated in the urine during the 4 days following administration and most of the remaining radioactivity (24%) excreted with the feces. Tissue distribution studies with [^{3}H]TNP-470 in the rat indicate that radioactivity was distributed rapidly and widely into the tissues following a single 5 mg/kg intravenous dose. Generally, the maximal concentrations of radioactivity in each tissue were detected at 5 minutes following administration (kidney, 58 μg eq/g; lung, 16 μg eq/g; blood, 14 μg eq/g; thyroid, 13 μg eq/g; liver, 12 μg eq/g) after which the levels in most tissues, with the exception of blood, declined fairly rapidly. *In vitro* protein binding studies of [^{3}H]TNP-470 at concentrations from 0.01 to 1 μg/mL indicate it was moderately protein bound in rat (56.3-57.5%), dog (63.1-64.0%), and human (77.1-77.4%) plasma.

Table II: Summary of toxicology of 120 hours Continuous IV infusion studies of TNP-470 in dogs.

1.2.3 Preclinical Toxicology Studies

Fourteen- and 28-day toxicology studies were performed with intravenous administration of TNP-470 to rats. Rats were administered either 6 mg/kg, 20 mg/kg or 60 mg/kg as a

single iv dose every other day (qod) for 14 days. Although there were no deaths, the rats receiving 20 mg/kg and 60 mg/kg suffered 4-12% and 25-29% losses in body weight, respectively. Dose-related decreases in WBCs and platelets were also seen in all dose groups. At necropsy, lesions were seen in the thymus, spleen and adrenal glands at the highest dose levels. Microscopic lesions (microhemorrhages) were also seen in this group in the bone marrow, thymus, spleen and liver. Renal tubular vacuolization was seen at the highest dose; however, these changes were felt to be secondary to the cyclodextrin vehicle. A second study in rats evaluating a 28-day qod administration of TNP-470 was performed. Doses of the drug were 3, 6, 20, and 40 mg/kg iv. Neurotoxicity consisting of seizures and increased startle response were seen at the highest dose levels and there was one death on Day 15 in the 40 mg/kg group. Dose-related losses in body weight were seen in all groups except for the lowest dose level. Decreases in WBCs and platelets were also seen in the two highest group levels. At necropsy, lesions were again seen in the thymus, spleen, prostate and gonads in the 20 mg/kg and 40 mg/kg dose groups. Histopathology revealed lymphoid depletion in the spleen, thymus, lymph nodes, and bone marrow in the highest dose group. Again, renal vacuolization, thought to be due to the cyclodextrin, was seen at the 40 mg/kg dose. Hematologic and lymphoid change and atrophy of accessory sex organs were reversible with 4 weeks of recovery. Renal vacuolization, degeneration of ameloblasts and dysplasia of dentine in the incisor teeth were seen after 4 weeks of recovery in rats given 20 and 40 mg/kg. The maximum tolerated dose (MTD) under the conditions of this study was 6 mg/kg (36.9 mg/m^2).

A second set of studies with beagle dogs was performed to evaluate both the 14- and 28-day toxicities of qod treatment with TNP-470. The 14-day study consisted of iv administration of 3, 10 or 30 mg/kg of TNP-470. There were no deaths in this study, although the dogs receiving the highest dose experienced an 18% decrease in body weight. There was also a drop in WBCs and platelets at both the 10 and 30 mg/kg dose levels. At necropsy, lesions were seen in the lung and thymus in the 10 and 30 mg/kg groups as well as lesions in the stomach and small intestines in the 30 mg/kg group. Microscopically, these lesions consisted of congestion and hemorrhage in the intestines and the lungs at the 30 mg/kg dose level and there was evidence of focal hepatic necrosis in the 10 and 30 mg/kg dose groups. Peak plasma levels of TNP-470 and AGM-1883 were <0.05 and 0.4 μg/mL for the 3 g/mL group, 0.75 and 1.1 μg/mL for the 10 mg/kg group, and 0.83 and 2.3 μg/mL for the 30 mg/kg group.

A study evaluating the 28-day toxicity of TNP-470 administered qod to beagle dogs was conducted using doses of 2.5, 5, and 10 mg/kg. Severe neurologic toxicity was seen in the dogs at the highest dose level and consisted of seizures, tremors, and ataxia. In addition, retinal hemorrhages and narrowing of retinal vessels were seen at the highest dose level. One dog was sacrificed moribund on Day 24. Weight losses of 6-13% and 19-26% were seen in the 5 and 10 mg/kg dose levels, respectively. Increased liver transaminases were seen at 5 mg/kg qod or higher. Decreases in WBCs were seen while minor increases in activated partial thromboplastin times (APTT) and glucose were noted only in the 10 mg/kg group. At necropsy, thymic and splenic atrophy were found at the highest dose levels. Histologic examination revealed microscopic evidence of hemorrhage in the lungs as well as proliferation of alveolar epithelium in the 2.5, 5, and 10 mg/kg dose groups. Brain hemorrhages were seen in the 5 and 10 mg/kg groups as well as spheroid-

like substances in the brain in the 10 mg/kg group. Hemorrhage and necrosis of the cardiac papillary muscles were seen in the highest dose group. Thymic atrophy and bone marrow hypercellularity were seen in the 5 and 10 mg/kg groups and atrophy of the lymphoid follicles in the spleen, lymph nodes, tonsils, and small bowel were seen at the highest dose levels. Hepatic vacuolization was seen in the 5 and 10 mg/kg groups and hepatic atrophy was seen at the highest dose level. Choroidal hemorrhages were seen in the eyes of the animals at the highest dose level. In dogs allowed a 28-day recovery period following the last administration of TNP-470, most of the histopathologic abnormalities resolved with the exception of a slight amount of pulmonary alveolar epithelial proliferation at the lowest dose level and a slight amount of pulmonary hemosiderosis at the highest dose level. Extramedullary hematopoiesis was seen in all groups as well as bone marrow hyperplasia. Thymic atrophy continued to be seen at the highest dose level. The MTD was considered to be 2.5 mg/kg qod (52 mg/m^2). A subsequent study, conducted in order to determine the effects of TNP-470 on blood coagulation in dogs following the iv administration of 0.5 and 10 mg/kg TNP-470 qod for 28 days, confirmed the changes described above. Parameters such as bleeding times, APTT and platelet counts were closely monitored without any signs of abnormalities throughout this study.

This toxicity data is summarized in Table I.

Table I. Summary of chronic (qod for 4 weeks) IV toxicology for TNP-470 studies in dogs.

Dose (mg/kg)	Toxicity
0.5	Slight foam cell infiltration in the lung
2.5	Red foci in the lungs
5.0	Red foci in lungs and brain, ↓ weight, ↓ food intake, ↑ transaminase, hypocellular bone marrow
10.0	As above plus ↑ CPK, leukopenia, ↑ PTT, ataxic gait, tremors, convulsions, retinal, endocardial and cerebellar hemorrhage, lymphoid atrophy

Dosage levels employed in a 3-month study (with 3-month recovery period) in dogs were 0.5, 1.5 and 3.0 mg/kg/dose (administered as a 1-hour infusion qod). No drug-related deaths occurred during this study. Drug-related clinical signs noted in the high dosage group included low incidences of convulsions, ataxia, decreased activity, tremors and aggressive behavior (also observed in some dogs in the 1.5 mg/kg dosage group). An increased incidence of local irritation at the infusion site, consisting of discoloration and/or swelling, was observed in dogs in the 1.5 mg/kg and 3.0 mg/kg dosage groups. Group mean body weight gains for dogs of both sexes receiving ≥1.5 mg/kg/dose and female dogs in the low dosage group were significantly lower than those for controls during the treatment period. In some cases, this was concurrent with lower mean food consumption and necessitated dietary supplementation. No treatment-related abnormalities were

detected by electrocardiogram. Significant treatment-related changes in hematologic and blood chemistry parameters in dogs treated at ≥1.5 mg/kg/dose included: decreases in hemoglobin, hematocrit, red blood cell and white blood cell counts (mean neutrophil and lymphocyte counts), and serum phosphorus and increases in alanine aminotransferase. Decreases in serum phosphorus were also recorded for female dogs in the low dosage group. Urinalysis findings did not indicate treatment-related changes. Mean thymus weights were decreased for dogs in the high dosage group.

Ophthalmologic examinations performed at the end of the three-month treatment period demonstrated treatment-emergent cataracts in some dogs in each of the 1.5 mg/kg and 3.0 mg/kg dosage groups. Further, cataracts were detected at the end of the recovery period in all dogs in these dosage groups. Ophthalmologic examinations revealed no evidence of cataracts in dogs in the low dosage group (main study and recovery study), suggesting that this dose does not convey significant ocular toxicity. Histopathology findings were noted for the eye (lens), as well as the liver, lung, spleen, and injection site. These included degenerative changes in the posterior lens capsule, hepatocellular vacuolar swelling, pulmonary inflammation, increased splenic erythropoiesis, and venous thrombosis at injection sites.

With the exception of cataracts, increased alveolar foam cells, increased splenic erythropoiesis and decreased serum phosphorus values, all changes noted at the end of the treatment period were reversible after a three-month recovery period. While the lens changes appeared to progress during the recovery period, those noted in the lung and spleen and the serum phosphorus levels were partially reversible. Based on the data generated in this study, a dosage of 0.5 mg/kg/dose (10 mg/m^2) was considered to be the maximum-tolerated dose administered to dogs on a qod schedule for three months.

Table II. Summary of toxicology of 120 hours Continuous IV infusion studies of TNP-470 in dogs.

Dose (mg/kg/day)		Toxicity
Male Beagle Dogs	0.81	↓ Body weight, food consumption, occult blood in feces, Hematologic (↓ leucocytes, platelets, reticulocytes), Coagulation (↑ APTT), Hemorrhage & necrosis of alveolar epithelium, alveolar and foam cell infiltration, gastrointestinal epithelial necrosis, hypocellularity of the bone marrow, endocardial hemorrhage. One dog died during recovery on day 8
	2.43	As above, swelling at the injection site and claudication. One animal sacrificed in extremis on day 7
	7.0	As above, ↑ hepatic AST Both animals died on day 6
Female Beagle Dogs	0.03	↓ Food consumption
	0.09	As above, ↓ Body weight, Hematologic (↓ platelet count)
	0.27	As above, occult blood in feces, Hematology (↓ reticulocyte count), Hemorrhage, edema and foam cell infiltration of lung, hypocellularity of the bone marrow. No mortality in any treatment group.

In a set of studies evaluating a 120-hour continuous infusion of TNP-470 in groups of male and female beagle dogs, the dosage levels employed were 0.81, 2.43 and 7 mg/kg/day in male dogs and 0.03, 0.09 and 0.27 mg/kg/day in female dogs. There were treatment related deaths in all of the higher dose levels used in male dogs, while there were no deaths at the lower dose levels used in female dogs. The toxicities seen in the different dose levels and histopathology findings at necropsy are summarized in table II.**

1.2.4 **Clinical Experience.** Five open-label Phase I studies in patients with refractory solid tumors (four studies in adult and one in pediatric patient populations) and two similar studies in AIDS patients with Kaposi's sarcoma and Phase II studies in patients with glioblastoma, pancreatic, breast, cervical and renal cell cancer have been initiated to date. Maximum tolerated doses (MTDs) have been determined in four Phase I studies, one study (hormone-refractory prostate cancer) has been completed, and three others are nearing completion. Three dosing regimens have been employed in Phase I as follows: (1) in six studies, administration is as a 1-hour iv infusion either qod or on a Monday, Wednesday and Friday (MWF) schedule; (2) in one study, administration is as a 1-hour iv infusion once a week; and (3) in one study, administration is as a 4-hour iv infusion once a week. Generally, treatment cycles are four to six weeks in duration. To date, approximately 200 patients have been treated in these studies. Treatment was well tolerated by the majority of patients. The most common medical events reported include mild fatigue and mild nausea.

Two episodes of intratumoral bleeding in brain lesions (presumed lymphoma in an AIDS patient and glioma) have been reported. In the study in patients with hormone-refractory prostate cancer, dose-limiting toxicities (DLTs) involving the central nervous system presented as gait disturbance, increased anxiety, and emotional lability in three patients. In all cases, the symptoms resolved within one to three weeks following discontinuation of TNP-470 and did not require further intervention. Initial observations occurred in one patient at 106 mg/m^2 after 13 doses, one patient at 71 mg/m^2 after 14 doses and a 14-day rest period, and a second patient at 71 mg/m^2 after 13 doses. Similar DLTs have been reported for two patients at 71 mg/m^2 in a second study (cervical cancer). In both cases, dizziness and nystagmus were reported following approximately four weeks of treatment. Both patients have since died due to disease progression. Partial resolution of one patient's symptoms occurred within four weeks after discontinuation of TNP-470 with complete resolution noted eight weeks thereafter. Observations about toxicities and their resolution were complicated, however, due to implementation of chemotherapy during the recovery period. MRIs and CT scans of the brain ruled out the presence of lesions in these five patients. In both studies the dose escalation schedule allowed proportionally large increases (50%) between successive dose levels. Thus the MTD, defined as the next lower dose level at which toxicities were not observed, was determined to be 47.5 mg/m^2 (administration as a 1-hour iv infusion qod) in both studies. The safety of an intermediate dose level (60 mg/m^2) was established in the cervical cancer study. In a Phase I study enrolling patients with a variety of solid tumors, 57.4 mg/m^2 was determined the MTD based on DLTs reported for two of five patients treated at 76.5 mg/m^2 (MWF schedule). In one case, a patient with non-small cell lung cancer experienced hemoptysis; this was not a new occurrence and had occurred prior to treatment with TNP-470 as well. In the other case, a patient with prostate cancer experienced neurological impairment (ataxia, nystagmus and dizziness) after treatment for six weeks. Imaging studies were negative and the patient was much improved, but still not back to baseline, two weeks after discontinuation of TNP-470. In contrast, patients with AIDS-associated Kaposi's sarcoma have cleared the 57.4 mg/m^2 dose level and are currently being dosed at 76.5 mg/m^2 qod.

Phase I clinical experience at doses $\geq$50 mg/m^2 (i-hour iv infusion, qod or MWF schedule) includes 20 patients (dose levels of 57.4 mg/m^2 and 60 mg/m^2), as well as eight patients at 71 mg/m^2 and 76.5 mg/m^2 who did not experience DLTs. Phase I clinical experience at doses $\geq$177 mg/m^2 (4-hour iv infusion once weekly) is more limited because this schedule was used in only one Phase I study completed at the Lombardi Cancer Center. 31 patients (17 Males, 14 Females) with a median age of 57 (range 23-75) and different malignancies were enrolled. The number of patients at each dose level (mg/m^2) were: 6(25), 3(50), 3(75), 3(100), 3(133), 7(177) and 6(235).All patients were evaluable for toxicity. The MTD in this study was determined to be 177 mg/m^2 when given as a weekly infusion. The principal Dose Limiting Toxicity (DLT) was grade I-III cerebellar neurotoxicity which occured in 3 patients at the 235 mg/m^2 dose level after 6 to 14 weeks of treatment. All toxicities resolved within 4 weeks of stopping the drug. However, eight patients were treated at 177 mg/m^2 in addition to four patients at 235 mg/m^2 who did not experience DLTs. Phase II clinical experience (1-hour iv infusion, MWF schedule) to date includes approximately 40 glioma patients, treated at 50 mg/m^2, and approximately 30 patients treated at 60 mg/m^2 in the other Phase II studies.

Observations of efficacy have included several patients with disease stabilization (qod/MWF and once weekly schedules) as well as apparent eradication of disease in a patient with lung metastases secondary to cervical cancer following administration of TNP-470 at 71 mg/m^2 for approximately four months.[1,2] The patient remains disease free on treatment for approximately 20 months.

For further information, refer to *TNP-470, Information for Clinical Investigators.*

1.2.5 **Rationale for the study**. It is clear from the animal toxicology studies that TNP-470 behaves very differently when given as a continuous infusion instead of a weekly bolus injection, with myelosuppression and gastrointestinal epithelial toxicity being the prominent toxicities with prolonged infusion. In addition, the short half life that we have seen of the parent compound in human pharmacokinetic studies would support a continuous infusion for maximal therapeutic effect. In one study using a three times weekly bolus schedule of TNP-470 in patients with advanced cervical cancers, one complete response was seen at the 71.25 mg/m^2 dose level (**31**). Additionally, the DLT in that study, which was predominantly cerebellar neurotoxicity, and the MTD, which was a total dose of 213.75 mg/m^2 (71.25 mg/m^2 x 3 doses per week), were similar to those observed in our Phase-I study. This would argue for a schedule dependency of the drug rather than dose dependency, with an enhanced therapeutic effect with prolonged drug exposure. We thus think that a continuous infusion regimen of TNP-470 may demonstrate enhanced antiangiogenic and anti-tumour effect with clinically managable toxicity.

1.2.6 **Selection of Drug Doses.** In the 120 hrs continuous infusion toxicology studies in dogs, the Toxic Dose Low (TDL) was determined to be 0.09 mg/kg/day, which would be equal to 1.8 mg/m^2/day in humans. Based upon ⅓ of the TDL in dogs, the starting dose in humans would be 0.6 mg/m^2/day for a total dose of 3.0 mg/m^2 over a 5 day course. Dose escalations will be done using a modified Fibonacci scheme as detailed in **Table IV**.

2. OBJECTIVES

2.1 To determine the dose limiting toxicities (DLTs), maximum tolerated dose (MTD) and pharmacokinetics of TNP-470 when administered by a 120 hour continuous intravenous infusion once every three weeks in patients with advanced, incurable malignancies.

2.2 To document any objective antitumor responses that occur in patients treated on this protocol.

3. PATIENT ELIGIBILITY

3.1 Patient must meet all of the following criteria:

3.1.1 Patients must have a histologically confirmed, incurable malignancy with locally unresectable disease or distant metastasis. Patients must have malignancies considered to be unresponsive or poorly responsive to the best cancer treatments

currently available. Specifically, there must be no other mode of therapy which would have a greater chance of producing cure or significant palliation.

3.1.2 Patients must be 18 years of age or older.

3.1.3 Patients must have an anticipated survival of at least 8 weeks.

3.1.4 Patients must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible side effects), and must sign an informed consent.

3.1.5 Patients must be ambulatory, with an ECOG performance status of 0, 1 or 2 and must be maintaining a reasonable state of nutrition, consistent with weight maintenance.

3.1.6 Patients must have adequate organ function:
- 3.1.6.1 Hematologic: WBC $\geq$ 3,000/mm^3, granulocytes $\geq$ 1,500/mm^3 and platelet count $\geq$ 100,000/mm^3);
- 3.1.6.2 Coagulation: PT and PTT within the normal range;
- 3.1.6.3 Hepatic: bilirubin $\leq$ 1.2; SGOT, SGPT $\leq$2 x ULN; and
- 3.1.6.4 Renal: serum creatinine $\leq$ 1.5 (<u>or</u> creatinine clearance $\geq$ 60 ml/min).

3.1.7 Patients must be on stable doses of any drugs which may affect hepatic drug metabolism or renal drug excretion (e.g.--non-steroidal anti-inflammatory drugs, corticosteroids, diphenylhydantoin, barbiturates, narcotic analgesics, probenecid). Such drugs should not be initiated while the patient is participating in this study.

3.1.8 Patients must have recovered from the reversible side effects of prior therapy.

3.2 Contraindications to Enrollment

3.2.1 Recent major surgery (within 21 days).

3.2.2 History of a bleeding diasthesis

3.2.3 Recent ($\leq$ 6 weeks) history of seizures.

3.2.4 History of peripheral neuropathy $\geq$ Grade 2.

3.2.5 Frequent vomiting or severe anorexia.

3.2.6 History of weight loss > 10% of current body weight within the last 4 weeks.

3.2.7 Pregnant (obtain pregnancy test in women with child bearing potential) or lactating women. (NOTE: women and men enrolled in the study are to practice an effective method of birth control while on the study and for at least six months after their last treatment on protocol).

3.2.8 Serious intercurrent medical illnesses which would interfere with the ability of the patient to carry out the treatment program.

3.2.9 The following therapies are prohibited and may not be administered to patients being treated on this protocol: chemotherapy and immunotherapy. Limited field radiation is permitted for painful bony lesions or other palliation.

3.2.10 Patients who have been treated with a hormonal therapy for ≥ 6 months and who have evidence of progressive disease may be entered on this protocol and continued on their current hormonal therapy if the patient and their physician feel it is in the patient's best interest.

4. STUDY PARAMETERS (See **Table III**)

5. PHARMACEUTICAL DATA

5.1 **Drug Substance:** TNP-470 (A-98852, ABT-852, AGM-1470, *O*-chloracetylcarbamoyl fumagillol, fumagillin analogue).

5.2 **How Supplied:** Supplied by TAP Holdings Inc. as a lyophilized powder containing 100 mg of TNP-470, 726 mg of G_2-β-cyclodextrin and 33.3 μg of NaOH in each vial for injection.

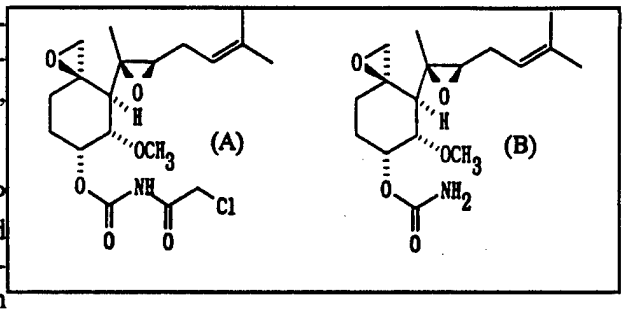


Figure 1. Structure of TNP-470 and its metabolite AGM-1883.

5.3 **Preparation:** When reconstituted with 9.5 mL of 5% Dextrose, USP, each mL contains 10 mg of TNP-470, 72.6 mg of G_2-β-cyclodextrin and 3.33 μg of NaOH at pH 3.5 to 5.5. TNP-470 should be further diluted with 5% Dextrose, USP, to yield a final concentration of >0.1 mg/mL. Total volume to be infused over the course of 24 hours is 50-100 mL. (NOTE: This text will be based on findings in stability/compatibility study being done in support of this protocol.)

5.4 **Storage:** The intact vials should be stored in the refrigerator (2-8°C), and protected from light.

5.5 **Stability:** Shelf-life surveillance of intact vials is ongoing. Intact vials are stable for 36 months at 15°C. TNP-470 vials contain no preservatives. Reconstituted drug should be administered within six hours. In the time interval between reconstitution and administration, drug should be covered (light protection) and maintained at room temperature.

5.6 **Route of Administration:** Intravenous.

5.7 **Procurement:** TNP-470 will be supplied under an IND held by TAP Holdings Inc.

5.8 **Drug Inventory and Control:** In accordance with Food and Drug Administration (FDA) regulations, the investigator must keep an inventory of all drug supplies received and dispensed for administration of drug at the clinic site. A copy of the drug inventory will be returned to TAP Holdings Inc. and the original shall be maintained by the investigator.

5.9 **Return of Drug Supplies:** All unused original study drug containers must be returned to either Abbott Laboratories or other specified recipient. The TAP Holdings Inc. study monitor will provide all necessary information and assistance.

Supplies returned to Abbott Laboratories should be sent to:

Ms. Betty Saylors
Abbott Laboratories
Department 504, Building P-1
1401 Sheridan Road
North Chicago, IL 60064
(847) 937-6007

Return shipments must be made by a means that will provide proof of delivery, and should be accompanied by a memo which includes the following information:

- Name of the principal investigator and investigator number.
- Protocol number.
- Name of the drug substance (TNP-470; ABT-852) and classification.
- NPRO number and/or lot numbers (as they appear on the shipping documentation).
- Inventory of quantities being returned.

A copy of the memo to be used when returning drug supplies to Abbott Laboratories is provided as Appendix F. The investigator will retain a copy of the returned disposition document with the study files.

Table III. Study Parameters

Parameter	**On study	Day 1 Day 5	Day 8 Day 15 Day 22	q 2 weeks starting on Day 22
History/Physical Exam	x		x	x
Height	x			
Weight	x		x	x
Performance Status	x		x	x
Metabolic Profile	x			
CBC, Diff, Platelets	x		x	x
Serum electrolytes	x		x	x
Chemistry Survey[1] and SGPT	x		x	x
Urinalysis	x		x	x
Ophthalmologic exam	x			q8 weeks[6]
CT scan of the brain	x			
TNP-470 Pharmacokinetics[3]		x		
Urine collections for TNP-470[3]		x		
Tumor Assessment[4]	x			q8 weeks
EKG	x			
Pregnancy test[5]	x			

**On study laboratory tests must be obtained within 2 weeks of starting on study.

1 Includes: BUN, creatinine, glucose, SGOT/AST, alkaline phosphatase, total bilirubin, LDH, calcium, and uric acid.

3 Obtain samples just prior to the infusion and then 20 and 40 minutes and 1, 2, and 4 hours during the infusion and 5, 15, 30, 60 and 120 minutes after the end of the infusion and at 24 hours after the beginning of the infusion and at 24 hours after the beginning of the infusion. Collect urine for the following time points: preinfusion, 0 - 4 hours (i.e., during the infusion); 0 - 4 and 4 - 20 hours after the end of the infusion. Required after the injections on days 1 and 22. *Record date and exact time infusion was started and completed and each blood sample was obtained.*

4 If measurable disease is present. If patient has prostate cancer, obtain Prostate Specific Antigen (PSA).

5 For fertile women in whom pregnancy cannot otherwise be ruled out pregnancy test must be negative prior to starting treatment.

6 Perform on Day 22 and then evry 8 weeks if no change from baseline; perform as indicated if changed from baseline.

6. TREATMENT PLAN

6.1 **Summary.** Eligible patients who have signed the consent form will receive TNP-470 by continuous IV infusion over 120 hours once every three weeks. In the absence of progressive disease, patients may be continued on treatment. Patients who experience dose limiting toxicities may resume treatment at a lower dose level if the side effects resolve within 3 weeks. In the absence of toxicities, subsequent cycles may be administered every two weeks.

The first 3 patients will begin on dose level 1. If no patients develop dose limiting toxicity during the first 4 weeks, then the next 3 patients will be started at dose level 2. If 1 of 3 patients experience dose limiting toxicity during the first 4 weeks of TNP-470, then an additional 3 patients will be started at that dose level. If less than 2 of 6 patients treated at any dose level experience dose limiting toxicity, the next patients will be started at the next dose level. As soon as two patients at a given dose level experience dose limiting toxicity, no additional patients will be started at that dose level. If at least six patients have been studied on the previous dose level then that dose level will be considered the MTD.

6.1.1 **Dose limiting toxicities** for TNP-470 have been defined by shading the appropriate boxes in the NCI Common Toxicity Criteria (Appendix B).

6.1.2 **Definition of the Maximum Tolerated Dose (MTD) and the Recommended Phase 2 Dose (RP2D).** The MTD is defined as the highest dose level which results in Dose Limiting Toxicity (DLT, defined by the shaded boxes in the NCI Common Toxicity Criteria, Appendix B) in fewer than 2/6 patients. When ≥ 2 patients experience DLT at a given dose level, the MTD will have been exceeded and the previous dose level will be declared the MTD provided 6 patients were treated at that level. Often the RP2D will be the same as the MTD. However, if the toxicities observed at the dose level above the MTD or in 1 of 6 patients at the MTD were particularly severe, irreversible or fatal, and clearly related to drug administration, the next lower dose level would be declared the RP2D provided the side effects observed in all 6 patients treated at this dose level were acceptable. As explained below, tolerance to the RP2D will then be confirmed by the study of 10 additional patients.

6.1.3 **Accrual of additional patients once the RP2D has been determined.** Once the RP2D has been determined an *additional 10 patients* with measurable disease and accessible tumor may be accrued. Tumor tissue will be provided to the laboratories of Drs. Martuza and Wellstein for characterization of:

6.1.3.1 Heparin binding growth factor expression (Wellstein)

6.1.3.2 Tumor growth following s.c. injection in nude mice (Wellstein)

6.1.3.3 Tumor growth and vascularity in nude mouse subrenal capsule assay (Martuza)

6.1.3.4 *In vitro* proliferation in the presence of TNP-470 (Martuza)

Metabolic profile and pharmacokinetic data obtained on these patients will be analyzed with that of other patients treated at the RP2D.

6.1.4 **Accrual of women and minorities.** Characterization of drug metabolism, pharmacokinetics and pharmacodynamics for all patient populations is a major objective of early clinical trials. If fewer than 50% of the patients treated at the RP2D are women, additional women may be accrued at the RP2D to evaluate any possible differences in drug processing. Since, by definition, minority patients (Black, Hispanic, Oriental, Native American) are less likely to be studied in any clinical trial, additional minority patients may be entered at the RP2D to obtain data relevant to these populations.

6.1.5 **Intrapatient dose escalation.** Patients may have their dose of TNP-470 increased given the following provisions: They must have completed at least 8 weeks at their original dose of TNP-470; They many not be advanced beyond a dose that has already been safely cleared in the study.

6.2 TNP-470 Dose levels

Table IV

Dose Level	TNP-470 Dose ($mg/m^2/day$)
1	0.6
2	1.2
3	1.8
4	2.4
5	3.2
6	4.25

Patients who require reductions below Dose Level 1 should be dose reduced by 50%. Dose escalations beyond Dose Level 5, if required, will be conducted in 33% increments.

7. PHARMACOKINETICS

7.1 Collection of blood samples.

- Blood samples (9 ml) will be collected in heparinized (nonseparator) tubes. At each sampling time 1 ml of whole blood will be withdrawn and discarded to remove blood diluted with the heparin used to maintain catheter patency. Vacutainer collection tubes are to be immediately placed on ice and centrifuged at 4°C for 5 - 10 min. To 1 ml of plasma, add 100 µl of 2% (wt.%) H_2SO_4 (Mallinckrodt, Paris, KY, USA). The addition of sulfuric acid to the samples has the effect of acidifying the plasma to a pH of 4 to 5, a pH range in

which TNP-470 is most stable. Acidification of the plasma also serves to partiality denature plasma proteins. Plasma is divided into 2 aliquots in screw top polyethylene tubes and then labeled and stored at -70°C or lower. Samples will be assayed by the Abbott Laboratories.

7.2 **Time points for sampling.**

7.2.1 *TNP-470 pharmacokinetics.* **Complete pharmacokinetics are mandatory on Day 1 and 5 of the infusion.** A blood sample should be obtained just prior to begining the infusion and 10, 20, 30, 45, 60 minutes and 2, 4, 24 hours after the start of the infusion on Day 1. A sample should be obtained just prior to the end of infusion on Day 5. The exact date and time the infusion was started and completed, and the time each blood sample was obtained must be recorded.

7.2.2 *Urinary collections for TNP-470.* A 10 cc aliquot of urine should be obtained prior to the start of infusion. Then a 24 hour collection should be started for Day 1 of drug infusion. Separate timed collections (10 cc) should be obtained at 4 and 24 hours from the start of infusion. On Day 5, a 10 cc aliquot should be obtained just prior to the end of infusion.

7.2.3 *Other fluids and tissues.* If available, other fluids (e.g., pleural, peritoneal, cerebrospinal) or tissues (e.g. bone marrow) will be studied to determine if TNP-470 is transported into such sites. Fluids or tissues collected will be as part of standard medical management and not obtained solely for the purposes of this research.

8. TREATMENT MODIFICATIONS AND MANAGEMENT OF TOXICITY

8.1 **Dose modification for toxicity.** Dose limiting toxicities (DLTs) are identified by the shaded boxes in the NCI Common Toxicity Criteria in Appendix B. When DLT occurs, treatment with TNP-470 will be interrupted until the toxicity resolves 2 Grades and may then be reinstituted at the next lowest dose level. (Patients who experience DLT on the first dose level should be restarted at 50% of the dose). Patients who experience toxicities 1 Grade or more above DLT will be considered to have had potentially life threatening toxicity from TNP-470. In general these patients should not be restarted on TNP-470 once toxicity resolves unless there is some indication of patient benefit. *In these cases the reason(s) for reinstituting TNP-470 must be clearly indicated in the case report form.*

8.2 **Management of anticipated toxicities.** Based upon preclinical toxicology studies, anticipated toxicities include hemorrhage, bone marrow and lymphoid hypoplasia, hepatotoxicity, and neuropathology (convulsions, tremor, and ataxia). Physical and neurologic exams and laboratory parameters (platelet counts and coagulation studies) will be closely monitored. TNP-470 will be discontinued at the first clinical evidence of bleeding (e.g.--cutaneous or retinal petechiae, guaiac positive stools), thrombocytopenia, coagulation abnormalities, seizures, or ataxia (see dose limiting toxicities that have been shaded in NCI Common Toxicity Criteria, Appendix B).

8.3 **Removal from study for prolonged toxicity**. Patients who do not experience DLTs may continue to receive treatment. If DLT occurs, treatment must be interrupted and the patient assessed at weekly intervals. Treatment may resume at the next lowest dose level when all

TNP-470 related toxicities have improved at least two grades. If it is not possible to resume therapy after a 3 week delay due to persistent treatment related toxicities, the patient should be taken off study.

8.4 **Continued treatment of patients who are experiencing significant clinical benefit**. It may be in the patient's best interest to continue on treatment despite the occurrence of prolonged or otherwise unacceptable toxicity. Patients who are experiencing a significant clinical response from treatment and in whom continued therapy is indicated may be continued at a reduced dose of TNP-470 as determined by the Principal Investigator.

8.5 **Unavoidable treatment delays for non-medical reasons.** Treatment interruptions for non-medical reasons (for any reason, at the discretion of the patient and physician) are at times unavoidable and are permissible under this protocol. However, every attempt should be made to avoid any non-medical treatment delays, especially during the first 4 weeks of treatment. Patients who require frequent or prolonged treatment interruptions should be taken off study. Patients who have their treatment interrupted for reasons not related to side effects during the first 14 days of treatment will not be included in the determination that it is safe to enter subsequent patients at the next higher dose level and an additional (replacement) patient will be started at this dose level.

9. TOXICITY MONITORING AND ADVERSE EXPERIENCE REPORTING

9.1 At each weekly visit during the first 4 weeks and every 2 weeks thereafter:

- 9.1.1 an interim history will be obtained and a directed physical examination (to include at a minimum ECOG performance status, weight, fundoscopic exam, examination of skin and mucosal surfaces for petechiae) will be performed;
- 9.1.2 obtain a CBC, differential, platelet count, coagulation studies;
- 9.1.3 obtain a chemistry survey (to include BUN, creatinine, LDH, SGOT/AST, alkaline phosphatase, total bilirubin, calcium, glucose, and uric acid), electrolytes and SGPT.
- 9.1.4 Obtain a urinalysis and stool guiac.

9.2 Laboratory studies will be repeated more frequently if clinically indicated, and any abnormalities potentially related to treatment will be followed until they have resolved, or have been determined to not be treatment-related.

9.3 **Departure from Protocol for an Individual Patient**

Only very unusual circumstances may justify a departure from protocol for an individual patient. Should such circumstances arise, the investigator must contact, request and receive permission from one of the TAP monitors listed below:

Lynn Hurtt, M.S., R.D.
Sr. Clinical Research Associate
Office: (708) 374-5453
Fax: (708) 317-5795

Rachelle A. Weiss, Ph.D.
Sr. Clinical Project Manager
Office: (708) 317-5760
Fax: (708) 317-5795

Home: (312) 929-1736 Home: (312) 561-7328

A monitor should be contacted as soon as possible so that a decision can be made whether the protocol may be modified. Any departure from the protocol will be authorized for only that individual patient. If permission is granted, a description of the departure from the protocol and the reasons necessitating it are to be recorded on the appropriate case report form.

9.4 Adverse Drug Reaction (ADR) Reporting

Adverse Drug Reactions. All adverse events, whether observed by the investigator or reported by the patient, whether or not thought to be related to study drug, must be recorded on the appropriate case report form. The description of each event will identify the date of onset, duration, grade (NCI Common Toxicity Criteria) or severity, any action taken, outcome of the event, and relationship to study drug. Medically accepted terminology should be used throughout. All patients experiencing adverse events will be followed by the investigator until there is a return to baseline or a clinically satisfactory resolution is achieved.

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, serious adverse events include all events associated with death, inpatient hospitalization or prolongation of hospitalization, or permanent disability, and also all events that are life-threatening or result in congenital anomaly, cancer or are from overdose. In the event of a serious adverse event identified as a clinically important symptom, or an adverse change in symptoms, physical examination, laboratory test, or other evaluation, the investigator or other physician in attendance will administer whatever therapy is indicated. Life threatening or unexpected toxicities will be reported immediately to TAP Holdings Inc. to any of the following study monitors:

Catherine Irvine
Sr. Clinical Research Associate
Office: (847) 374-5428
Home: (773) 278-9141

Rachelle A. Weiss, Ph.D.
Asst. Director Clinical Devt.
Office: (847) 317-5760
Home: (773) 561-7328

Karl Agre, M.D., Ph.D.
Director, Medical Affairs
Office: (847) 317-5755
Home: (847) 247-9117

Julie Rink
Clinical Research Associate
Office: (847) 317-3214
Home: (773) 477-4067

Lynn Hurtt, M.S., R.D.
Clinical Research Manager
Office: (847) 374-5453
Home: (773) 929-1736

All TAP Holdings Inc. monitoring personnel can be reached by fax at:
(847) 267-8699

10. CRITERIA FOR TERMINATING TREATMENT

10.1 Patients who experience substantial benefit attributed to treatment should continue to receive protocol therapy until progressive disease is discovered. Reasons for continued treatment are to be documented in the case records.

10.2 Rapid disease progression in the first month of treatment (≥ 50% enlargement of measurable disease) is grounds for termination of treatment. Patients with less rapid disease progression may remain on-study, at the discretion of the investigator after discussion with the patient.

10.3 Any disease progression (≥ 25%, or new metastases) occurring after the first month on study, requires treatment termination.

10.4 DLT that does not resolve within 3 weeks of stopping TNP-470.

10.5 Intercurrent illness which prevents further therapy.

10.6 General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator.

10.7 The patient or patient's physician is free to discontinue treatment and take the patient off study at any time, if this is believed to be in the patient's best interest.

11. STATISTICAL CONSIDERATIONS

11.1 This study will determine the Dose Limiting Toxicities (DLTs) and Maximum Tolerated Dose (MTD) for TNP-470 administered by IV injection once a week. The MTD is defined as the highest dose level which results in DLT during the first 4 weeks of treatment in fewer than 2/6 patients. When ≥ 2 patients experience DLT at a given dose level, the MTD will have been exceeded and the previous dose level will be declared the MTD.

11.2 TNP-470 will be assayed in plasma and urine for each patient treated on this study by Abbott Laboratories.

Because the T½ of TNP-470 in other studies has been short, we anticipate that we will achieve steady state drug concentrations within 2 hours of starting the infusion and will use standard pharmacokinetic analyses for infusions (**32**). We will determine the steady state concentratoin of TNP-470 by averaging the determinations taken at 1, 2, and 4 hours during the infusion. The total amount of TNP-470 and "metabolites" excreted into the urine over the first and last 24 hours of the infusion period will be estimated. The fractional rate of renal excretion of TNP-470 will also be estimated from the data.

The total body clearance of TNP-470 will be determined for each patient by dividing the infusion rate by the steady state concentration.

11.3 Patients will be characterized as extensive (EM) or poor (PM) metabolizers for each of 4 metabolic pathways: $P450_{2D6}$, $P450_{3A4}$, $P450_{2C18}$ and N-acetyltransferase. Toxicity, anti-tumor responses and the PK parameters detailed above will be described in the context of the metabolic profile as determined for each patient. Given the small numbers of patients that will be treated on this trial, these characterizations are expected to provide, at most, data that can be further evaluated as subsequent trials of this agent are initiated.

12. RESPONSE ASSESSMENT

Measurable disease will include any lesion with clearly defined borders which can be measured with rulers or calipers on physical exam or radiographically on Xrays or Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) scans. Measurement of lesions by ultrasound is not generally recommended for obtaining reproducible tumor measurements. Previously irradiated lesions, malignant hepatomegaly and lesions visible on bone scan will not be considered measurable. The longest perpendicular diameters for each lesion should be recorded. Photographs (which include a centimeter scale, the date and the patient's initials in the photographed field) should be obtained at the time of each tumor measurement for visible lesions.

At the time of each assessment of tumor response, the product of the longest perpendicular measurements for each lesion is calculated and the sum of all of these products is computed.

12.0.1 Complete Response:

Disappearance of all clinical and laboratory signs and symptoms of disease for a minimum of 4 weeks during which no new lesions may appear. Specifically, all tumor masses must disappear. There must be no cancer-associated deterioration in weight (>10%), performance status or symptoms. For bony metastases, CR means the recalcification of all lytic lesions or the biopsy-proven absence of tumor cells. Normalization of the bone scan is not necessary for the patient to be considered to have a CR; however, any worsening of the bone scan needs to be evaluated.

12.0.2 Partial Response:

A minimum reduction of at least 50% in the sum of the products of the longest perpendicular diameters of all indicator lesions. If the bone scan was abnormal due to metastatic disease, it must show improvement; malignant hepatomegaly, if present, must decrease by 30%. There may be no new lesions and the response must last for at least 4 weeks during which time there should be no cancer-associated deterioration in weight, performance status or symptoms.

12.0.3 Stable Disease:

Patients who fail to qualify for complete or partial response or progressive disease. This condition should persist for at least 3 months.

12.0.4 Progressive Disease:

The appearance of new lesions or an increase of at least 25% in the sum of the products of the longest perpendicular diameters of measurable lesions.

Deterioration in performance status, weight or symptoms will not be considered indicative of progressive disease but should prompt an evaluation for other evidence of disease progression.

13. DATA REPORTING

13.1 Case Report Forms

Case report forms will be used to transmit the information collected in the performance of this study to TAP Pharmaceuticals Inc. and the FDA. All case report forms must be typewritten or filled out with a black ballpoint pen. When changes or corrections are made on the case report forms, draw a single line through the error in black ink, add the correction, initial and date. Data are not to be obliterated by blacking out or using correction fluid or an eraser. The investigator must review each case report for completeness and accuracy and sign and date the forms where indicated.

Completed case report forms will be submitted to TAP Pharmaceuticals Inc. pursuant to instructions. Case report forms will be reviewed by the TAP Pharmaceuticals Inc. monitor for adherence to protocol, completeness, accuracy and acceptability. Portions of the patient's medical and hospital records pertinent to the study will be reviewed at the study site to assure accuracy.

13.2 Monitor Visit Log

Monitors are to keep a record of each visit to the study site. The record will include the monitor's name, date of visit, and study personnel who were seen during the visit. The original Monitor Visit Log will be retained at the study site, and a copy will be returned to TAP Pharmaceuticals Inc. upon completion of the study.

13.3 Source Documents

Federal regulations require that the investigator prepare and maintain adequate and accurate records for each patient treated with study drug. Source documents such as hospital, clinic or office charts, laboratory reports, and the signed Informed Consent, as well as the patient's study records, are to be retained for a period of two years following the date of approval of a New Drug Application or discontinuation of all investigations.

13.4 Patient Confidentiality

All reports and communications relating to patients in the study will identify each patient only by initials and study number. The investigator will collect complete patient identification of the Confidential Follow-up Form, which will be used for purposes of long-term follow-up, if needed. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at TAP Pharmaceuticals Inc. under adequate security and restricted accessibility. The investigator or institution may elect to seal the Confidential Follow-up Form in an envelope, which will be filed unopened at TAP Pharmaceuticals Inc. The outside of the envelope must contain the patient's initials, patient study number, and investigator's name. In those cases where submission of the Confidential Follow-up Form is precluded by institutional policy, the investigator must certify in writing (1) that institutional policy prohibits an investigator from providing confidential patient information to a sponsor, and (2) that the Confidential Follow-up Form will be completed and retained indefinitely by the investigator.

13.5 USE OF INFORMATION AND PUBLICATIONS

All information concerning TNP-470 and TAP Holdings Inc. operations, such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by TAP Holdings Inc. and not previously published are considered confidential by TAP Holdings Inc. The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without written consent of TAP Holdings Inc.

It is understood by the investigator that the information developed in this clinical study will be used by TAP Holdings Inc. in connection with the development of TNP-470 and, therefore, may be disclosed by TAP Holdings Inc. as required to other clinical investigators, other pharmaceutical companies, to the U.S. Food and Drug Administration, and to other government agencies. In order to allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide to TAP Holdings Inc. complete test results and all data developed in this study.

The responsibility for the preparation and maintenance of a single database for this study shall reside with TAP Holdings Inc. This database shall be shared with the investigator and used for reporting the results of this study. The principal investigator retains the right to publish the results of the study and agrees that at least thirty (30) days before a manuscript is submitted for publication, it shall be provided to TAP Holdings Inc. for review and comments.

14. REFERENCES

1. Liotta LA, Steeg PS, Stetler-Stevenson WG. Cancer metastasis and angiogenesis: An imbalance of positive and negative regulation. *Cell* 1991;64:327-336.

2. Denekamp J, Hobson B. Endothelial-cell proliferation in experimental tumours. *Br J Cancer* 1982;46:711-720.

3. Hirst DG, Denekamp J, Hobson B. Proliferation kinetics of endothelial cells and tumour cells in three mouse mammary carcinomas. *Cell Tissue Kinet* 1982;15:251-261.

4. Wellstein A, Lippman ME. Fibroblast growth factors and breast cancer. In: Broder S, ed. *Molecular Foundations of Oncology*. Baltimore: Williams and Wilkins, 1991. p.403.

5. Denekamp J. The current status of targeting tumour vasculature as a means of cancer therapy: an overview. *Int J Radiat Biol* 1991;60:401-408.

6. Maione ET, Sharpe RJ. Development of angiogenesis inhibitors for clinical applications. *TIPS* 1990;11:457-461.

7. Cross M, Dexter TM. Growth factors in development,transformation, and tumorigenesis. *Cell* 1991;64:271-280.

8. Folkman J. How is blood vessel growth regulated in normal and neoplastic tissue?- G.H.A. Clowes memorial award lecture. *Cancer Res* 1986;46:467-473.

9. Folkman J, Klagsburn M. Angiogenic factors. *Science* 1987;235:442-447.

10. Denekamp J. Endothelial cell proliferation as a novel approach to targeting tumour therapy. *Br J Cancer* 1982;45:136-139.

11. Kandel J, Bossy-Wetzel E, Radvanyi F, Klagsbrun M, Folkman J, Hanahan D. Neovascularization is associated with a switch to the export of bFGF in the multistep development of fibrosarcoma. *Cell* 1991;66:1095-1104.

12. Baird A, Klagsbrun M. The fibroblast growth factor family. *Cancer Cells* 1991;3:239-243.

13. Maciag T, Tevie M, Friesel R. Heparin binds endothelial cell growth factor, the principal endothelial cell mitogen in bovine brain. *Science* 1984;225:932-935.

14. Burgess WH, Maciag T. The heparin-binding (fibroblast) growth factor family of proteins. *Annu Rev Biochem* 1989;58:575-606.

15. Wellstein A, Fang WJ, Khatri A, et al. A heparin-binding growth factor secreted from breast cancer cells homologous to a developmentally regulated cytokine. *J Biol Chem* 1992;(in press)

16. Li YS, Milner PG, Chauhan AK, et al. Cloning and expression of a developmentally regulated protein that induces mitogenic and neurite outgrowth activity. *Science* 1990;250:1690-1694.

17. Merenmies J, Rauvala H. Molecular cloning of the 18-kDa growth-associated protein of developing brain. *J Biol Chem* 1990;265:16721-16724.

18. Ingber D, Fujita T, Kishimoto S, Sudo K, Kanamaru T, Brem H and Folkman J. Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumor growth. Nature 348:555-557, 1990.

19. Kusaka M, Sudo K, Fujita T, Marui S, Itoh F, Ingber D and Folkman J. Potent anti-angigenic action of AGM-1470: Comparison of the fumagillin parent. Biochem Biophys Res Commun. 174: 1070-1076, 1991.

20. Kusaka M, Sudo K, Matsutani E, Kozai Y, Marui S, Fujita T, Ingber D and Folkman J. Cytostatic inhibition of endothelial cell growth by angiogenesis inhibitor TNP-470 (AGM-1470). Brit J Cancer 69:212-216, 1994.

21. Takamiya Y, Brem H, Ojeifo J, Mineta T and Martuza RL. AGM-1470 inhibits the growth of human glioblastoma cells *in vitro* and *in vivo*. Neurosurgery 34 (5):869-875, 1994.

22. Yanase T, Tamura M, Fujita K, Kodama S and Tanaka K. Inhibitory effect of angiogenesis TNP-470 on tumor growth and metastasis of human cell lines *in vitro* and *in vivo*. Cancer Res. 53:2566-2570, 1993.

23. Yamaoka M, Yamamoto T, Masaki T, Ikeyama S, Sudo K and Fujita T. Inhibition of tumor growth and metastasis of rodent tumors by the angiogenesis inhibitor *O*-(chloroacetyl-carbamoyl) fumagillol (TNP-470; AGM-1470). Cancer Res. 53:4262-4267, 1993.

24. Yanai S, Okada H, Misaki M, Saito K, Kuge Y, Ogawa Y and Toguchi H. Antitumor activity of a medium-chain triglyceride solution of the angiogenesis inhibitor TNP-470 (AGM-1470) when administered via the hepatic artery to rats bearing Walker 256 carcinosarcoma in the liver. J. Pharmacol. Exp Ther. 271(3):1267-1273, 1994.

25. Teicher BA, Holden SA, Ara G, Alvarez Sotomayor E, Huang ZD, Chen Y-N and Brem H. Potentiation of cytotoxic cancer therapies by TNP-470 alone and with other anti-angiogenic agents. Int J Cancer 57 (6):920-925, 1994.

26. Kato T, Sato K, Kakinuma H and Matsuda Y. Enhanced suppression of tumor growth by combination of angiogenesis inhibitor *O*-(chloroacetyl-carbamoyl) fumagillol (TNP-470) and cytotoxic agents in mice. Cancer Res. 54(19):5143-5147, 1994.

27. Folkman J. Tumor angiogenesis: Therapeutic implications. NEJM 285:1182-86, 1971.

28. Antoine N, Greimers R, DeRoanne C, Kusaka M, Heinen E, Simar LJ and Castronovo V. AGM-1470, a potent angiogenesis inhibitor, prevents the entry of normal but not transformed endothelial cells into the G_1 phase of the cell cycle. Cancer Res. 54:2073-2076, 1994.

29. Abe J, Zhou W, Takuwa N, Taguchi J, Kurokawa K, Kumada M and Takuwa Y. A fumagillin derivative angiogenesis inhibitor, AGM-1470, inhibits activation of cyclin-dependent kinases and phosphorylation of reitnoblastoma gene product but not protein tyrosyl phosphorylation or protooncongene expression in vascular endothelial cells. Cancer Res 54(13): 34073412, 1994.

30. Hori A, Ikeyama S and Sudo K. Suppression of cyclin D1 mRNA expression by the angiogenesis inhibitor TNP-470 (AGM-1470) in vascular endothelial cells. Biochem Biophys Res Commun. 204(3):1067-1072, 1994.

31. Levy T, Kudelka A, Verschraegen CF, et al. A phase I study of TNP-470 administered to patients with advanced squamous cell cancer of the cervix. Proc Am Assoc Cancer Res 37: March 1996 (abstract no. 1140).

32. Rowland, M and Toyer, TN. Clinical Pharmacokinetics: Constant Rate Intravenous Infusion, pp. 97-108.

APPENDIX B: NCI COMMON TOXICITY CRITERIA

SHADING INDICATES DOSE LIMITING TOXICITIES

TOXICITY	GRADE 0	1	2	3	4
White Blood Count	≥ 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
Platelets	WNL	75.0 - WNL	50.0 - 74.9	25.0 - 49.9	< 25.0
Hemoglobin	WNL	10.0 - WNL	8.0 - 10.0	6.5 - 7.9	< 6.5
Granulocytes/Bands	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Lymphocytes	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 -0.9	< 0.5
Hemorrhage (Clinical)	None	Mild, no transfusion; petechiae	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, > 4 units per episode
Infection	None	Mild	Moderate	Severe	Life threatening
Nausea	None	Able to eat; reduced but reasonable intake	Intake significantly decreased but still can eat	No significant intake	---
Vomiting	None	1 episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hours	> 10 episodes in 24 hours, or requiring Parenteral support
Diarrhea	None	Increase of 2-3 stools/day over pre-Rx	Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	Increase of 7-9 stools/day, or incontinence, or severe cramping	Increase of ≥ 10 stools/day or grossly bloody diarrhea, or need for parenteral support
Skin	None or no change	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Generalized symptomatic macular, papular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
Local	None	Pain	Pain and swelling with inflammation or phlebitis	Ulceration	Plastic surgery indicated
Hand-Foot Syndrome	No symptoms	Mild paresthesias +/or numbness of fingers +/or toes	Moderate paresthesias +/or numbness with or without local dermatitis	Painful swelling of distal phalanges with or without local dermatitis	Not applicable
Stomatitis	None	Painless ulcers, erythema, or mild soreness	Painful erythema, edema, or ulcers, but can eat	Painful erythema, edema, or ulcers, and cannot eat	Requires parenteral or enteral support
Bilirubin	WNL	---	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
Transaminase (SGOT, SGPT)	WNL	≤ 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Alk Phos or 5'Nucleotidase	WNL	≤ 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver--- clinical	No change from baseline	---	---	Precoma	Hepatic coma
Creatinine	WNL	< 1.5 x N	1.5 - 3.0 N	3.1 - 6.0 x N	> 6.0 x N

Lombardi Cancer Research Center
Georgetown University Medical Center
Shading added for TNP-470: February, 1993

NCI COMMON TOXICITY CRITERIA (continued)

TOXICITY	GRADE				
	0	1	2	3	4
Proteinuria	No change	1+ or < 0.3 g% or < 3 g/l	2-3+ or 0.3 - 1.0 g% or 3 - 10 g/l	4+ or > 1.0 g% or > 10 g/l	Nephrotic syndrome
Hematuria	Neg	Micro only	Gross, no clots	Gross + clots	Requires transfusion
Alopecia	No loss	Mild hair loss	Pronounced or total hair loss	---	---
Pulmonary	None or no change	Asymptomatic, with abnormality in PFT's	Dyspnea on significant exertion	Dyspnea at normal level of activity	dyspnea at rest
Cardiac: dysrhythmias	None	Asymptomatic, transient requiring no therapy	Recurrent or persistent, no therapy required	Requires treatment	Requires monitoring; or ventricular tachycardia or fibrillation
Cardiac: function	None	Asymptomatic decline of resting ejection fraction by less than 20% of baseline value	Asymptomatic decline of resting ejection fraction by more than 20% of baseline value	Mild CHF responsive to therapy	Severe or refractory CHF
Cardiac: ischemia	None	Non-specific T-wave flattening	Asymptomatic ST and T-wave changes suggesting ischemia	Angina without evidence for infarction	Acute infarction
Cardiac: pericardial	None	Asymptomatic effusion, no intervention required	Pericarditis (rub, chest pain, ECG changes)	Symptomatic effusion; drainage required	Tamponade; drainage urgently required
Hypertension	None or no change	Asymptomatic transient increase > 20 mm Hg (Dia) or to > 150/100 if BP previously nl. No treatment required.	Recurrent or persistent increase > 20 mm Hg (Dia) or to > 150/100 if BP previously nl. No treatment required.	Requires therapy	Hypertensive crisis
Hypotension	None or no change	Changes requiring no therapy (including transient orthostatic hypotension)	Requires fluid replacement or other therapy but not hospitalization	Requires therapy and hospitalization resolves within 48 hrs of stopping the agent	Requires therapy and hospitalization for > 48 hrs after stopping the agent
Neuro: sensory	None or no change	Mild paresthesias, loss of deep tendon reflexes	Mild or moderate objective sensory loss; moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	---
Neuro: motor	None or no change	Subjective weakness; no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis

Lombardi Cancer Research Center
Georgetown University Medical Center
Shading added for TNP-470: February, 1993

NCI COMMON TOXICITY CRITERIA (continued)

TOXICITY	GRADE				
	0	1	2	3	4
Neuro: seizures	None	---	Simple partial seizures in which consciousness is preserved; self-limited and/or controlled	Complex partial seizures with altered consciousness or generalized seizures with loss of consciousness; self-limited and/or controlled	Seizures of any type which are prolonged, repetitive or difficult to control (status epilepticus)
Neuro: cortical	None	Mild somnolence or agitation	Moderate somnolence or agitation	Severe somnolence, agitation, confusion, disorientation or hallucinations	Coma, seizures, toxic psychosis
Neuro: cerebellar	None	Slight incoordination, dysdiadokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis
Neuro: mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
Neuro: headache	None	Mild	Moderate or severe but controllable	Unrelenting and severe	---
Neuro: constipation	None or no change	Mild	Moderate	Severe	Ileus > 96 hrs
Neuro: hearing	None or no change	Asymptomatic hearing loss on audiometry	Tinnitus	Hearing loss interfering with function but correctable with hearing aid	Deafness not correctable
Neuro: vision	None or no change	---	Blurred vision or diplopia	Symptomatic subtotal loss of vision	Blindness
Allergy	None	Transient rash or drug fever ≥ 38° C (100.4° F)	Urticaria, drug fever ≥ 38° C (100.4° F), mild bronchospasm	Serum sickness or bronchospasm; requires parenteral medication	Anaphylaxis
Fever in absence of infection	None	37.1 - 38.0° C (98.7 - 100.4° F)	38.1 - 40.0° C (100.5 - 104.0° F)	> 40.0° C (> 104.0° F) for less than 24 hours	> 40.0° C (> 104.0° F) for ≥ 24 hours, or fever with hypotension
Fatigue	No change in Performance score (ECOG) *and* not PS 4	Performance score (ECOG) decrease in 1 level, but not to PS 4	Performance score (ECOG) decrease in 2 levels, but not to PS 4	Performance score (ECOG) decrease in 3 levels, but not to PS 4	Performance score (ECOG) decrease to PS 4
Chills	None	Chilly sensation, no rigors	Mild rigors, no medication required	Severe rigors, requires medication	Not applicable.
Myalgias	None	Mild muscular aching; no medication required.	Moderate aching requiring medication; no associated enzyme (CPK) elevation.	Severe muscular aching requiring medication; associated enzyme (CPK) elevation.	Not applicable.

Lombardi Cancer Research Center
Georgetown University Medical Center
Shading added for TNP-470: February, 1993

NCI COMMON TOXICITY CRITERIA (continued)

TOXICITY	GRADE				
	0	1	2	3	4
Weight gain/loss	< 5.0%	5.0 - 9.9%	10.0 - 19.9%	>20.0%	---
Hyperglycemia	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	> 2.1 - 5.0 x N	> 5.1 x N
Hypercalcemia	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	> 13.5
Hypocalcemia	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	≤ 6.0
Hypomagnesemia	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤ 0.5
Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≤ 0.24 x N
Prothrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N

Lombardi Cancer Research Center
Georgetown University Medical Center
Shading added for TNP-470: February, 1993

CONSENT TO PARTICIPATE IN A RESEARCH STUDY OF CONTINUOUS INFUSION OF TNP-470 OVER 120 HOURS

Approved 6.19.97 (Date)
Georgetown University Institutional Review Board

Project Director: Michael J. Hawkins, M.D.
Telephone: 202-687-8469

INTRODUCTION

The purpose of this document is to explain the nature of the treatment and what is known about the side effects, risks, inconveniences and discomforts so that you can decide whether you wish to participate. You are encouraged to ask any questions you have about this study.

Your illness is at a stage where conventional treatment approaches using currently available drugs, surgery, or radiation therapy have not proven to be effective. The new drug therapy which has been recommended to you in connection with this study is considered to be potentially helpful in controlling your disease, although benefit cannot be promised nor can the chance of benefit be accurately predicted.

PURPOSE OF THE TREATMENT

TNP-470 is a new drug that is being tested as an anti-cancer treatment. The purpose of this research is to determine the ability of patients to tolerate treatment with TNP-470, to determine the level of TNP-470 in the blood and urine, and to determine how the drug is removed from your body. We will also be watching for any reduction in the size of your tumor while you are receiving the drug. Prior to receiving TNP-470 we will ask you to take two pills and to provide a urine collection and a blood sample so that we may determine how fast your body eliminates different drugs. This information may help us in determining better ways to give cancer drugs to patients. You will be asked to sign a separate consent form for these studies.

TREATMENT

Treatment will be given by an intravenous infusion over 120 hours once every 3 weeks. Although we do not know if it will be the case for TNP-470, any beneficial effects from most cancer treatments become evident within 4 to 8 weeks. If you do respond to this treatment, you may continue to receive the injections for as long as this treatment is of benefit to you. Generally a worsening of your illness while on treatment indicates that TNP-470 is not effective in your case and that treatment should be discontinued. However, if your disease worsens soon after starting TNP-470 (for example, during the first 4 weeks of treatment) it may still be an option to continue for another 4 weeks. If your tumor is growing after 8 to 10 weeks of treatment we generally recommend that your treatment be changed. Your physician will discuss these issues and the other options for treatment with you if it is determined that your tumor is getting worse. If your tumor is approximately the same size (not better but not worse) after 8 to 10 weeks of treatment your physician will discuss with you whether you should continue to receive the

injections.

To determine how TNP-470 is processed in your body we will obtain multiple blood samples from you during the first day of infusion. We will also collect your urine so that we can determine if TNP-470 is eliminated from your body through your kidneys.

For convenience in administering TNP-470 and blood drawing, you may wish to have a permanent intravenous line placed (a minor surgical procedure).

SIDE-EFFECTS

Drug treatments for cancer usually cause side-effects but usually these side-effects get better between treatments or when treatment is stopped. However we can not be sure that any side effects you experience will be reversible. In addition, it is possible that other side effects which have not yet occurred in other patients could occur on this study. The major side effect in animals who were given TNP-470 was bleeding into the brain, lungs, heart and eyes; seizures, tremors and lack of coordination; anemia; decreased appetite and weight loss. The animals also developed temporary liver abnormalities and decreased numbers of white blood cells and platelets, which could lead to infection (which could be serious or life threatening) and bleeding. In a human trial at the Lombardi Cancer Center with TNP-470 administered over 4 hours once a week, the major side effects were lack of coordination and problems in balance, mild forgetfulness and confusion, nausea and vomiting, and fatigue. Side effects in other patients that may be due to TNP-470 have included irregular heart beats, rash, and bleeding. However, most of these patients have had AIDS and it has been difficult to know whether the side effects were due to TNP-470 or their disease. Early signs of bleeding may appear as small red dots on the skin or inside your mouth *If you experience bleeding of any type you should notify us as soon as possible.* You will be notified if your white blood cell count is low. *During this time period, if you develop a fever, it is very important that you notify us immediately.* If your blood tests show abnormalities from your liver, white blood cells, or clotting factors it may be necessary to stop TNP-470 until the blood tests return to normal.

As noted above, you may wish to have an intravenous line placed for blood drawing and administration of TNP-470. Placement of a permanent intravenous line is occasionally complicated by bleeding, or (if a lung is injured by a needle during line placement) collapse of a lung. Also, permanent intravenous lines can become infected, and this may require removal of the line and antibiotic treatment. If an intravenous line is considered, you will receive more information about permanent intravenous lines from the doctor in charge of doing this procedure, and you will also be asked to give your consent before this is done.

Because severe side effects are possible with TNP-470, we will be watching your physical condition and laboratory tests very closely while you are on this study. **It is very important that you tell us immediately if you notice anything unusual because side effects are more**

reversible when detected early. You should call your physician about such changes in your condition, or Medical Oncology Clinic at (202) 687-2223, or (nights and weekends) you can call the oncology doctor on call at (202) 687-7243.

ADDITIONAL COSTS

While there is no charge for TNP-470, there will be charges associated with its administration that will be your responsibility. Because TNP-470 is an investigational agent, it is possible that your health insurance company will not pay for the costs associated with its administration. Costs related to this treatment, and any complications, side-effects, and/or consequences which may occur are anticipated to be similar to costs of alternative treatments for your disease. All medications, laboratory fees, physicians fees and hospital costs will be charged to you in the same way as if you were not part of this study. If TNP-470 becomes commercially available while you are on this study, it may be necessary for you to then purchase the drug.

There will be no charge to you for the blood and urine testing to determine how TNP-470 is processed in your body (the pharmacokinetic studies).

PROBLEMS OR QUESTIONS

The Lombardi Cancer Research Center physicians involved in your care are available to answer any questions now or in the future about this program. In addition, this research was approved by the Georgetown University Institutional Review Board. For information on research subject's rights, contact the office of the Institutional Review Board at (202) 687-1506.

VOLUNTARY PARTICIPATION

Your participation in this research study is voluntary. You are free to withdraw from this study at the Lombardi Cancer Research Center and seek care from any physician of your choice at any time. There is no penalty for withdrawing from this study. Withdrawal from this study will not harm your relationship with your doctor, the Lombardi Cancer Center, Georgetown University Hospital, nor result in loss of entitled benefits.

CONFIDENTIALITY

Information regarding your medical record will be made available to the Lombardi Cancer Center and TAP Pharmaceuticals, the company that is supplying TNP-470. These records may also be reviewed by the Food and Drug Administration (FDA) and could be made available to other pharmaceutical companies to assist them in gaining FDA approval for TNP-470. Otherwise all information about you will be kept strictly confidential. Although the results of this study will be published somewhere, you will never be identified by name in any published report.

COMPENSATION

In the event of any injury resulting from participation in this study, acute medical care will be provided at the usual charge, but no Federal, District of Columbia Government or Georgetown University funds will be available for compensation. Additional information on this subject, and about your rights as a participant in a research study, may be obtained from the Medical Director, Georgetown University Hospital at 784-3011.

Anyone who agrees to participate in this research may change his/her mind at any time.

QUALIFICATION

You have been informed that you cannot participate in this study if you are a woman who is pregnant or breast feeding. Regardless of your sex, you also agree to use standard methods of birth control during and for at least 6 months after the last day you receive TNP-470.

OTHER CHOICES FOR TREATMENT

You understand that other choices for treatment for your disease could be (1) supportive care only (no treatment such as chemotherapy to reduce the size of your tumor), or (2) different drugs or drug combinations which have often been given to patients with your disease (conventional or standard treatments), though there is no clear evidence that these different drugs or drug combinations help people to live longer.

AUTHORIZATION

Signing below indicates that you have read the above description of a research project (or it was read to you by _____); anything that you did not understand was explained to you by: _____; all of your questions were answered to your satisfaction; and **that you agree to participate in this research.**

After signing below you will receive your own copy of this form.

_____ _____
(Participate or Legal Representative) Date

_____ _____
(Witness) Date

_____ _____
(Investigator) Date

Appendix 2: Thalidomide protocol documentation

GEORGETOWN UNIVERSITY MEDICAL CENTER

Vincent T. Lombardi Cancer Research Center
School of Medicine
Department of Medicine
Division of Hematology/Oncology

July 22, 1997

Dale G. Vander Hamm
Major, Medical Service Corps
Chief, Human Use Review and Regulatory Affairs Division.

Dear Sir

Attached please find the revised cover sheet for NCI protocol **T94-0202, " Phase II Evaluation of Thalidomide in Patients with Metastatic Breast Cancer"**. The cover sheet has been revised to list University of Chicago as a participating institution in the study.

If further information is needed, please feel free to contact me at 202-687-2198.

Sincerely

Said Baidas, M.D.
Assistant Professor of Medicine
Division of Hematology/Oncology

3800 Reservoir Road NW Washington, DC 20007-2197
Faculty/Administration: 202-687-2198 FAX: 202-687-4429
Ambulatory Services: 202-687-2223 FAX: 202-687-3302

THALIDOMIDE PROTOCOL

Phase II Evaluation of Thalidomide In Patients with Metastatic Breast Cancer

Principal Investigator:

Said Baidas, M.D.
Department of Medicine
Division of Hematology Oncology
Georgetown University Medical Center
3800 Reservoir Road, N.W.
Washington, D.C. 20007

Participating Institutions:

University of Chicago
Responsible Investigator: Geni Florence Fleming, M.D.
University of Chicago Medical Center
5841 S. Maryland Ave, MC 2115
Chicago, IL 60637

The University of Chicago
The Division of Biological Sciences · The Pritzker School of Medicine
The University of Chicago Hospitals

Institutional Review Board
5841 S. Maryland Avenue
AMB S-138 · MC 1108
Chicago, Illinois 60637
(312) 702-6505, ext. 5-5753

NOTICE OF FULL APPROVAL

Principal Investigator: Gini Fleming
Faculty Exchange: MC2115
IRB Protocol Number: 08786
Informed Consent: Written
Minor's Assent Required: No
Protocol Title:
Phase II Evaluation of Thalidomide In Patients With Metastatic Breast Cancer

This notification certifies that the research protocol and/or consent form described above now has the full approval of the Institutional Review Board. PLEASE NOTE THAT ANY EXTERNALLY FUNDED RESEARCH, EVEN IF APPROVED BY THE IRB, MAY NOT BE INITIATED UNTIL A FULLY EXECUTED AGREEMENT HAS BEEN APPROVED BY UNIVERSITY RESEARCH ADMINISTRATION.

Date: 6-27-97 Signature of Chair: [signature]

c.c.: Fleming
Denise

GEORGETOWN UNIVERSITY Date: August 6, 1997

To: **Dr. Said Baidas**
Hematology/Oncology

From: **Elisabeth O. Crigler**
Executive Officer
Institutional Review Board

Subject: **Action on your protocol entitled: "Action on your protocol entitled: "Phase II Evaluation of Thalidomide in Patients with Metastatic Breast Cancer""**
(94-346)

The revised cover sheet, as stated in the July 22, 1997 memorandum, to your above referenced protocol was given approval through expedited review by Dr. Harry Preuss, acting Chair of the Institutional Review Board.

This is to inform you that you may continue your project.

Please remember to:

1. Seek and obtain prior approval for any modifications to the approved protocol.

2. Promptly report any unexpected or otherwise significant adverse effects encountered in the course of this study to the Institutional Review Board within 72 hours. This includes information obtained from sources outside Georgetown that reveals previously unknown risks from the procedures, drugs or devices used in this study.

Please refer to the above mentioned date and protocol number when making inquiries concerning this protocol.

RECEIVED
AUG 8 1997
PROTOCOL OFFICE

GEORGETOWN UNIVERSITY MEDICAL CENTER

Vincent T. Lombardi Cancer Research Center
School of Medicine
Department of Medicine
Division of Hematology/Oncology

DATE: July 22, 1997

TO: Elisabeth O. Crigler
Executive Officer, Institutional Review Board

FROM: Said Baidas, M.D.
Hematology/Oncology

THROUGH: Clinical Research Management Office

SUBJECT: Revised Cover Sheet for IRB 94-346, Protocol entitled, **"PHASE II EVALUAION OF THALIDOMIDE IN PATIENTS WITH METASTIC BREAST CANCER"**

Attached please find the revised cover sheet for the above referenced protocol. The cover sheet has been revised to list University of Chicago as a participating institution in the study.

If further information is needed, please feel free to contact me.

3800 Reservoir Road NW Washington, DC 20007-2197
Faculty/Administration: 202-687-2198 FAX: 202-687-4429
Ambulatory Services: 202-687-2223 FAX: 202-687-3302

THALIDOMIDE PROTOCOL

Phase II Evaluation of Thalidomide In Patients with Metastatic Breast Cancer

Principal Investigator:

Said Baidas, M.D.
Department of Medicine
Division of Hematology Oncology
Georgetown University Medical Center
3800 Reservoir Road, N.W.
Washington, D.C. 20007

Participating Institutions:

University of Chicago
Responsible Investigator: Geni Florence Fleming, M.D.
University of Chicago Medical Center
5841 S. Maryland Ave, MC 2115
Chicago, IL 60637

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

AMENDMENT REVIEW

AUG 27 1997

Date:
NCI Protocol #: T94-0202
Local Protocol #:
Amendment #: A5
Amendment Date: 07/22/97
Protocol Chairman: BAIDAS,S.

Said Baidas, M.D.
Department of Medicine
Division of Hematology Oncology
Georgetown University Medical Ctr.
3800 Reservoir Road, N.W.
Washington, D.C. 20007

Dear DR. BAIDAS:

An amendment to your protocol, NCI # T94-0202 entitled, "PHASE II EVALUATION OF THALIDOMIDE IN PATIENTS WITH METASTATIC BREAST CANCER", was received by the Cancer Therapy Evaluation Program of the Division of Cancer Treatment, Diagnosis, and Centers, National Cancer Institute on 07/30/97 . The amendment has been reviewed with the following status:

✓ Approved as written.
____ Approved with recommendations. See attached review.
____ Pending your response to the attached amendment review.
____ Pending receipt of adequate documentation. See attached Guidelines.
____ Disapproved.

Sincerely,

Susan G. Arbuck, M.D.
Head
Developmental Chemotherapy Section
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment, Diagnosis, and Centers

cc: DMAS
Edward P. Gelman, M.D.

THALIDOMIDE PROTOCOL

Phase II Evaluation of Thalidomide In Patients with Metastatic Breast Cancer

Principal Investigator:

Said Baidas, M.D.
Department of Medicine
Division of Hematology Oncology
Georgetown University Medical Center
3800 Reservoir Road, N.W.
Washington, D.C. 20007

Participating Institutions:

University of Chicago
Responsible Investigator: Geni Florence Fleming, M.D.
University of Chicago Medical Center
5841 S. Maryland Ave, MC 2115
Chicago, IL 60637

Phase II Evaluation of Thalidomide in Patients with Metastatic Breast cancer

IND # 48,832

Principal Investigator:
Said Baidas, M.D.
(202) 687-2198
(202) 687-4429-FAX

Co-Investigators:

Andrea Denicoff, C.A.N.P.
Matthew Ellis, M.D.
Annette Galassi, C.A.N.P.
Edward P. Gelmann, M.D.
Daniel Hayes, M.D.
Michael Hawkins, M.D.
Claudine Isaacs, M.D.
Marc E. Lippman, M.D.
John L. Marshall, M.D.
Kenneth Meehan, M.D.
Department of Medicine
Division of Hematology Oncology

Biostatistics:
Edmund Gehan, Ph.D.
John Hanfelt, Ph.D.

Georgetown university Medical Center
3800 Reservoir Rd, N.W.
Washington, D.C. 20007

February, 1995
Revised: October, 1995
Revised: February, 1996
Revised: June 21, 1996
Revised: August 20, 1996
Revised: August 27, 1996
Revised: September 29, 1996
Revised: March 4, 1997
Revised: April 10, 1997
Revised: July 22, 1997

TABLE OF CONTENTS

Section		Page No.
1.	BACKGROUND AND RATIONALE	1
2.	OBJECTIVES	4
3.	STUDY DESIGN	5
4.	PATIENT SELECTION AND ELIGIBILITY	5
5.	THALIDOMIDE CLINICAL SUPPLIES	8
6.	DRUG ADMINISTRATION	8
7.	BIOASSAYS	8
8.	CLINICAL AND LABORATORY MEASURES	10
9.	STUDY PARAMETERS	10
10.	TREATMENT MODIFICATIONS AND MANAGEMENT OF TOXICITY	10
11.	PATIENT MANAGEMENT	13
12.	RESPONSE ASSESSMENT	14
13.	STATISTICAL CONSIDERATIONS	15
14.	ADMINISTRATIVE ASPECTS	18
15	DCT GUIDELINES FOR MULTICENTER INVESTIGATIONAL AGENT STUDIES	19
16.	REFERENCES	22
17.	APPENDICES	26
INFORMED CONSENT		1

1. BACKGROUND AND RATIONALE

1.1 Metastatic Breast Cancer

Breast cancer is the most common cancer in women in North America, with 182,000 new cases anticipated for 1994 and 46,000 deaths[1]. It is the leading cause of cancer mortality for women aged 15-54, and is only second to lung cancer for women aged 55-74. From 1983-7, 7% of women newly diagnosed with breast cancer presented with distant disease. In addition 24-30% of women with node negative disease and 50-60% of women with positive nodes at diagnosis will recur despite adjuvant therapy. Based on these percentage and on the predicted number of new cases of breast cancer, over 12,000 women are expected to present yearly with advanced disease; 22,800 women with node negative breast cancer will relapse; and 47,200 women with stage II or stage III disease will recur. Thus, large number of women develop metastatic disease on annual basis. Metastatic breast cancer is incurable with present therapies. Standard therapies include chemotherapy, hormonal therapy or combination of both. While initial response to therapy is high, all tumors eventually develop resistance and can no longer be controlled. The use of modulators of drug resistance and the dose intense chemotherapy supported with bone marrow or peripheral stem transplant have been encouraging but have not resulted in appreciable difference in cure rate. Thus, it is imperative to develop new treatment strategies as the use of differentiating or antiangiogenesis agents.

1.2 Introduction to Thalidomide:

Thalidomide was introduced in 1954 by the drug manufacturer Chemie Grunethal as a sedative/ hypnotic and was used as a sleep aid and to ameliorate nausea and vomiting in pregnancy. It had no apparent toxicity or addictive properties in humans and animals at therapeutic exposure level. There were reports of peripheral neuritis attributable to thalidomide but only occurred in patients with long term use[2].

In 1960 a large increase in incidence of newborns with limb malformations (Amelia & Phocomelia) was recorded in W. Germany. Lenz[3] in Germany and McBride[4] in Australia independently identified thalidomide as the causative agent. Thalidomide was withdrawn from the market by the end of 1961.

In 1965, Sheskin described immunosuppressive activity of thalidomide in the treatment of reactive lepromatous leprosy.[4] Over the last two decades further therapeutic trials in dermatologic diseases showed thalidomide to be effective in the treatment of cutaneous lupus erythematosus[5] , recurrent erythema multiforme[6] and recurrent aphthous[7] ulcers especially in AIDS patients[8].

Recently the benefits of thalidomide as an immunosuppressive agent has been described in animal models of GVHD after bone marrow transplant[9] [10] and renal transplantation[11] .Also there are reports of possible additive or synergistic action between thalidomide and cyclosporine in preventing acute rejection of rat cardiac transplant model [12] and in prophylaxis of GVHD[13].The exact mechanism of this immunosuppression is unclear although might be secondary to inhibition of lymphocyte proliferation[14] or to simultaneous up and down regulation of different integrin receptors on human WBCs[15]. Thalidomide inhibit TNF-α production by stimulated human lymphocytes[16] possibly by enhancing mRNA degradation[17].

An antiangiogenesis activity of thalidomide has been recently described by D'mato and J. Folkman. Thalidomide when administered orally was shown to inhibit angiogenesis induced by basic-FGF in the rabbit corneal micropocket assay while no angiogenic activity was seen in CAM assay, suggesting that thalidomide must be metabolized in the liver to form an epoxide that may be also the active teratogenic compound. Also the inhibition of angiogenesis in immunosuppressd animals and the lack of effect of the functionally related immunosuppressive agent cyclosporin A argue for a direct effect of thalidomide on angiogenesis[18].

This direct antiangiogenesis activity of thalidomide and the availability of a generally safe and effective birth control measures directs thalidomide use in the treatment of diabetic retinopathy, macular degeneration and solid tumors.

Thalidomide generally is well tolerated. Side effects and toxicities that were noticed before include somnolence, nausea, dry mouth and skin, constipation, urticaria, erythema, increase appetite, headache, irregularities in menstrual cycles, hypothyroidism, edema of lower extrimities, teratoginicity and peripheral neuropathy[19],[42,43]. This peripheral neuropathy was first reported by Florence in 1960[1], several reports appeared latter describing mostly sensory (occasionally motor), symmetrical, distal neuropathy that might not be reversible. Recent reports in patients treated with thalidomide for dermatological conditions describe 20-50% incidence of neuropathy[20], with increase incidence in females and older patients. No clear relation between dose, duration of treatment and neuropathy was found, although a possible relation between slow acetylators and development of thalidomide neuropathy was found[21]. Early detection of this neuropathy with serial electophysiological tests might be possible[21]. The immunosuppressive action of thalidomide has not been described to be associated with increased incidence of infections.

In a study by Olsen[42], Thalidomide was administered to 21 patients with fourteen types of cancer with a total dose ranging from 4.2 to 354.0 gm. No tumor regression was noted but there was subjective palliation in 7 patients. In 2 patients, (multiple myeloma, fibrosarcoma), the rapid progression of the disease appeared to be slowed.

Another study by Grabstald[43], 71 patients with a wide spectrum of cancers were treated with thalidomide at variable doses ranging from 300 mg to 2000 mg per day. There was only one objective response in a patient with renal cell cancer whose pulmonary lesions disappeared after treatment (this patient has a nephrectomy which also reported to be followed occasionally with disappearing of pulmonary metastasis).

1.3 Tumor induced angiogenesis:

Angiogenesis is a normal physiological process in the growing embryo, wound healing and ovulation[22]. In 1971, Folkman found that angiogenesis is an essential step in tumor development[23]. Progressive recruitments of blood vessels to the tumor site are thought to result in a self perpetuating loop helping to drive the growth of solid tumors[24]. This new vasculature also allows competent tumor cells to find access to the vascular system and facilitate distant spread of the tumor cells[25]. Neovascularization is apparently an absolute prerequisite for physical expansion of solid tumors to grow beyond the volume of about 1-2 mm in diameter[26]. Several molecular and cellular mechanisms have been identified by which tumor parenchyma may exert its angiogenic effect on host endothelial cells[27,23,25]. There is also evidence that endothelial cells themselves, and like other stromal cells, may act reciprocally to alter the

behavior of adjacent tumor cells in a paracrine or cell contact mediated fashion. There is now known to be a diverse family of angiogenic growth factors, foremost among them being basic fibroblast growth factor and acidic FGF[25]. Several angiogenic peptide genes have been sequenced and cloned.[28]

More recently, the degree of vascularization has acquired importance as an independent prognostic indicator in various types of solid tumors. Studies showed that tumor angiogenesis in invasive breast cancer, expressed as the number of capillaries in localized regions of angiogenesis within the tumor, is correlated with the presence of local and distant metastasis[29,30,31]. Similarly, it has been reported that capillary density may also be associated with progression in prostatic carcinoma[32]. Also earlier studies with skin melanoma suggested that increased vascularity at the base of the tumor, as determined by percent vessel area, may have prognostic significance in lesions of intermediate thickness[33].

1.4 Rationale for Use

Advances in our understanding of molecular and cellular basis of cancer development and progression have been impressive during the last two decades. Unfortunately our ability to apply such basic research discoveries towards developing new strategies for cancer treatment and cure has been slow and limited. Tumor cells continue to acquire resistance to chemotherapy and hormonal therapy. If the instability of tumor cell genome makes acquisition of resistance to tumor specific or associated cytotoxic agents by solid tumors virtual certainty, it would seem appropriate to think of a therapeutic strategy in which the therapy is directed at a normal (genetically stable) diploid cell population whose integrity is required for progressive tumor growth and spread. Endothelial cells, which comprise microvascular blood vessel capillaries in tumors represent such a targetable normal cell population. The inhibition of tumor angiogenesis as a form of cancer therapy to be realistic should have minimal effect on established blood vessels else where in the body. The results of Folkman and colleagues using cortisone and heparin demonstrate that such specificity of toxicity can sometimes be achieved[34], at least at experimental level. This implies that there are indeed differences between tumor and normal blood vessels that can be exploited as therapeutic targets. The nature of these differences which include cellular composition, vessel permeability and stability-have been reviewed by several authors[35,36,37,38].

As studies in breast cancer suggest that microvascular quantitation as a measure of angiogenesis might be one of the most powerfull prognostic tools for tumor growth and metastasis,[28,29,30,39,40] angiogenesis as a form of cancer treatment becomes an attractive mode of therapy in breast cancer.

The recent report by Folkman of the antiangiogenic activity of thalidomide [18] directs its use as antiangiogenic agent for treatment of breast cancer. Antiangiogenic therapy will require prolonged use of the active agent to achieve the therapeutic goal. Thalidomide given in the oral form, with tolerable side effects, makes it attractive for this form of therapy. Antiangiogenesis therapy might not bring the cure for cancer, but if it can prolong the time of tumor stability or reduce its size to a degree that it might be amenable to other form of treatment, antiangiogenesis therapy will be a success.

1.5 Overview of Pharmacology (Thalidomide Invistigator's Brochure)

Thalidomide (N-Phthalidoglutarimide: C13O4N2H9) is a racemate. The S(-) l and R(+)/d forms represent derivatives of l- and d- glutamic acid, respectively. The maximal solubelity of racemic thalidomide in water is approximately 2 x 10^4 mol/L (45 to 60 mg/L). The ultraviolet spectrum of thalidomide is characterized by an absorbance maximum at 300nm which is dependent on an intact phthalimide moiety.

Non enzymatic cleavage of one or more of the amide bonds in the thalidomide molecule produces hydrolysis products which contain at least one carboxyl group. They are more polar and can be expected to cross biological membranes less efficiently than the parent compound. Thalidomide constitute a transport form for its hydrolysis products: the non polar parent compound enters cells or tissues and is converted to polar derivatives which has been shown to accumulate in erythrocytes and in the embryo. Considering the possible combinations of hydrolysis, hydroxylation and optical activity, there may be more than 50 metabolites of thalidomide in vivo.

Studies in experimental animals showed high concentration of the drug in the gastrointestinal tract, liver and kidneys, and lower concentrations in muscle, brain and adipose tissue. In pregnant animals, thalidomide is able to pass across the placental barrier. The main pathway of degradation in animals appears to be non enzymatic hydrolytic cleavage. Minor amounts of hydroxylated products have been detected in the urine of some species. Hepatic metabolism of thalidomide probably involves enzymes of the cytochrome P450 family. Only the parent compound is enzymatically modified. Thalidomide itself does not cause P450 enzyme induction, but possibly interferes with enzyme induction by other compounds.

The John Hopkins Oncology Center has evaluated the plasma pharmacokinetics and Urinary excretion of thalidomide in eight healthy male volunteers receiving a single oral dose of 200mg of thalidomide with the following results: Plasma concentration vs. time data were well fit by a one compartment model. The mean ($\pm$SD) peak concentration, 1.15 $\pm$ 0.2 μg/ml, was achieved at 4.39$\pm$ 1.27 hr, absorption and elimination half lives were 1.70$\pm$ 1.05 hr and 8.70$\pm$ 4.11 hr respectively, with a lag time of 0.41$\pm$ 0.71 hr observed in six subjects. The apparent volume of distribution and total body clearence rate, based on assumed complete bioavailability, were 120.69$\pm$ 45.63 liters and 10.41$\pm$2.04 liters/hr. The urinary excretion of thalidomide accounted for only 0.6$\pm$ 0.22% of total dose administered over 24 hr, and the renal clearence rate was 0.08$\pm$ 0.03 liter/hr. This suggests that the major route of elimination of thalidomide is nonrenal[41].

2. OBJECTIVES

A. Primary objective:

1. To assess if there is difference in activity (by evaluating time to progression) and safety profile between the low dose and high dose arm of thalidomide.

B.Secondary Objectives:

1. To determine the objective response rate (complete and partial response rates) of Thalidomide in patients with measurable metastatic breast cancer at both arms. To determine time to response and survival.

2. To compare the post versus pre treatment tumor growth rates in patients with known rate of

tumor growth over the 2-4 month period prior to starting thalidomide.

3. To analyze growth factors expression and matrix metalloproteinase activity in patients receiving thalidomide.

4. To study thalidomide pharmacokinetics.

3. STUDY DESIGN

This investigation is a Multicenter, open label, randomized Phase II study to evaluate the safety and efficacy of daily oral administration of Thalidomide as therapy for a maximum of 50 patients with metastatic breast cancer.
As it is unclear what dose of thalidomide is sufficient for in vivo biological activity, therefore, in an attempt to obtain information regarding this issue patients will be randomized into two arms with 6 patients in each :

a. Low dose arm: 200mg/day, qhs. 9 pm.
b. High dose arm; 800mg/day, qhs. 9 pm. Increase by 200mg/day q 2 weeks as tolerated up to total dose daily dose of 1200mg/day, qhs. 9 pm.

Thalidomide was given at higher doses with tolerable side effects. In a study by Olson[42] for the treatment of advanced cancer with thalidomide a dose of 200mg three times a day was used and in the absence of toxicity the dose was increased as tolerated to as high as 1,400mg per day. At this dose the chief side effect was sedation. Another report by Grabstald[43], 71 patients with advanced cancer were treated with thalidomide at variable doses ranging from 300mg to 2000mg per day with main side effect being sedation.

Patients will receive the drug as long as there is no evidence of tumor progression, and as long as there is no dose limiting toxicity.

The first tumor response assessment in the absence of new symptoms will be made at week 8 of therapy. Patients with progressive disease will go off study. All others may continue therapy if toxicity is acceptable. Tumor assessment thereafter will be repeated every 2 months.

Efficacy and safety will be assessed by histories and physical examinations, vital signs, assessment of performance status, laboratory tests, and X-ray evaluations. Patients will be evaluated initially every two weeks during the first cycle (first 8 weeks) and then monthly for toxicity. Section 7 and Table I outline the types and frequency of parameters to be obtained. Toxicities will result in dose modifications as described in section 10.

Prior hormonal and/or chemotherapy will be allowed, as Thalidomide has a mechanism of action different from the above-described agents. Thus, resistance to conventional therapy does not necessarily imply resistance to thalidomide.

4. PATIENT SELECTION AND ELIGIBILITY

4.1 Specific Criteria Required for Patient Entry

4.1.1 Patients must have histologically confirmed advanced breast cancer.

4.1.2 Patients must have evaluable or bidimensionally measurable disease in at least 1 site: For measurable disease, minimum indicator lesion size must be 1 cm. Patients with evaluable bone only disease must have a lytic lesion on plain X ray, CT scan or MRI, that has not been previously irradiated. Ascites and pleural effusions are not considered as measurable or evaluable advanced cancer.

4.1.3 Documented objective progressive disease as per section 12.4.

4.1.4 Patients may have had no more than 3 prior chemotherapy regimens. One adjuvant chemotherapy regimen is permitted in addition to two regimens for metastatic disease. If patient has no adjuvant chemotherapy, then, up to three chemotherapy regimens for metastatic disease are allowed. No limitations on the previous hormonal or biological therapies.

4.1.5 Patients must be 18 years of age or older.

4.1.6 Patients must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible side effects), must agree to cooperate and comply with the study requirements, and must sign an informed consent.

4.1.7 Patients must be ambulatory, with an ECOG performance status of 0, 1 or 2 and must be maintaining a reasonable state of nutrition.

4.1.8 Patients must have clinically adequate function of all organ systems and meet the minimum requirements as outlined below:

4.1.8.1 Hematological: WBC ≥ 3,000/mm and hemoglobin of 8g /dl and platelet count ≥ 75,000/mm^3;

4.1.8.2 Coagulation: PT and APTT < 1.25 normal.

4.1.8.3 Hepatic: bilirubin, SGOT (AST), SGPT (ALT) and ALK PHOS no greater than 1.5 X the normal range. For patients with hepatic metastasis for whom the disease is felt to be the cause of transaminase elevations, the enzyme value should be ≤ 2.5 times normal. Mg≥1.8 (if less than 1.8 Mg should be supplemented). In Mg deficient rats with an elevated TNF level an increase in cardiomyopathic lesion was observed when treated with thalidomide, although there was complete inhibition of the increase in TNF.

4.1.8.4 Renal: serum creatinine no greater than 1.5 times the upper limit of the normal range (and/or creatinine clearance 60 ml/min/1.72m^2 BSA);

4.1.9 Patients must have recovered from the reversible side effects of any prior therapy; permanent and stable side effects/changes are acceptable.

4.1.10 HIV: negative antibody assay

4.1.11 Pregnancy test: Negative serum pregnancy test within 48 hours of the first dose, and monthly thereafter, for all women of childbearing potential.

4.2 Exclusion Criteria (Contraindications to Enrollment)

4.2.1 Recent major surgery (within 21 days);

4.2.2 Frequent vomiting or severe anorexia;

4.2.3 Cytotoxic chemotherapy, hormonal therapy, or radiation therapy within 4 weeks of study entry (Day 1); (6 weeks for mitomycin C or nitrosourea therapy.)

4.2.4 Presence of, or history of brain metastases, carcinomatous meningitis, and/or cardiomyopathy;

4.2.5 Pregnant or lactating women (NOTE: women and men enrolled in the study must agree to practice an effective method of birth control for at least nine months after their last treatment on protocol);

4.2.6 Serious inter-current medical illnesses which would interfere with the ability of the patient to carry out the treatment program.

4.2.7 Patients with a history of other malignancies except basal cell carcinoma of the skin and cervical carcinoma in situ.

4.2.8 Grade 2 neurotoxicity.

4.3 Prohibitions and Restrictions

The following therapies are prohibited during this study and may not be administered to patients being treated on this protocol:

4.3.1 Radiation therapy

4.3.2 Anti-cancer chemotherapy;

4.3.3 Anti-cancer hormonal therapy;

4.3.4 Anti-cancer immunotherapy.

4.3.5 Concurrent investigational drug therapy.

4.3.6 All concomitant medications must be recorded in the Case Report Form (CRF). The name, daily dose, and duration of treatment must be listed.

4.3.7 Sedatives and hypnotics should be tapered and if possible stopped while on study.

5. THALIDOMIDE CLINICAL SUPPLIES

Thalidomide will be provided in tablet form. Each thalidomide tablet contains: Thalidomide Powder "100.00 mg", Microcrystalline Cellulose "133.75 mg", Poloxamer "10.00 mg", Croscarmellose Sodium "5.00 mg" and Magnesium Stearate "1.25 mg".

Thalidomide will be supplied by the NCI.

6. DRUG ADMINISTRATION

Thalidomide will be administered orally at a dose of:

a. Low dose arm: 200 mg/day, qhs. 9 pm.
b. High dose arm: 800mg/day, qhs. 9 pm. Increase by 200mg/day q 2 weeks as tolerated up to a total daily dose of 1200mg/day, qhs. 9 pm.

Patients will be encouraged to take laxative regularly while on thalidomide treatment unless there is a contraindication for taking laxatives.

Eight weeks of therapy will be considered one cycle. There is no interruption of treatment between cycles as long as there is no toxicity requiring holding thalidomide.

7. BIOASSAYS

7.1 Serum levels of TNF, VEGF, bFGF, plasma levels of matrix metalloproteinase (MMP-9) and urinary bFGF will be measured before entering the study and on week 2,4,6 and 8 of the first cycle and monthly after that. TNF, VEGF, bFGF assays will be done at Dr Wellstein lab. And MMP at Dr Dickson la.

TNF, VEGF and bFGF:

Serum samples will be obtained on all patients immediately before the first dose and then on week 2, 4, 6 and 8 of the first cycle and monthly after that. During each time point 7 mL of blood will be collected in a red top tube and placed on ice immediately. The serum will then be pipetted off and placed into 2 NUNC® sample mailing tubes and stored in the - 70°C freezer until shipment to Anton Wellstein, M.D., Ph.D. laboratory in the preclinical science building.

TNF, VEGF and bFGF levels in the serum will be measured by Quantikine ELISA kit (R&D Systems, Minneapolis, MN) according to the guidelines suggested by the supplier of the kits.

Matrix Metalloproteinase (MMP-9):

Plasma samples will be obtained on all patients immediately before the first dose and then on week 2, 4, 6 and 8 of the first cycle and monthly after that. During each time point 5 mL of blood will be collected in a purple top containing EDTA (Potassium Chloride) and placed on ice immediately. The sample will then be placed in a refrigerated centrifuge and spun down at 3000 rpm for 15 minutes. The plasma will be pipetted off and placed in a NUNC® sample mailing tube and stored in the - 70°C freezer until shipment

to Robert Dickson, Ph.D. laboratory in the New Research Building.

Urine:
Urine samples will be obtained on all patients immediately before the first dose and then on week 2, 4, 6 and 8 of the first cycle and monthly after that. During each time point 20 mL of urine will be collected in a standard urine collection container without preservative and placed on ice immediately. The urine will then be transferred to 30 mL container for storage in the - 70°C freezer until shipment to Anton Wellstein, M.D., Ph.D. laboratory in the preclinical science building.

Each institution will batch their own bioassay specimens until the trial is completed then will be mailed on dry ice by Federal Express to Dr. Said Baidas at:

Said Baidas, M.D.
Lombardi Cancer Center, Room 416
Georgetown University Hospital
3800 Reservoir Road, NW
Washington, D.C., 20007

7.2 Pharmacokinetics:

7.2.1 The first dose of thalidomide will be given at 9 am, all doses after that will be given qhs at 9 pm. Plasma samples will be obtained on all patients immediately before the first dose on day 1 and then ½, 1 , 1 ½, 2, 3, 4, 5, 6, 7 and at 9:00 am and 1:00 pm the second day. Chronic serum level will be done every 2 weeks first cycle and monthly after that.
During each time point 5 ml of blood will be collected in a green top containing NAH (sodium heparin) and placed on ice immediately. Chronic plasma levels will be done every 2 weeks first cycle and monthly after that. The sample will then be placed in a refrigerated centrifuge and spun down at 3000 rpm for 15 minutes. Equal part 0.025 M Sorenson's citrate buffer solution will then be placed in the Corning sample mailing tube along with the pipetted plasma. The mailing tube will then be stored at -20° C and transferred that afternoon to the Analytical Core Laboratory for extraction and assaying by Dr. David Flockhart, M.D., Ph.D.

Each institution will batch their own specimens until the study is completed then will be mailed on dry ice by Federal Express to Dr Baidas at:

Said Baidas, M.D.
Lombardi cancer center, room 416
Georgetown University hospital
3800 reservoir Road, NW
Washington, D.C., 20007

7.2.2 Extraction and assay of thalidomide: Assay developed by Dr. David Flockhart:
Standard amount of thalidomide powder were added to 1 ml of whole blood and then directly transferred to a glass tube containing equal volume of 0.025 M Sorenson's citrate buffer (pH 1.5) to which was added 50 ul of phenacetin as internal standard. This

solution was mixed with 5 ml of diethyl ether and the solvent layers were separated by centrifusion at 1200x g for 15 min and the organic layer aspirated and then evaporated under nitrogen. The dried residue was reconstituted in 50 ul of a mobile phase of acetonitrile: water(35:65) and injected using a WISP (Waters-Millipore) autoinjector into a Lichrocart (Merck) RP-18, 7 u column (250x4mm) at a flow rate of 1.2 ml/min. A detection wavelength of 220 nm was used and under these conditions thalidomide eluted with a retention time of 14.6 min and phenacetin with a retention time of 25.7 min. The limit of quantification in the assay was 5ng/ml and the intr-and inter-assay coefficients of variation were less than 7.1 and 12.6% respectively.

8. CLINICAL AND LABORATORY MEASURES

Upon entry into the study and throughout the study, including a post-treatment "follow-up" evaluation, various clinical and diagnostic laboratory quantitative and qualitative measures are to be obtained as described below and detailed on the protocol-specific patient case report forms. The purpose of obtaining these detailed parameters is to allow full safety and efficacy assessment of the drug treatment.

8.1 Initial Evaluations Upon Entry

In addition to meeting the Selection criteria (Section 3), patients must also have a number of "baseline" assessments performed prior to or upon entry to the study. These measurements are outlined in Table 1. Also, patients should be evaluated for the possibility of tapering any sedative or antidepressant drug taken by the patient. Sedatives and hypnotics should be tapered and if possible stopped while on study.

Patient should have a careful and complete neurologic examination at entry, with evaluation for peripheral neuropathy at each visit. Patients with childbearing potential should have a negative serum pregnancy test within 48 hours of the first dose and monthly after that.

8.2 Evaluations During the Study

Throughout the study, upon study termination and in follow-up of study termination, the patient is to have multiple evaluations performed at various time points as outlined in Table 1.

8.2.1 Tumor biopsy

Patients who have accessible tumor and are willing to have biopsies performed, a biopsy will be performed at entry, every 8 weeks, and at the time of removal from the study. Specimens will have angiogenic index determined. Also, assessment of tumor associated TNF, bFGF, or other tests will be performed.

If as a result of non-study clinical needs, a biopsy sample of the patient's tumor is obtained, special laboratory studies may be performed on tissue derived from that biopsy sample.

9. STUDY PARAMETERS (See Table I)

10. TREATMENT MODIFICATIONS AND MANAGEMENT OF TOXICITY

10.1 Dose modification for toxicity.

a. For hematologic toxicity , only grade 4 toxicity should be dose limiting. For patients with grade 4 hematologic toxicity, drug should be held until resolution to grade 1 and then restarted at 75% the original dose reduction. Patients with recurrent grade 4 hematologic toxicity would then be removed from the study.

b. For non hematologic toxicity

1. Any grade 4 toxicity: Patient should be taken off study.

2. Neurotoxicity: Drug should be held for grade 2 toxicity until resolved to grade 1 and then restart at 75% the original dose. For recurrent grade 2 toxicity restart at 50% of the original dose when resolved to grade 1 or remove patient from study (discretion of principal investigator).

3. For other DLT: (see shaded toxicities in the NCI common toxicity criteria appendix A): At shaded toxicities drug should be held until resolved to grade 1 toxicity then restart at 75% the original dose. Re-evaluation should occur at 1-week intervals. If it is not possible to resume therapy after three weeks delay due to persistent treatment related toxicities, the patient should be taken off study. For recurrent shaded toxicities drug should be held until toxicity resolved to grade one then restart at 50% the original dose. For recurrent shaded toxicities while at 50% dose reduction, patient should be taken off study.
If patient is very drowsy at the starting dose of 200 mg/day reduce by 50% (give 100mg/day). If patient is very drowsy at the starting dose of 800 mg/day reduce dose to 600 mg and if continued to be drowsy reduce dose to 400 mg then to 200 mg/day and lastly to 100 mg/day. If patient can not tolerate this dose she should be taken off study.

Table I. Study Parameters

Parameter	**On Study	week 2	week 4	week 6	q 8 weeks	Monthly After Cycle 1
History/Physical Exam (with neuro- exam for peripheral neuropathy)/Vital Signs[3]	x	x	x	x	x	x
Height	x					
Weight	x	x	x	x	x	x
Performance Status	x	x	x	x	x	x
CBC, Diff, Platelets	x	x	x	x	x	x
Serum electrolytes, Mg, PT, PTT, FVIII	x	x	x	x	x	x
Chemistry Survey[1] and SGPT	x	x	x	x	x	x
Thyroid Function tests[3]	x					
Urinalysis	x					x
Chest X-ray	x				x[5]	
Bone Scan	x				x[5]	
Abdominal CT	x				x[5]	
Growth factors, MMP, and TNF assay	x[6]	x	x	x	x	x
Tumor assessment (any tests required to assess tumor size)	x				x[4]	
EKG	x					
Pregnancy test[2]	x		x	x		
HIV	x					
PK	x	x	x	x	x	x
CEA		x	x	x	x	x

**On study laboratory tests and X rays must be obtained within 2 weeks starting on study.

[1] Includes: BUN, creatinine, glucose, SGOT/AST, alkaline phosphatase, total bilirubin, LDH, calcium, and uric acid
[2] For fertile women in whom pregnancy cannot otherwise be ruled out pregnancy test must be negative prior to starting treatment.
[3] At 12 weeks or another time point only if clinically indicated.
[4] Any other studies required to assess tumor size/extent.
[5] If required to assess tumor size/extent
[6] growth factors and MMP assay to be done before enrollment, every 2 weeks during the 1st cycle then monthly.

10.2 **Management of anticipated toxicities.** Based upon preclinical toxicology studies, anticipated toxicities include: nausea, constipation, somnolence, urticaria, erythema, increased appetite, increase weight, edema of lower limbs, headache and teratoginicity. Therefore, physical exam and laboratory parameters will be closely monitored. Thalidomide will be discontinued or dose will be adjusted at the first clinical evidence of toxicities as discussed in section 10 (see shaded toxicities in NCI Common Toxicity Criteria, Appendix A). Dose adjustment for peripheral neuropathy as in section 10.1. Patients will be encouraged to take laxatives while on study as constipation is a common side effect of thalidomide. If the patient is on a sedative or antidepressant drugs assessment for possibility of tapering these drugs before starting thalidomide should be done, every effort to stop sedatives and hypnotics before starting thalidomide should be done. Although thalidomide is an immunosuppressive agent, no increase in incidence of infection has been reported, patients should be observed for signs and symptoms of infection.

10.3 **Unavoidable treatment delays for non-medical reasons.** Treatment interruptions for non-medical reasons (for any reason, at the discretion of the patient and physician) are at times unavoidable and are permissible under this protocol. However, every attempt should be made to avoid any non-medical treatment delays, especially during the first 8 weeks of treatment. Patients who require frequent or prolonged treatment interruptions should be taken off study.

11. PATIENT MANAGEMENT

11.1 Patient Follow-up

All patients who enter the study and receive at least one dose of study drug and then have treatment terminated, regardless of reason for withdrawal or study termination, should, if at all possible, have full follow-up evaluation 4 to 6 weeks following their last dose.

11.2 Criteria for Terminating Treatment

The following criteria for terminating treatment must be followed:

11.2.0 During the initial 8 weeks dosing period, patients should remain on the study unless they have progression with life threatening progression or progression requiring immediate palliative therapy.
Progression of disease at the week 8 staging by ≥25% of the measurable disease or with a new lesion will be considered progressive disease and the patient would be removed from the study. All new bone lesions should be evaluated by plain radiography, CT scan or MRI. A new bone scan lesion will only be considered progreassion if it is associated with the appearence of a new or enlarging lytic lesion on plain bone radiography, CT scan or MRI.
Progression of disease while on study according to this criteria requires termination of treatment, unless the investigator documents on the patient's case report forms the specific reasons and rationale for continuing treatment under such circumstances.

11.2.1 Toxicity that does not resolve within 3 weeks of stopping Thalidomide requires termination from any further treatment.

11.2.2 Changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator require withdrawal from study treatment.

11.2.3 Withdrawal of Patients

The patient's physician(s) are free to and should discontinue treatment and take the patient off the study at any time, if this is believed to be in the patient's best interest. Further, a patient is free to withdraw from study treatment and participation at any time for any reason. Full documentation of the reasons and circumstances of all patients who withdraw must be documented on the appropriate case report forms.

11.2.4 Pregnancy.

12. RESPONSE ASSESSMENT

12.1 Complete Response

Disappearance of all clinical and laboratory signs and symptoms of disease for a minimum of 4 weeks during which no new lesions may appear. Specifically, all tumor masses must disappear. There must be no cancer-associated deterioration in weight (>10%), performance status or symptoms. For bony metastases, Complete Response (CR) means the re-calcification of all lytic lesions or the biopsy-proven absence of tumor cells. Normalization of the bone scan is not necessary for the patient to be considered to have a CR; however, any worsening of the bone scan needs to be evaluated.

12.2 Partial Response

A minimum reduction of at least 50% in the sum of the products of the longest perpendicular diameters of all indicator lesions. If the bone scan was abnormal due to metastatic disease, it must show improvement; malignant hepatomegaly, if present, must decrease by 30%. There may be no new lesions and the response must last for at least 4 weeks during which time there should be no cancer-associated deterioration in weight, performance status or symptoms.

12.3 Stable Disease

Patients who fail to qualify for complete or partial response or progressive disease. This condition should persist for at least 3 months.

12.4 Progressive Disease

The appearance of new lesions or an increase of at least 25% in the sum of the products of the longest perpendicular diameters of measurable lesions. A new bone scan lesion would only be considered progression if it is associated with appearence of a new or enlarging lytic lesion on plain bone radiography, CT scan or MRI.

Deterioration in performance status, weight or symptoms will not be considered indicative of progressive disease but should prompt an evaluation for other evidence of disease progression.

12.5 Data Reporting

All study data are to be recorded on local research center flow sheets.

13. STATISTICAL CONSIDERATIONS

13.1 Sample Size

A two-stage sample design will be used to evaluate whether thalidomide has any activity in patients with metastatic breast cancer who have previously received 0-3 regimens of chemotherapy. We consider thalidomide to be active in this patient population if at least 20% of the patients remain progression-free after two months on study. In the first stage, 14 patients will be entered on each of the two arms by random assignment. The randomization will be stratified by the number of prior chemotherapy regimens received (0-1 vs. 2-3). If all of the first 14 patients progress within two months on study, then the arm will be terminated and it will be concluded that there is 95% confidence that thalidomide at the administered dose level is not active (Gehan, 1961)[44]. Alternatively, if at least one of the first 14 patients has stable disease or an objective response after two months on study, then the trial will proceed to the second stage. In the second stage, an additional 11 patients will be entered on the arm to better assess the toxicity profile and activity of thalidomide. In this case, the total sample size (Stage One plus Stage Two) will be 25 patients at a given dose level.

If both low-dose and high-dose thalidomide demonstrate some activity in this trial (i.e., if both arms proceed to the second stage of sampling), then we will compare the efficacy of the two dose levels using time to progression (TTP) as the endpoint. Given the heterogeneity in the patient population and the relatively small sample size of 25 patients per arm, this Phase II trial will not have adequate power to detect modest differences in benefit between dose levels. Rather, the objective will be to identify the optimal dose level, if in fact one dose level is truly superior to the other. Otherwise, if the true difference in TTP between the two dose levels is not large, then we are indifferent about which arm will appear more promising in this trial and will proceed to more different studies with the lower dose (e.g., Simon, Wittes and Ellenberg, 1985)[45]. In order to compute the probability of correctly identifying the superior dose level of thalidomide, we make the following five (5) assumptions:

1) little is known about the natural history of metastatic breast cancer in patients who are not being treated with chemotherapy, but we expect that most of the patients on study will have been heavily pretreated and that the median TTP will be 2-4 months;

2) a superior dose level of thalidomide is one that doubles the median TTP in the patient population;

3) TTP follows an exponential distribution with true hazard rate λ and observed hazard rate λ^*, say;

4) the observed hazard rate λ^* is approximately normally distributed with variance $\phi(\lambda)/n$.

where n is the sample size per arm and (Lachin, 1981, Equation 26)[46]

$$\phi(\lambda_i) = \lambda^2 / [1 - \{\exp(-\lambda F) - \exp(-\lambda F - \lambda A)\}/(\lambda A)],$$

where A, F denote the length of the accrual period and follow-up period, respectively; and

5) patients will be accrued over a 15 month period and the follow-up period will be 2 months (i.e., A=15 and F=2 in the above equation).

The second arm will be declared the "winner" over the first arm if the observed hazard ratio, λ_1^*/λ_2^*, exceeds 1.0. The larger the observed hazard ratio, the stronger the evidence that the second arm is superior to the first arm. Based on the above 5 assumptions, the probability that the observed hazard ratio exceeds some arbitrary value, c, is given by:

$$P(\lambda_1^* / \lambda_2^* > c) = P(\lambda_1^* > c\lambda_2^* > c) = \int_{-\infty}^{\infty} [1 - F(\frac{c\lambda_2^* - \lambda_1}{\sqrt{\Phi(\lambda_1)/n}})] dF(\frac{\lambda_2^* - \lambda_2}{\sqrt{\Phi(\lambda_2)/n}})$$

where F(·) denotes the standard normal cumulative distribution function. In the following table, Arm 2 represents a dose level that is truly superior to Arm 1. As shown in the table, the probability that the correct arm will be chosen as the winner (i.e., the probability that the observed hazard ratio exceeds 1.0) is at least 96%. The probability of attaining stronger evidence about the superiority of Arm 2, such as observing a hazard ratio of 1.25 or 1.5, will be at least 90% or 78%, respectively.

True Median TTP (in months):		True Hazard Rate:[1]		True Hazard	Probability that Observed Hazard Ratio is Greater Than ...		
Arm 1	Arm2	Arm 1	Arm 2	Ratio	1.00	1.25	1.50
2	4	0.347	0.173	2.0	98.2%	93.1%	82.3%
3	6	0.231	0.116	2.0	97.5%	91.5%	80.2%
4	8	0.173	0.087	2.0	96.8%	90.1%	78.6%

[1] hazard rate: $\lambda = \ln(2)/\text{median TTP}$.

13.2 Statistical Analysis

The primary endpoint in the efficacy analysis will be time to progression (TTP). Time will start on the day that the patient is randomized. The two dose levels will be compared using a stratified Cox proportional-hazards regression model, where the stratification variable will be the number of prior chemotherapy regimens (0-1 versus 2-3). If there are imbalances between the two arms with respect to age or other prognostic factors, these factors will be included as covariates in the regression model. The analysis will follow the intent-to-treat principle, i.e., patients will be classified according to their assigned dose level rather than dose actually received. The outcome of the regression analysis will be an estimate of the hazard ratio, which quantifies the instantaneous risk of

progression on Arm 1 relative to Arm 2. As explained in Section 13.1, an observed hazard ratio greater than 1.0 constitutes evidence that dose level 2 is more beneficial than dose level 1. Conversely, an observed hazard ratio less than 1.0 provides evidence that dose level 1 is preferred. The actual decision about which dose level to use in future Phase III trials will be based on toxicity considerations as well as the hazard ratio.

In a secondary analysis, we will compare the post- versus pre-treatment tumor growth rates in patients with known rate of tumor growth over the 2-4 month period prior to starting thalidomide. To standardize the rates, we will need to adopt a probability model for the tumor growth curve over time. A simple and plausible model for the tumor growth curve per unit time is the exponential growth model

$$V(t) = (1 + r)\, V(t - 1)\, \epsilon(t),$$

where $V(t)$ is the tumor size at time t, r is the growth rate and $\epsilon(t)$ is a random perturbation. The tumor size will be measured as described in Section 12.2. In this study the time unit of interest is 8 weeks, so r is the growth rate <u>per 8 weeks</u>. The post-treatment (r_2) versus pre-treatment (r_1) growth rate of a patient's tumor can be compared based on the tumor sizes V_1, V_2 and V_3 measured before treatment, at start of treatment, and after treatment with Thalidomide, respectively. Let t_1, t_2 and t_3 denote the dates of the three tumor measurements, and let $\Delta_1 = t_2 - t_1$ and $\Delta_2 = t_3 - t_2$ denote the pre- and post-treatment time intervals, respectively. Of interest is the ratio of the post-treatment versus pre-treatment growth rate (r_2/r_1). If $r_2/r_1 = 1$ then thalidomide has no effect on the growth rate, whereas if $r_2/r_1 = 0.5$, say, then thalidomide reduces the growth rate by 50%. We will assume that $\ln\{\epsilon(t)\}$ has a normal distribution with mean zero and standard deviation σ. For a given patient, the maximum likelihood (and unbiased) estimate of $\ln(1 + r)$ is $\{\ln(V_2) - \ln(V_1)\}/\Delta_1$ before treatment and $\{\ln(V_3) - \ln(V_2)\}/\Delta_2$ after treatment with Thalidomide. Let R_1 and R_2 denote the maximum likelihood estimates of growth rates r_1 and r_2, respectively. It follows that the maximum likelihood estimate of the relative growth rate for an individual patient is

$$R_2 / R_1 = \frac{(V_3^{1/\Delta_2} - V_2^{1/\Delta_2}) / V_2^{1/\Delta_2}}{(V_2^{1/\Delta_1} - V_1^{1/\Delta_1}) / V_1^{1/\Delta_1}} .$$

We will compute each evaluable patient's estimated baseline (R_1) and relative (R_2/R_1) tumor growth rates as described above. The relative growth rate will be transformed to achieve approximate normality and tested using 1- and 2-sample t-tests for within- and between-arm hypotheses, respectively. We will also perform nonparametric analogues of these tests, i.e. the one-sample sign test and two-sample Mann-Whitney test, respectively. For tumor measurements after the initial 8-week dosing period, reductions in the tumor growth rate will be investigated using a random effects regression model. Prognostic factors that might be predictive of efficacy will be included as explanatory variables in the regression model. If there is extensive patient withdrawal following the initial 8-week dosing period, the regression analysis will be adjusted for potentially informative right censoring (e.g., Mori, Woodworth and Woolson, 1992; Follman and Wu, 1995)[47,48].

14: ADMINISTRATIVE ASPECTS

14.1 Patient Entry

Patients will be evaluated and registered by the principal investigator Said Baidas, M.D. at Georgetown University Hospital, 3800 Reservoir Road, NW, Washington D.C. 20007 Phone 202-687-2198.

The study coordinator is Barbara Brogan, RN, MS, at Georgetown University Hospital, 3800 Reservoir Road, NW, Washington D.C. 20007 Phone 202-687-2198.

14.1 Institutional Review Board/Committee

This protocol, the proposed consent form and any advertisement for patient recruitment must be reviewed and approved by the Institutional Review Board/Committee (IRB), prior to the start of the study. During the course of the study, the investigator shall make timely and accurate reports to the IRB on the progress of the trial, at intervals not exceeding one year, as well as satisfying any other local IRB regulations regarding reporting. Further, at the completion or early termination of the study, a final report should be made to the IRB by the investigator within 90 days of termination.

Any significant changes or revisions in the study protocol or any changes that may alter patient risk must be approved in writing by the IRB prior to implementation.

14.2 Informed Consent

The proposed informed consent form must contain a full explanation of the purpose and nature of the study, the possible advantages, risks, alternate treatment options, and a statement regarding voluntary compensation and availability of treatment in the case of injury, in accordance with the Federal Regulations.

The investigator will be responsible for obtaining written informed consent from potential subjects prior to any study specific screening and entry into the study. A copy of the signed document will be given to the subject, the original will be retained by the investigator with his copy of the case report forms.

14.3 Data Recording

All study data are to be recorded on Lombardi Cancer center flow sheets.

14.4 Drug Accountability

The investigational drug is to be prescribed only by the investigator or the sub-investigators . Under no circumstances will the Investigator(s) allow the investigational drug to be used other than as directed by this protocol.

The investigator must maintain accurate records accounting for the receipt of the investigational

drug supplies and for the disposition of the drug. This should consist of a dispensing record including the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing, and any unused drug returned. NCI Drug Accountability Record form will be used for record keeping.

14.5 Investigator's Final Report

Upon completion or termination of the study, the investigator will submit a final written report to the sponsor as required by Federal Regulations. The report should be submitted to the sponsor within 90 days of completion or termination of the study. The report should include, but not be limited to, a description of the study objectives, methodology (including any deviations from protocols), results, and conclusions regarding attainment of study objectives (from the standpoint of drug safety). All significant adverse experiences must be described, with the investigator's opinions as to whether they were or were not related to the study drug administration.

15: DCT Guidlines for Multicenter Investigational Agent Studies:

15.1 Protocol Development:

15.1.1 Georgetown institution will be designated as the "Coordinator Center."

15.1.2 The Protocol Chairman (Dr. Baidas) at the coordinator center (Georgetown University) will be the single liaison with CTEP protocol and information office (PIO). Dr. Baidas will coordinate the development, submission, and approval of the protocol as well its subsequent amendments, results reports, and publications.

15.2 Protocol Document:

15.2.1 There will be only one version of the protocol and each participating institution will use that document. It should not be rewritten or modified by any one other than the Protocol Chairman (said Baidas) at the coordinator Center (Georgetown University) who is solely responsible for obtaining CTEP approval and distributing the protocol to all participants, as well as formulating protocol amendments to all participants.

15.2.2 Patient Entry Procedure:

Patients will be evaluated and registered by the principal investigator Said Baidas, M.D. at the coordinator center at Georgetown University Hospital, 3800 reservoir Road, NW, Washington, D.C. 20007 Phone 202-687-2198

The study coordinator is Barbara Brogan, RN, MS, at Georgetown University Hospital, 3800 Reservoir road, NW, Washington, D.C. 20007. Phone 202-687-2198

Registration procedure should include a check of eligibility and regulatory issues (see quality assurance)

15.2.3 Records to be kept:

The coordinator center is responsible for developing common repot forms, and all data should be submitted to the coordinating center on these forms. The forms to be used will be submitted with the protocol.

On study informed consent and eligibility check should be submitted to the coordinator center no latter than 14 days after registration.

Flow sheets should be submitted no latter than 14 days after completing each cycle of treatment (8 weeks) and after the off study date.

Data t...ms should be mailed on hard copies to :

Said Baidas, M.D.
Lombardi Cancer Center, Room 416
Georgetown University Hospital
Reservoir road, NW., Washington, D.C. 20007

15.2.4 Adverse Drug Experience (ADE) Definition and Reporting

A. Report to the Investigational Drug Branch by telephone or FAX within 24 hours (301/230-2330 or FAX 301/230-0159), and to the Human Use Review and Regulatory Affairs Division (DSN 343-2165 or 301-619-2165 or FAX toDSN 343-7803 or 301-619-7803), and to the study chairman Said Baidas, M.D. (202-687-2198 or Fax 202-687-4429):

1. All life threatening (Grade 4) and (Grade 5) unknown reactions. Written report to follow within 10 working days.

2. Report in writing within 10 working days:

   A) life threatening and lethal (Grade 4 and 5) known reactions. (This does not include myelosuppression. Grade 4 myelosuppression should be submitted as part of study results.).
   B) Grade 2 and 3 unknown reactions.

   Note: Grade 1-3 known reactions should be submitted as part of the study results.

3. Address for submitting reports:
   Investigational Drug Branch
   P.O.Box 30012
   Bethesda, Maryland 20824

B. DEFINITIONS

The following definitions of terms apply to this section:

Associated with the use of the drug means that there is a reasonable possibility that the experience may have been caused by the drug.

Serious adverse experience. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or over-dose.

Unexpected adverse experience means any adverse experience that is not identified in nature, severity, or frequency in the current Investigational Drug Brochure.

Life-threatening, for the purpose of reporting ADEs, means that the patient was, in the

view of the Investigator, at ***immediate*** risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious, might have caused death.

The approving Institutional Review Board (IRB) must be notified of any significant life-threatening and/or serious adverse reactions or experiences regardless of cause on a timely basis and must be appraised of all adverse experiences by written report on a periodic and timely basis, at least annually.

A written report of all adverse effects or experiences and deaths will be submitted by the investigator. In this report, the investigator will advise whether or not the adverse experience or effect is judged to be attributable to the study medication. All such subjects should be followed clinically and by the appropriate diagnostic studies. Side-effect or subjective symptomatology volunteered by a subject will be noted and recorded as to type and severity on the individual's case report form. If no side effects are experienced, this also will be reported on the case report form.

15.2.5 Study Conduct

15.2.5.1 The protocol will be conducted as a single research effort and data from each participant will be included in the analysis of results.

15.2.5.2 The protocol Chairman Said Baidas, M.D. will be responsible for the conduct of the study and the monitoring of the progress, he will review all case report forms from each participant, uncritical acceptance of summary data from other institution is not sufficient.

15.2.6 Quality Assurance

15.2.6.1 The individual accepting registration should ascertain the date of IRB approval at each institution before registering the first patient from that institution.

15.2.6.2 During the registration call, eligibility criteria should be reviewed. The registrar should ascertain that the informed consent document has been signed before registering each patient.

15.2.6.3 Multicenter study records at each participating institution will be randomly selected for audit when that institution is selected for periodic on-site audits by DCT and its Clinical Trials Monitoring Service (at least once every three years).

15.2.7 Drug Ordering

The NCI Assigned protocol number T94-0202 should be used for ordering the investigational agent (thalidomide). Orders should be submitted directly from each participating institution.

15.2.8 Protocol Amendments/Status Changes

15.2.8.1 Each change to the protocol must be organized and documented by the coordinator center. The protocol chairman at the coordinator center should submit the amendment to CTEP for approval and then distribute it to study participants.

15.2.8.2 The amendment should be written so that no other institution needs to reformat the information but can simply copy and distribute. Amendments need to display the NCI protocol number. The changes must be clearly outlined and supported by amended protocol pages or replacement protocol document.

15.2.8.3 The coordinator center should keep CTEP abreast of each study status change by submitting the information on the protocol submission checklist to PIO.

15.2.9 Result Reporting

The protocol chairman at the coordinating center will be responsible for submitting study results to CTEP as required.

16 REFERENCES

1. Boring CC; Cancer statistics 1994, CA Cancer J Clin 1994, 44:7-26 Jan-Feb.

2. Fullerton,P. M., and Kremer, M.: Neuropathy after intake of thalidomide. Br. Med. j.,2:2855-858, 1961.

3. Lenz,W.: Das thalidomide-syndrome., 81:148-153, 1963. Malformation caused by drugs in pregnancy. Am. J. Child., 112:99-106, 1966.

4. McBride, W. G.: Thalidomide and congenital anomalies. Lancet,II : 1358, 1961

4. Sheskin J. (1965) Thalidomide in the treatment of lepra reaction. Clin Pharmcol ther 6:303

5. Knop J, Bonsman G, Happle R,Ludolph A, Matz DR, Macher E (1983) Thalidomide in the treatment of 60 cases of discoid lupus erythematosus. Br J Dermatol 108; 461-466.

6. Bahmer FA, Zaun H, Luszpiski p. Thalidomide treatment of recurrent erythema multiforme. Acta dermatol Venereol 1982; 62;449-450.

7. Mascaro JM, Lecha m, Torras h. Thalidomide in the treatment of recurrent necrotic and giant mucocutaneous aphthae and aphthosis. Arch Dermatol. 1979;115; 636-637

8. Ghigliotti G, Repetto T, Farris A, Posy MT, De Marchi R. Thalidomide treatment of choice for aphthous ulcers in patients seropositive for HIV. J Am Acad Darmatol 28(2 pt 1): 271-2 1993 Feb..

9. Vogelsang GB, Hess AD, Gordon G, Brundrette R, Santos GW.: Thalidomide induction of bone marrow transplantation tolerance. Transplant proc 1987, 19; 2658.

10. Vogelzang GB, Hess Ad, Santos GW. : thalidomide for treatment of graft versus host disease: Bone Marrow transplant 1988;3:393.

11. Murphy GP. Brede HD. Weber HW. Gronewald JH. Williams PD.: Thalidomide immunosuppression in canine renal allotransplantation. J Med Exp Clin 1970;1:66

12. Tamura F. Vogelsang GB. Reitz BA. Baumgartner WA. Herskowitz a. Combination thalidomide and cyclosporine for cardiac allograft rejection. Transplantation 1990;49:20.

13. Vogelsang GB. Wells MC. Santos GW. Chen TI. Hess AD. Combination low dose thalidomide and cyclosporine for acute graft versus host disease in a rat mismatched model. Transplant Proc 1988;20; 226.

14. Coulson AS. Summer LJ. Lindhal-Keissling K. Tucker D. Helman K. The effect of two soluble thalidomide derivatives on lymphocytes stimulation. Clin Exp immunol 1970;7: 241.

15. Nogueira AC., Neubert R ., Helge H., Neubert D.: Thalidomide and the immune system. Simultaneous up and down regulation of different integrin receptor on human white blood cells. Life Sci. 55(2): 77-92. 1994

16. Sampaio EP. Sarno EN. Galilly R. Cohn ZA. Kaplan G. Thalidomide selectively inhibits tumor necrosis facto alpha production by stimulated human monocytes. J Exp Med. 173(3): 699-703. 1991 Mar 1.

17. Moreira AI. Sampaio EP. Zmuidzinas A. Frindt P. Smith KA. Kaplan G. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. J Exp Med. 177(6):1675-80. 1993 June 1.

18. D'mato M. Loughnan M. Flynn E. Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc. Natl. Acad. Sci. USA Vol 91,pp. 4082-4085. April 1994.

19. Grinspan D., Blanco GF., Aguero S.: Treatment of aphthae with thalidomide.J AM Acad Dermatol 1989;20:1060-3.

20. Ochonisky S. Veroust J. Bastuji-Garin s. Gherhadi r. Revus J. Thalidomide neuropathy incidence and clinicoelectrophysiologic findings in 42 patients. Arch Dermt 130, 66-69. Jan 1994.

21. Hess CW. Hunziker T. Kupfer A. Ludin HP. Thalidomide induced peripheral neuropathy. J Neurol(1986) 233: 83-89.

22. Folkman J. (1985), Toward an understanding of angiogenesis: search and discovery. Perspective in Biol. Med. 29, 10-36.

23. Folkman J. (1971). Tumor Angiogenesis:,therapeutic implications. NEJM. 285, 1182-1186.

24. Ra J. Hegmann EJ. Kerble RS,. The role of angiogenesis in tumor progression and metastasis. In Heppner GH. ed. Advances in Molecular and cell biology. JAI Press, inc., 1993; 205-251.

25. Blood CH. Zetter BR. Tumor interaction with the vasculature: angiogenesis and tumor metastasis. Bioch Biophys Acta 1990; 1032: 89-118.

26. Folkman J. Klagsbrun M,. (1987) Angiogenic Factors Science 235, 442-447.

27. Paweletz N. Knierim M. Tumor related angiogenesis. In: CRC critical reviews in oncology hematology. Orlando: Academic press, 1988, 197-242.

28. Folkman J. (1990). Introductory preface to: Endothelial cells and angiogenic growth factors in cancer growth and metastasis,. Cancer metastasis Rev. 9(3): 171-174. 1990 Nov.

29. Weidner N, Semple JP, Welch WR, Folkman J: Tumor angiogenesis and metastasis-correlation in invasive breast cancer. NEJM 1991, 324:1-8.

30. Weidner N, Folkman J, Pozza F, Bevilacqua P, Allerd EN, Moore DH, Meli S, Gasparini G: Tumor Angiogenesis: A new significant and independent prognostic indicator in early stage breast carcinoma. J Nat Can Inst 1992, 84:1875-1887.

31. Bosari s, Lee AKC, Delellis RA, Wiley BD, Heatly GJ, Silverman ML: Microvessel quantitation and prognosis in invasive breast carcinoma. Human path 1992, 23: 755-761.

32. Wakui S, Furusato M, Itho T, Sasaki H, Akiyama A, Kinoshita I, Asano k, Tokuda T, Aizawa S, Ushigome S: tumor angiogenesis in prostatic carcinoma with and without bone marrow metastasis: a morphometric study. Am J Path 1992, 168:257-262.

33. Srivastava A, Laidler P, Davis RP, Hogran K, Hughes LE: The prognostic significance of tumor vascularity in intermediate thickness(0.75-4.0) skin melanoma. Am J Path 1988, 133:419-423.

34. Folkman J., Langer, R., Linhardt, R.J., Haudenschild, C., Taylor, S. (1983) Angiogenesis inhibition and tumor regression caused by heparin or heparin fragment in the presence of cortisone. Science 221, 719-725.

35. Jain, R. K. (1989). Delivery of novel therapuetic agents in tumors: physiological barriers and strategies. JNCI 81, 570-576.

36. Jain, R. K.(1990). Vascular and interstitial barriers to delivery of therapeutic agents in tumors. Cancer Metastasis rev. 9

37. Blood, C. H.,Zetter, B.R. Tumor interaction with vasculature: Angiogenesis and tumor metastasis. Bioch. Biophys. Acta 1032, 89-118.

38. Denekamp, J. (1990). Vascular attack as a therapeutic strategy for cancer. Cancer Metastasis Rev. 9, 267-282.

39. Vartanian, RK., Weidner, N.: Correlation of intratumoral endothelial cell proliferation with microvessel density (Tumor Angiogenesis) and tumor cell proliferation in breast cancer. Am J Path, vol.144, no. 6, June 1994.

40. Fox ST., Leek, RD., Smith K., Hollyer, J., Greenall, M., Harris, A.: Tumor angiogenesis in node negative breast cancer-relation with epidermal growth factor receptor, estrogen receptor and survival. Breast Cancer Research and Treatment 29: 109-116, 1994.

41. Tian-Ling Chen, Vogelsang G., Petty B., Brundrett R., Noe D., Santos G., Colvin M.: Plasma Pharmacokinetics and urinary excretion of thalidomide after oral dosing in healthy male

volunteer. Drug Metab dispos. 1989. 17 (4): 402-5.

42. Olson KB., Hall T., Horton J., Khung C., Hosley H.: Thalidomide in the treatment of advanced cancer. Clin Pharmcol ther. 1965. Vol 6, number, 3 292-297.

43. Grabstald H., Golbey R.: Clinical experience with thalidomide in patients with cancer.Clin Pharmcol ther. 1965. vol 6, number 3, 298-302.

44. Gehan EA. The determination of the number of patients required in a preliminary and follow-up trial of a new chemotherapeutic agent. J. Chronic disease, 13:346-353,1961.

45. Simon R, Wittes RE, and Ellenberg SS. Randomized phase II trials. Cancer treatment reports, 69:1375-1381,1985.

46. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. Controleled Clinical Trials, 2: 93-113, 1981.

47. Mori M, Woodworth GG and Woolson RF. Application of empirical bayes inference to estimation of rate of change in the presence of informative right censoring. Statistics in Medicine, 11: 621-631, 1992.

48. Follman D and Wu M. An approximate generalized linear model with random effects for informative missing data. Biometric, 51: 151-168, 1995.

17 APPENDICES

APPENDIX A: NCI COMMON TOXICITY CRITERIA

TOXICITY	GRADE [GRADES AT OR ABOVE SHADED LEVEL INDICATE DLT]				
	0	1	2	3	4
White Blood Count	≥ 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
Platelets	WNL	75.0 - WNL	50.0 - 74.9	25.0 - 49.9	< 25.0
Hemoglobin	WNL	10.0 - WNL	8.0 - 10.0	6.5 - 7.9	< 6.5
Granulocytes/Bands	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Lymphocytes	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 -0.9	< 0.5
Hemorrhage (Clinical)	None	Mild, no transfusion ; petechiae	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, > 4 units per episode
Infection	None	Mild	Moderate	Severe	Life threatening
Nausea	None	Able to eat; reduced but reasonable intake	Intake significantly decreased but still can eat	No significant intake	---
Vomiting	None	1 episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hours	> 10 episodes in 24 hours, or requiring Parenteral support
Diarrhea	None	Increase of 2-3 stools/day over pre-Rx	Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	Increase of 7-9 stools/day, or incontinence, or severe cramping	Increase of ≥ 10 stools/day or grossly bloody diarrhea, or need for parenteral support

TOXICITY	GRADE [GRADES AT OR ABOVE SHADED LEVEL INDICATE DLT]				
	0	1	2	3	4
Skin	None or no change	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Generalized symptomatic macular, papular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
Local	None	Pain	Pain and swelling with inflammation or phlebitis	Ulceration	Plastic surgery indicated
Hand-Foot Syndrome	No symptoms	Mild paresthesias +/or numbness of fingers +/or toes	Moderate paresthesias +/or numbness with or without local dermatitis	Painful swelling of distal phalanges with or without local dermatitis	Not applicable
Stomatitis	None	Painless ulcers, erythema, or mild soreness	Painful erythema, edema, or ulcers, but can eat	Painful erythema, edema, or ulcers, and cannot eat	Requires parenteral or enteral support
Bilirubin	WNL	---	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
Transaminase (SGOT, SGPT)	WNL	≤ 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Alk Phos or 5'Nucleotidase	WNL	≤ 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver--- clinical	No change from baseline	---	---	Precoma	Hepatic coma

TOXICITY	GRADE [GRADES AT OR ABOVE SHADED LEVEL INDICATE DLT]				
	0	1	2	3	4
Creatinine	WNL	< 1.5 x N	1.5 - 3.0 N	3.1 - 6.0 x N	> 6.0 x N
Proteinuria	No change	1+ or < 0.3 g% or < 3 g/l	2-3+ or 0.3 - 1.0 g% or 3 - 10 g/l	4+ or > 1.0 g% or > 10 g/l	Nephrotic syndrome
Hematuria	Neg	Micro only	Gross, no clots	Gross + clots	Requires transfusion
Alopecia	No loss	Mild hair loss	Pronounced or total hair loss	---	---
Pulmonary	None or no change	Asymptomatic, with abnormality in PFT's	Dyspnea on significant exertion	Dyspnea at normal level of activity	dyspnea at rest
Cardiac: dysrhythmias	None	Asymptomatic, transient requiring no therapy	Recurrent or persistent, no therapy required	Requires treatment	Requires monitoring; or ventricular tachycardia or fibrillation
Cardiac: function	None	Asymptomatic decline of resting ejection fraction by less than 20% of baseline value	Asymptomatic decline of resting ejection fraction by more than 20% of baseline value	Mild CHF responsive to therapy	Severe or refractory CHF
Cardiac: ischemia	None	Non-specific T-wave flattening	Asymptomatic ST and T-wave changes suggesting ischemia	Angina without evidence for infarction	Acute infarction

TOXICITY	GRADE [GRADES AT OR ABOVE SHADED LEVEL INDICATE DLT]				
	0	1	2	3	4
Cardiac: pericardial	None	Asymptomatic effusion, no intervention required	Pericarditis (rub, chest pain, ECG changes)	Symptomatic effusion; drainage required	Tamponade; drainage urgently required
Hypertension	None or no change	Asymptomatic transient increase > 20 mm Hg (Dia) or to > 150/100 if BP previously nl. No treatment required.	Recurrent or persistent increase > 20 mm Hg (Dia) or to > 150/100 if BP previously nl. No treatment required.	Requires therapy	Hypertensive crisis
Hypotension	None or no change	Changes requiring no therapy (including transient orthostatic hypotension)	Requires fluid replacement or other therapy but not hospitalization	Requires therapy and hospitalization resolves within 48 hrs of stopping the agent	Requires therapy and hospitalization for > 48 hrs after stopping the agent

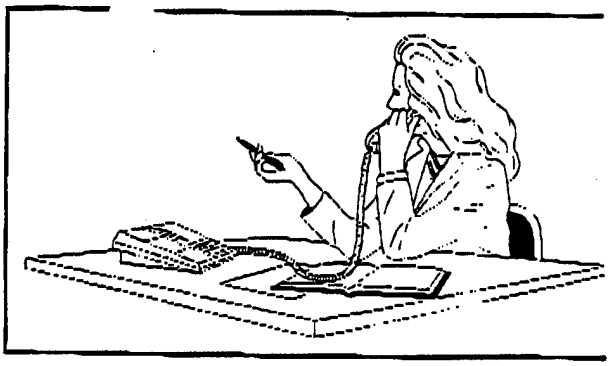
TOXICITY	GRADE [GRADES AT OR ABOVE SHADED LEVEL INDICATE DLT]				
	0	1	2	3	4
Neuro: sensory	None or no change	Mild paresthesias , loss of deep tendon reflexes	Mild or moderate objective sensory loss; moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	---
Neuro: motor	None or no change	Subjective weakness; no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis
Neuro: seizures	None	---	Simple partial seizures in which consciousness is preserved; self-limited and/or controlled	Complex partial seizures with altered consciousness or generalized seizures with loss of consciousness; self-limited and/or controlled	Seizures of any type which are prolonged, repetitive or difficult to control (status epilepticus)
Neuro: cortical	None	Mild somnolence or agitation	Moderate somnolence or agitation	Severe somnolence , agitation, confusion, disorientation or hallucinations	Coma, seizures, toxic psychosis

TOXICITY	GRADE [GRADES AT OR ABOVE SHADED LEVEL INDICATE DLT]				
	0	1	2	3	4
Neuro: cerebellar	None	Slight incoordination, dysdiadokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis
Neuro: mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
Neuro: headache	None	Mild	Moderate or severe but controllable	Unrelenting and severe	---
Neuro: constipation	None or no change	Mild	Moderate	Severe	Ileus > 96 hours
Neuro: hearing	None or no change	Asymptomatic hearing loss on audiometry	Tinnitus	Hearing loss interfering with function but correctable with hearing aid	Deafness not correctable
Neuro: vision	None or no change	---	Blurred vision or diplopia	Symptomatic subtotal loss of vision	Blindness

TOXICITY	GRADE [GRADES AT OR ABOVE SHADED LEVEL INDICATE DLT]				
	0	1	2	3	4
Allergy	None	Transient rash or drug fever ≥ 38°C (100.4°F)	Urticaria, drug fever ≥ 38°C (100.4°F), mild bronchospasm	Serum sickness or bronchospasm; requires parenteral medication	Anaphylaxis
Fever in absence of infection	None	37.1 - 38.0°C (98.7 - 100.4°F)	38.1 - 40.0°C (100.5 - 104.0°F)	> 40.0°C (> 104.0°F) for less than 24 hours	> 40.0° C (> 104.0°F) for ≥ 24 hours, or fever with hypotension
Fatigue	No change in Performance score (ECOG) *and* not PS 4	Performance score (ECOG) decrease in 1 level, but not to PS 4	Performance score (ECOG) decrease in 2 levels, but not to PS 4	Performance score (ECOG) decrease in 3 levels, but not to PS 4	Performance score (ECOG) decrease to PS 4
Chills	None	Chilly sensation, no rigors	Mild rigors, no medication required	Severe rigors, requires medication	Not applicable.
Myalgias	None	Mild muscular aching; no medication required.	Moderate aching requiring medication; no associated enzyme (CPK) elevation.	Severe muscular aching requiring medication; associated enzyme (CPK) elevation.	Not applicable.
Weight gain/loss	< 5.0%	5.0 - 9.9%	10.0 - 19.9%	>20.0%	---
Hyperglycemia	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	> 2.1 - 5.0 x N	> 5.1 x N

TOXICITY	GRADE [GRADES AT OR ABOVE SHADED LEVEL INDICATE DLT]				
	0	1	2	3	4
Hypercalcemia	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	> 13.5
Hypocalcemia	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	≤ 6.0
Hypomagnesemia	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤ 0.5
Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≤ 0.24 x N
Prothrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N

Headquarters, U.S. Army Medical Research and Materiel Command (USAMRMC)



From the Desk of Catherine Smith
Human Use Review Specialist

Number of pages including this page = 3

From: U.S. Army Medical Research and Materiel Command
504 Scott Street
Fort Detrick, MD 21702-5012
ATTN: MCMR-RCQ-HR (Ms. Smith)

Office: Human Use Review and Regulatory Affairs Division

FAX: 301-619-7803, DSN 343-7803

Internet: Cathy_Smith@ftdetrck-ccmail.army.mil

TO:

Doctor Bandas

202-687-4429

RECEIVED
MAY 21 1997
PROTOCOL OFFICE

Acknowledge receipt: Yes___ Phone # DSN 343-2165
Call DSN 343-2165 Comm. 301-619-2165 if you experience difficulty with transmission

te

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH VA 22041-3258

REPLY TO
ATTENTION OF

May 14, 1997

Office of the Deputy Chief of Staff
for Regulatory Compliance and Quality
Human Use Review and
Regulatory Affairs

SUBJECT: Protocol Entitled "Phase II Evaluation of Thalidomide in Patients with Metastatic Breast Cancer," Submitted by Michael Hawkins, M.D., Georgetown University, Proposal Log No. CC950002 (HURRA Log No. A-7285)

Said Baidas, M.D.
Georgetown University
37th and O Street, NW
Washington, DC 20057

Dear Doctor Baidas:

Human Use Review and Regulatory Affairs has reviewed your correspondence dated April 29, 1997, for compliance with all applicable human use regulations.

The revisions indicated in protocol and consent form do not increase the risk to the research subjects. These changes are administratively approved.

However, this study has been changed from a single site to multiple sites. A listing of all study sites must be provided to this office. Documentation of IRB review and approval must be provided from each site.

You will be notified by our contracting office, in writing, when each additional site is approved to begin. You should not initiate any research until you have received written approval from our contracting office to begin at that particular site.

Request the additional documentation be provided this office no later than May 30, 1997.

Printed on Recycled Paper

This correspondence should not be construed as an approval for award of any contract funding. Only the Contracting Officer may commit Federal Government funds.

Please TELEFAX any questions you might have to the undersigned at 301-619-7803 or Internet address Cathy_Smith@ftdetrck-ccmail.army.mil. TELEFAX transmission of the requested documentation is preferred. However, if it is more practical for you to mail documents, you may send them to the following address: Commander, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ-HR/Mrs. Smith, Fort Detrick, Frederick, MD 21702-5012.

Sincerely,

Dale G. Vander Hamm
Major, Medical Service Corps
Chief, Human Use Review and
Regulatory Affairs

Copies Furnished:

U.S. Army Medical Research Acquisition Activity,
ATTN: Ms. Sil Heller

U.S. Army Medical Research and Materiel Command,
ATTN: MCMR-PLF

GEORGETOWN UNIVERSITY MEDICAL CENTER

Vincent T. Lombardi Cancer Research Center
School of Medicine
Department of Medicine
Division of Hematology/Oncology

April 29, 1997

Dale G. Vander Hamm
Major, Medical Service Corps
Chief, Human Use Review and Regulatory Affairs Division.

Dear Sir

The following changes have been made on the NCI Protocol T94-0202 "Phase II evaluation of thalidomide in patients with metastatic breast cancer":

Changes dated March 4, 1997

(1). Remove the following physicians from the list t of co-investigators : Kevin Cullin, M.D., Carl Freter, M.D., Lyndsy Harris, M.D., Amitabha Mazumder,M.D. and Chitra Rajagopal, M.D.
Add to the following co-investigators : Andrea Denicoff, C.A.N.P., Matthew Ellis, M.D., and Daniel Hayes, M.D.

(2). Change section 2 (the objectives) to the following:
A. Primary objective:

1. To assess if there is difference in activity (by evaluating time to progression) and safety profile between the low dose and high dose arm of thalidomide.

B. Secondary Objectives:

1. To determine the objective response rate (complete and partial response rates) of Thalidomide in patients with measurable metastatic breast cancer at both arms. To determine time to response and survival.

2. To compare the post versus pre treatment tumor growth rates in patients with known rate of tumor growth over the 2-4 month period prior to starting thalidomide.

3. To analyze growth factors expression and matrix metalloproteinase activity in patients receiving thalidomide.

4. To study thalidomide pharmacokinetics.

3800 Reservoir Road NW Washington, DC 20007-2197
Faculty/Administration: 202-687-2198 FAX: 202-687-4429
Ambulatory Services: 202-687-2223 FAX: 202-687-3302

(3). In section 3 (study Design) the following changes have been made:

1. Change single center to multicenter in the first paragraph.

2. Change total number of patients in first paragraph to 50 patients.

3. Delete the third paragraph that reads: During the initial 8 weeks dosing period, patients should remain on the study unless they have a ≥ 50% progression by measurable disease, or unless they have a ≥ 25% progression with life threatening progression or progressive disease requiring immediate palliative therapy. However once evaluated at the 8 week mark, any additional progression from that point on of ≥255 from the status at 8 weeks would be considered progressive disease and the patient removed from the study.

(4). In section 4 (patient selection and eligibility) the following changes have been made:

1. Change item 4.1.2 to:
Patients must have evaluable or bidimensionally measurable disease in at least 1 site: For measurable disease, minimum indicator lesion size must be 1 cm. Patients with evaluable bone only disease must have a lytic lesion on plain X ray, CT scan or MRI, that has not been irradiated before. Ascites and pleural effusions are not considered as measurable or evaluable advanced cancer.

2. Change item 4.1.3 to:
Documented objective progressive disease as per section 12.4.

3. Change item 4.1.4 to:
Patients may have had no more than 3 prior chemotherapy regimens. One adjuvant chemotherapy regimen is permitted in addition to two regimens for metastatic disease. If patient has no adjuvant chemotherapy, then, up to three chemotherapy regimens for metastatic disease are allowed. No limitations on the previous hormonal or biological therapies.
4. Item 4.1.8.3: delete albumin, total protein, and LDH.

(5). In section 7 the following changes has been made :

7.1 Serum levels of TNF, VEGF, bFGF, plasma levels of matrix metalloproteinase (MMP-9) and urinary bFGF will be measured before entering the study and on week 2,4,6 and 8 of the first cycle and monthly after that. TNF, VEGF, bFGF assays will be done at Dr Wellstein lab. And MMP at Dr Dickson la.

TNF, VEGF and bFGF:
Serum samples will be obtained on all patients immediately before the first dose and

then on week 2, 4, 6 and 8 of the first cycle and monthly after that. During each time point 7 mL of blood will be collected in a red top tube and placed on ice immediately. The serum will then be pipetted off and placed into 2 NUNC® sample mailing tubes and stored in the - 70°C freezer until shipment to Anton Wellstein, M.D., Ph.D. laboratory in the preclinical science building.
TNF, VEGF and bFGF levels in the serum will be measured by Quantikine ELISA kit (R&D Systems, Minneapolis, MN) according to the guidelines suggested by the supplier of the kits.

Matrix Metalloproteinase (MMP-9):
Plasma samples will be obtained on all patients immediately before the first dose and then on week 2, 4, 6 and 8 of the first cycle and monthly after that. During each time point 5 mL of blood will be collected in a purple top containing EDTA (Potassium Chloride) and placed on ice immediately. The sample will then be placed in a refrigerated centrifuge and spun down at 3000 rpm for 15 minutes. The plasma will be pipetted off and placed in a NUNC® sample mailing tube and stored in the - 70°C freezer until shipment to Robert Dickson, Ph.D. laboratory in the New Research Building.

Urine:
Urine samples will be obtained on all patients immediately before the first dose and then on week 2, 4, 6 and 8 of the first cycle and monthly after that. During each time point 20 mL of urine will be collected in a standard urine collection container without preservative and placed on ice immediately. The urine will then be transferred to 30 mL container for storage in the - 70°C freezer until shipment to Anton Wellstein, M.D., Ph.D. laboratory in the preclinical science building.

7.2.1 The first dose of thalidomide will be given at 9 am, all doses after that will be given qhs at 9 pm. Plasma samples will be obtained on all patients immediately before the first dose on day 1 and then ½, 1 , 1 ½, 2, 3, 4, 5, 6, 7 and at 9:00 am and 1:00 pm the second day. Chronic serum level will be done every 2 weeks first cycle and monthly after that.
During each time point 5 ml of blood will be collected in a green top containing NAH (sodium heparin) and placed on ice immediately. Chronic plasma levels will be done every 2 weeks first cycle and monthly after that. The sample will then be placed in a refrigerated centrifuge and spun down at 3000 rpm for 15 minutes. Equal part 0.025 M Sorenson's citrate buffer solution will then be placed in the Corning sample mailing tube along with the pipetted plasma. The mailing tube will then be stored at -20° C and transferred that afternoon to the Analytical Core Laboratory for extraction and assaying by Dr. David Flockhart, M.D., Ph.D.

(6). Table I (study parameter) the following changes have been made:

1. q 2 weeks changed to week 2.

2. q4 weeks changed to week 4.

3. The first sentence below the table is changed to :
On study laboratory **and X rays must be obtained within 2 weeks starting on study.

(7). Item 11.2.0 has been changed to:

During the initial 8 weeks dosing period, patients should remain on the study unless they have progression with life threatening progression or progression requiring immediate palliative therapy.
Progression of disease at the week 8 staging by ≥25% of the measurable disease or with a new lesion will be considered progressive disease and the patient would be removed from the study.
A new bone scan lesion will only be considered progression if it is associated with appearance of a new or enlarging lytic lesion on plain bone radiography, CT scan or MRI.
Progression of disease while on study according to this criteria requires termination of treatment, unless the investigator documents on the patient's case report forms the specific reasons and rationale for continuing treatment under such circumstances.

(8). Item 13 (statistical consideration) has been changed to:

13.1 Sample Size

A two-stage sample design will be used to evaluate whether thalidomide has any activity in patients with metastatic breast cancer who have previously received 0-3 regimens of chemotherapy. We consider thalidomide to be active in this patient population if at least 20% of the patients remain progression-free after two months on study. In the first stage, 14 patients will be entered on each of the two arms by random assignment. The randomization will be stratified by the number of prior chemotherapy regimens received (0-1 vs. 2-3). If all of the first 14 patients progress within two months on study, then the arm will be terminated and it will be concluded that there is 95% confidence that thalidomide at the administered dose level is not active (Gehan, 1961). Alternatively, if at least one of the first 14 patients has stable disease or an objective response after two months on study, then the trial will proceed to the second stage. In the second stage, an additional 11 patients will be entered on the arm to better assess the toxicity profile and activity of thalidomide. In this case, the total sample size (Stage One plus Stage Two) will be 25 patients at a given dose level.

If both low-dose and high-dose thalidomide demonstrate some activity in this trial (i.e., if both arms proceed to the second stage of sampling), then we will compare the efficacy of the two dose levels using time to progression (TTP) as the endpoint. Given the heterogeneity in the patient population and the relatively small sample size of 25 patients per arm, this Phase II trial will not have adequate power to detect modest differences in benefit between dose levels.

Rather, the objective will be to identify the more beneficial dose level, if in fact one dose level is truly superior to the other. Otherwise, if the true difference in TTP between the two dose levels is not large, then we are indifferent about which arm will appear more promising in this trial (e.g., Simon, Wittes and Ellenberg, 1985). In order to compute the probability of correctly identifying the superior dose level of thalidomide, we make the following five (5) assumptions:

1) little is known about the natural history of metastatic breast cancer in patients who are not being treated with chemotherapy, but we expect that most of the patients on study will have been heavily pretreated and that the median TTP will be 2-4 months;

2) a <u>superior</u> dose level of thalidomide is one that doubles the median TTP in the patient population;

3) TTP follows an exponential distribution with true hazard rate λ and observed hazard rate λ^*, say;

4) the observed hazard rate λ^* is approximately normally distributed with variance $\phi(\lambda)/n$, where n is the sample size per arm and (Lachin, 1981, Equation 26)

$$\phi(\lambda) = \lambda^2 / [1 - \{\exp(-\lambda F) - \exp(-\lambda F - \lambda A)\}/(\lambda A)],$$

where A, F denote the length of the accrual period and follow-up period, respectively; and

5) patients will be accrued over a 15 month period and the follow-up period will be 2 months (i.e., A=15 and F=2 in the above equation).

The second arm will be declared the "winner" over the first arm if the observed hazard ratio, λ_1^*/λ_2^*, exceeds 1.0. The larger the observed hazard ratio, the stronger the evidence that the second arm is superior to the first arm. Based on the above 5 assumptions, the probability that the observed hazard ratio exceeds some arbitrary value, c, is given by:

$$P(\lambda_1^* / \lambda_2^* > c) = P(\lambda_1^* > c\lambda_2^* > c) = \int_{-\infty}^{\infty} [1 - F(\frac{c\lambda_2^* - \lambda_1}{\sqrt{\phi(\lambda_1)/n}})] dF(\frac{\lambda_2^* - \lambda_2}{\sqrt{\phi(\lambda_2)/n}})$$

where $F(\cdot)$ denotes the standard normal cumulative distribution function. In the following table, Arm 2 represents a dose level that is truly superior to Arm 1. As shown in the table, the probability that the correct arm will be chosen as the winner (i.e., the probability that the observed hazard ratio exceeds 1.0) is at least 96%. The probability of attaining stronger evidence about the superiority of Arm 2, such as observing a hazard ratio of 1.25 or 1.5, will be at least 90% or 78%, respectively.

True Median TTP (in months):		True Hazard Rate:[1]		True Hazard	Probability that Observed Hazard Ratio is Greater Than ...		
Arm 1	Arm2	Arm 1	Arm 2	Ratio	1.00	1.25	1.50
2	4	0.347	0.173	2.0		98.2%	93.1%
82.3%							
3	6	0.231	0.116	2.0		97.5%	91.5%
80.2%							
4	8	0.173	0.087	2.0	96.8%	90.1%	78.6%

[1] hazard rate: $\lambda = \ln(2)/\text{median TTP}$.

13.2 Statistical Analysis

The primary endpoint in the efficacy analysis will be time to progression (TTP). Time will start on the day that the patient is randomized. The two dose levels will be compared using a stratified Cox proportional-hazards regression model, where the stratification variable will be the number of prior chemotherapy regimens (0-1 versus 2-3). If there are imbalances between the two arms with respect to age or other prognostic factors, these factors will be included as covariates in the regression model. The analysis will follow the intent-to-treat principle, i.e., patients will be classified according to their assigned dose level rather than dose actually received. The outcome of the regression analysis will be an estimate of the hazard ratio, which quantifies the instantaneous risk of progression on Arm 1 relative to Arm 2. As explained in Section 13.1, an observed hazard ratio greater than 1.0 constitutes evidence that dose level 2 is more beneficial than dose level 1. Conversely, an observed hazard ratio less than 1.0 provides evidence that dose level 1 is preferred. The actual decision about which dose level to use in future Phase III trials will be based on toxicity considerations as well as the hazard ratio.

In a secondary analysis, we will compare the post- versus pre-treatment tumor growth rates in patients with known rate of tumor growth over the 2-4 month period prior to starting thalidomide. To standardize the rates, we will need to adopt a probability model for the tumor growth curve over time. A simple and plausible model for the tumor growth curve per unit time is the exponential growth model

$$V(t) = (1 + r)\, V(t - 1)\, \epsilon(t),$$

where $V(t)$ is the tumor size at time t, r is the growth rate and $\epsilon(t)$ is a random perturbation. The tumor size will be measured as described in Section 12.2. In this study the time unit of interest

is 8 weeks, so r is the growth rate per 8 weeks. The post-treatment (r_2) versus pre-treatment (r_1) growth rate of a patient's tumor can be compared based on the tumor sizes V_1, V_2 and V_3 measured before treatment, at start of treatment, and after treatment with Thalidomide, respectively. Let t_1, t_2 and t_3 denote the dates of the three tumor measurements, and let $\Delta_1 = t_2 - t_1$ and $\Delta_2 = t_3 - t_2$ denote the pre- and post-treatment time intervals, respectively. Of interest is the ratio of the post-treatment versus pre-treatment growth rate (r_2/r_1). If $r_2/r_1 = 1$ then thalidomide has no effect on the growth rate, whereas if $r_2/r_1 = 0.5$, say, then thalidomide reduces the growth rate by 50%. We will assume that $\ln\{\epsilon(t)\}$ has a normal distribution with mean zero and standard deviation σ. For a given patient, the maximum likelihood (and unbiased) estimate of $\ln(1 + r)$ is $\{\ln(V_2) - \ln(V_1)\}/\Delta_1$ before treatment and $\{\ln(V_3) - \ln(V_2)\}/\Delta_2$ after treatment with Thalidomide. Let R_1 and R_2 denote the maximum likelihood estimates of growth rates r_1 and r_2, respectively. It follows that the maximum likelihood estimate of the relative growth rate for an individual patient is

$$R_2 / R_1 = \frac{(V_3^{1/\Delta_2} - V_2^{1/\Delta_2}) / V_2^{1/\Delta_2}}{(V_2^{1/\Delta_1} - V_1^{1/\Delta_1}) / V_1^{1/\Delta_1}} .$$

We will compute each evaluable patient's estimated baseline (R_1) and relative (R_2/R_1) tumor growth rates as described above. The relative growth rate will be transformed to achieve approximate normality and tested using 1- and 2-sample t-tests for within- and between-arm hypotheses, respectively. We will also perform nonparametric analogues of these tests, i.e. the one-sample sign test and two-sample Mann-Whitney test, respectively. For tumor measurements after the initial 8-week dosing period, reductions in the tumor growth rate will be investigated using a random effects regression model. Prognostic factors that might be predictive of efficacy will be included as explanatory variables in the regression model. If there is extensive patient withdrawal following the initial 8-week dosing period, the regression analysis will be adjusted for potentially informative right censoring (e.g., Mori, Woodworth and Woolson, 1992; Follman and Wu, 1995).

(9). The following references were added to reference section

44. Gehan EA. The determination of the number of patients required in a preliminary and follow-up trial of a new chemotherapeutic agent. J. Chronic Diseases 13: 346-353, 1961.

45. Simon R, Wittes, RE and Ellenberg, SS. Randomized Phase II trials. Cancer Treatment Reports 69: 1375-1381, 1985.

46. Lachin JM. Introduction to sample size determination and power analysis for clinical trials.

Controlled Clinical Trials 2: 93-113, 1981.

47. Mori M, Woodworth GG and Woolson RF. Application of empirical Bayes inference to estimation of rate of change in the presence of informative right censoring. Statistics in Medicine 11: 621-631, 1992.

48. Follman D and Wu M. An approximate generalized linear model with random effects for informative missing data. Biometrics 51: 151-168, 1995.

(10). Delete appendix B.

(11) In the consent form under(description of research) , last paragraph, change total number of patients to 50.

(12) Item 12.4 first paragraph has been changed to:

The appearance of new lesions or an increase of at least 25% in the sum of the products of the longest perpendicular diameters of measurable lesions. A new bone scan lesion would only be considered progression if it is associated with appearance of a new or enlarging lytic lesion on plain bone radiography, CT scan or MRI.

Chages dated April 10, 1997

Section 3 - The word "Pilot" has been replaced by "Phase II".

7.1 and 7.2 - The address of Dr. Baidas has been added.

A new section 15 - "DCT Guidelines for Multicenter Investigational Agent Studies" has been added.

The above changes were submitted to the NCI and Georgetown Univesity IRB.

Sincerely

Said Baidas, M.D.
Assistant Professor of Medicine
Division of Hematology/Oncology

GEORGETOWN UNIVERSITY Date: April 7, 1997

To: **Dr. Said Baidas**
Hematology/Oncology

From: **Elisabeth O. Crigler**
Executive Officer
Institutional Review Board

Subject: **Action on your protocol entitled: "Phase II Evaluation of Thalidomide in Patients with Metastatic Breast Cancer" (94-346)**

The modifications, as stated in the March 11, 1997 memorandum, to your above referenced protocol and the revised consent form were given approval through expedited review by Dr. Harry Preuss, Acting Chair of the Institutional Review Board.

This is to inform you that you may continue your project.

Please remember to:

1. Seek and obtain prior approval for any modifications to the approved protocol.

2. Promptly report any unexpected or otherwise significant adverse effects encountered in the course of this study to the Institutional Review Board within 72 hours. This includes information obtained from sources outside Georgetown that reveals previously unknown risks from the procedures, drugs or devices used in this study.

Please refer to the above mentioned date and protocol number when making inquiries concerning this protocol.

GEORGETOWN UNIVERSITY MEDICAL CENTER

Vincent T. Lombardi Cancer Research Center
School of Medicine
Department of Medicine
Division of Hematology/Oncology

DATE: March 11, 1997

TO: Elisabeth O. Crigler
Executive Officer, Institutional Review Board

FROM: Said Baidas, M.D.
Principal Investigator

SUBJECT: Protocol Revision for IRB # 94-346, protocol entitled "**PHASE II EVALUATION OF THALIDOMIDE IN PATIENTS WITH METASTATIC BREAST CANCER**"

The above referenced protocol has been revised as follows:

(1). Remove the following physicians from the list of coinvestigators: Kevin Cullen, M.D., Carl Freter, M.D., Ph.D., Lindsey Harris, M.D., Amitabha Mazumder, M.D., and Chitra Rajagopal, M.D.
Add the following as co-investigators: Andrea Denicoff, C.A.N.P., Matthew Ellis, M.D., and Daniel Hayes, M.D.

(2). Change section 2 (the objectives) to the following:
A. Primary objective:

1. To assess if there is difference in activity (by evaluating time to progression) and safety profile between the low dose and high dose arm of thalidomide.

B. Secondary Objectives:

1. To determine the objective response rate (complete and partial response rates) of Thalidomide in patients with measurable or evaluable metastatic breast cancer at both arms. To determine time to response and survival.

2. To compare the post versus pre treatment tumor growth rates in patients with known rate of tumor growth over the 2-4 month period prior to starting thalidomide.

3800 Reservoir Road NW Washington, DC 20007-2197
Faculty/Administration: 202-687-2198 FAX: 202-687-4429
Ambulatory Services: 202-687-2223 FAX: 202-687-3302

3. To analyze growth factors expression and matrix metalloproteinase activity in patients receiving thalidomide.

4. To study thalidomide pharmacokinetics.

(3). In section 3 (study Design) the following changes have been made:

1. Change single center to multicenter in the first paragraph.

2. Change total number of patients in first paragraph to 50 patients.

3. Delete the third paragraph that reads: During the initial 8 weeks dosing period, patients should remain on the study unless they have a ≥ 50% progression by measurable disease, or unless they have a ≥ 25% progression with life threatening progression or progressive disease requiring immediate palliative therapy. However once evaluated at the 8 week mark, any additional progression from that point on of ≥255 from the status at 8 weeks would be considered progressive disease and the patient removed from the study.

(4). In section 4 (patient selection and eligibility) the following changes have been made:

1. Change item 4.1.2 to:
Patients must have evaluable or bidimensionally measurable disease in at least 1 site: For measurable disease, minimum indicator lesion size must be 1 cm. Patients with evaluable bone only disease must have a lytic lesion on plain X ray, CT scan or MRI, that has not been irradiated before. Ascites and pleural effusions are not considered as measurable or evaluable advanced cancer.

2. Change item 4.1.3 to:
Documented objective progressive disease as per section 12.4.

3. Change item 4.1.4 to:
Patients may have had no more than 3 prior chemotherapy regimens. One adjuvant chemotherapy regimen is permitted in addition to two regimens for metastatic disease. If patient has no adjuvant chemotherapy, then, up to three chemotherapy regimens for metastatic disease are allowed. No limitations on the previous hormonal or biological therapies.

4. Item 4.1.8.3: delete albumin, total protein, and LDH.

(5). In section 7 the following changes has been made :

7.1 Serum levels of TNF, VEGF, bFGF, plasma levels of matrix metalloproteinase (MMP-9) and urinary bFGF will be measured before entering the study and on week 2,4,6 and 8 of the first cycle and monthly after that. TNF, VEGF, bFGF assays will be done at Dr Wellstein lab. And MMP at Dr Dickson la.

TNF, VEGF and bFGF:
Serum samples will be obtained on all patients immediately before the first dose and then on week 2, 4, 6 and 8 of the first cycle and monthly after that. During each time point 7 mL of blood will be collected in a red top tube and placed on ice immediately. The serum will then be pipetted off and placed into 2 NUNC® sample mailing tubes and stored in the - 70°C freezer until shipment to Anton Wellstein, M.D., Ph.D. laboratory in the preclinical science building.
TNF, VEGF and bFGF levels in the serum will be measured by Quantikine ELISA kit (R&D Systems, Minneapolis, MN) according to the guidelines suggested by the supplier of the kits.

Matrix Metalloproteinase (MMP-9):
Plasma samples will be obtained on all patients immediately before the first dose and then on week 2, 4, 6 and 8 of the first cycle and monthly after that. During each time point 5 mL of blood will be collected in a purple top containing EDTA (Potassium Chloride) and placed on ice immediately. The sample will then be placed in a refrigerated centrifuge and spun down at 3000 rpm for 15 minutes. The plasma will be pipetted off and placed in a NUNC® sample mailing tube and stored in the - 70°C freezer until shipment to Robert Dickson, Ph.D. laboratory in the New Research Building.

Urine:
Urine samples will be obtained on all patients immediately before the first dose and then on week 2, 4, 6 and 8 of the first cycle and monthly after that. During each time point 20 mL of urine will be collected in a standard urine collection container without preservative and placed on ice immediately. The urine will then be transferred to 30 mL container for storage in the - 70°C freezer until shipment to Anton Wellstein, M.D., Ph.D. laboratory in the preclinical science building.

7.2.1 The first dose of thalidomide will be given at 9 am, all doses after that will be given qhs at 9 pm. Plasma samples will be obtained on all patients immediately before the first dose on day 1 and then ½, 1 , 1 ½, 2, 3, 4, 5, 6, 7 and at 9:00 am and 1:00 pm the second day. Chronic serum level will be done every 2 weeks first cycle and monthly after that.

During each time point 5 ml of blood will be collected in a green top containing NAH (sodium heparin) and placed on ice immediately. Chronic plasma levels will be done every 2 weeks first cycle and monthly after that. The sample will then be placed in a refrigerated centrifuge and spun down at 3000 rpm for 15 minutes. Equal part 0.025 M Sorenson's citrate buffer solution will then be placed in the Corning sample mailing tube along with the pipetted plasma. The mailing tube will then be stored at -20° C and transferred that afternoon to the Analytical Core Laboratory for extraction and assaying by Dr. David Flockhart, M.D., Ph.D.

(6). Table I (study parameter) the following changes have been made:

1. q 2 weeks changed to week 2.

2. q4 weeks changed to week 4.

3. The first sentence below the table is changed to :
On study laboratory **and X rays must be obtained within 2 weeks starting on study.

(7). Item 11.2.0 has been changed to:

During the initial 8 weeks dosing period, patients should remain on the study unless they have progression with life threatening progression or progression requiring immediate palliative therapy.

Progression of disease at the week 8 staging by ≥25% of the measurable disease or with a new lesion will be considered progressive disease and the patient would be removed from the study. A new bone scan lesion will only be considered progression if it is associated with appearance of a new or enlarging lytic lesion on plain bone radiography, CT scan or MRI.

Progression of disease while on study according to this criteria requires termination of treatment, unless the investigator documents on the patient's case report forms the specific reasons and rationale for continuing treatment under such circumstances.

(8). Item 13 (statistical consideration) has been changed to:

13.1 Sample Size

A two-stage sample design will be used to evaluate whether thalidomide has any activity in

patients with metastatic breast cancer who have previously received 0-3 regimens of chemotherapy. We consider thalidomide to be active in this patient population if at least 20% of the patients remain progression-free after two months on study. In the first stage, 14 patients will be entered on each of the two arms by random assignment. The randomization will be stratified by the number of prior chemotherapy regimens received (0-1 vs. 2-3). If all of the first 14 patients progress within two months on study, then the arm will be terminated and it will be concluded that there is 95% confidence that thalidomide at the administered dose level is not active (Gehan, 1961). Alternatively, if at least one of the first 14 patients has stable disease or an objective response after two months on study, then the trial will proceed to the second stage. In the second stage, an additional 11 patients will be entered on the arm to better assess the toxicity profile and activity of thalidomide. In this case, the total sample size (Stage One plus Stage Two) will be 25 patients at a given dose level.

If both low-dose and high-dose thalidomide demonstrate some activity in this trial (i.e., if both arms proceed to the second stage of sampling), then we will compare the efficacy of the two dose levels using time to progression (TTP) as the endpoint. Given the heterogeneity in the patient population and the relatively small sample size of 25 patients per arm, this Phase II trial will not have adequate power to detect modest differences in benefit between dose levels. Rather, the objective will be to identify the more beneficial dose level, if in fact one dose level is truly superior to the other. Otherwise, if the true difference in TTP between the two dose levels is not large, then we are indifferent about which arm will appear more promising in this trial (e.g., Simon, Wittes and Ellenberg, 1985). In order to compute the probability of correctly identifying the superior dose level of thalidomide, we make the following five (5) assumptions:

1) little is known about the natural history of metastatic breast cancer in patients who are not being treated with chemotherapy, but we expect that most of the patients on study will have been heavily pretreated and that the median TTP will be 2-4 months;

2) a superior dose level of thalidomide is one that doubles the median TTP in the patient population;

3) TTP follows an exponential distribution with true hazard rate λ and observed hazard rate λ^*, say;

4) the observed hazard rate λ^* is approximately normally distributed with variance $\phi(\lambda)/n$, where n is the sample size per arm and (Lachin, 1981, Equation 26)

$$\phi(\lambda) = \lambda^2 / [1 - \{\exp(-\lambda F) - \exp(-\lambda F - \lambda A)\}/(\lambda A)],$$

where A, F denote the length of the accrual period and follow-up period, respectively; and

5) patients will be accrued over a 15 month period and the follow-up period will be 2 months (i.e., A=15 and F=2 in the above equation).

The second arm will be declared the "winner" over the first arm if the observed hazard ratio, λ_1^*/λ_2^*, exceeds 1.0. The larger the observed hazard ratio, the stronger the evidence that the second arm is superior to the first arm. Based on the above 5 assumptions, the probability that the observed hazard ratio exceeds some arbitrary value, c, is given by:

$$P(\lambda_1^* / \lambda_2^* > c) = P(\lambda_1^* > c\lambda_2^* > c) = \int_{-\infty}^{\infty} [1 - F(\frac{c\lambda_2^* - \lambda_1}{\sqrt{\Phi(\lambda_1)/n}})] dF(\frac{\lambda_2^* - \lambda_2}{\sqrt{\Phi(\lambda_2)/n}})$$

where F(·) denotes the standard normal cumulative distribution function. In the following table, Arm 2 represents a dose level that is truly superior to Arm 1. As shown in the table, the probability that the correct arm will be chosen as the winner (i.e., the probability that the observed hazard ratio exceeds 1.0) is at least 96%. The probability of attaining stronger evidence about the superiority of Arm 2, such as observing a hazard ratio of 1.25 or 1.5, will be at least 90% or 78%, respectively.

True Median TTP (in months):		True Hazard Rate:[1]		True Hazard	Probability that Observed Hazard Ratio is Greater Than ...		
Arm 1	Arm2	Arm 1	Arm 2	Ratio	1.00	1.25	1.50
2	4	0.347	0.173	2.0	98.2%	93.1%	82.3%
3	6	0.231	0.116	2.0	97.5%	91.5%	80.2%
4	8	0.173	0.087	2.0	96.8%	90.1%	78.6%

[1] hazard rate: $\lambda = \ln(2)/\text{median TTP}$.

13.2 Statistical Analysis

The primary endpoint in the efficacy analysis will be time to progression (TTP). Time will start on the day that the patient is randomized. The two dose levels will be compared using a stratified Cox proportional-hazards regression model, where the stratification variable will be the number of prior chemotherapy regimens (0-1 versus 2-3). If there are imbalances between the two arms with respect to age or other prognostic factors, these factors will be included as covariates in the regression model. The analysis will follow the intent-to-treat principle, i.e., patients will be classified according to their assigned dose level rather than dose actually

received. The outcome of the regression analysis will be an estimate of the hazard ratio, which quantifies the instantaneous risk of progression on Arm 1 relative to Arm 2. As explained in Section 13.1, an observed hazard ratio greater than 1.0 constitutes evidence that dose level 2 is more beneficial than dose level 1. Conversely, an observed hazard ratio less than 1.0 provides evidence that dose level 1 is preferred. The actual decision about which dose level to use in future Phase III trials will be based on toxicity considerations as well as the hazard ratio.

In a secondary analysis, we will compare the post- versus pre-treatment tumor growth rates in patients with known rate of tumor growth over the 2-4 month period prior to starting thalidomide. To standardize the rates, we will need to adopt a probability model for the tumor growth curve over time. A simple and plausible model for the tumor growth curve per unit time is the exponential growth model

$$V(t) = (1 + r)\, V(t - 1)\, \epsilon(t),$$

where $V(t)$ is the tumor size at time t, r is the growth rate and $\epsilon(t)$ is a random perturbation. The tumor size will be measured as described in Section 12.2. In this study the time unit of interest is 8 weeks, so r is the growth rate <u>per 8 weeks</u>. The post-treatment (r_2) versus pre-treatment (r_1) growth rate of a patient's tumor can be compared based on the tumor sizes V_1, V_2 and V_3 measured before treatment, at start of treatment, and after treatment with Thalidomide, respectively. Let t_1, t_2 and t_3 denote the dates of the three tumor measurements, and let $\Delta_1 = t_2 - t_1$ and $\Delta_2 = t_3 - t_2$ denote the pre- and post-treatment time intervals, respectively. Of interest is the ratio of the post-treatment versus pre-treatment growth rate (r_2/r_1). If $r_2/r_1 = 1$ then thalidomide has no effect on the growth rate, whereas if $r_2/r_1 = 0.5$, say, then thalidomide reduces the growth rate by 50%. We will assume that $\ln\{\epsilon(t)\}$ has a normal distribution with mean zero and standard deviation σ. For a given patient, the maximum likelihood (and unbiased) estimate of $\ln(1 + r)$ is $\{\ln(V_2) - \ln(V_1)\}/\Delta_1$ before treatment and $\{\ln(V_3) - \ln(V_2)\}/\Delta_2$ after treatment with Thalidomide. Let R_1 and R_2 denote the maximum likelihood estimates of growth rates r_1 and r_2, respectively. It follows that the maximum likelihood estimate of the relative growth rate for an individual patient is

$$R_2 \,/\, R_1 = \frac{(V_3^{1/\Delta_2} - V_2^{1/\Delta_2}) \,/\, V_2^{1/\Delta_2}}{(V_2^{1/\Delta_1} - V_1^{1/\Delta_1}) \,/\, V_1^{1/\Delta_1}} .$$

We will compute each evaluable patient's estimated baseline (R_1) and relative (R_2/R_1) tumor growth rates as described above. The relative growth rate will be transformed to achieve approximate normality and tested using 1- and 2-sample t-tests for within- and between-arm

hypotheses, respectively. We will also perform nonparametric analogues of these tests, i.e. the one-sample sign test and two-sample Mann-Whitney test, respectively. For tumor measurements after the initial 8-week dosing period, reductions in the tumor growth rate will be investigated using a random effects regression model. Prognostic factors that might be predictive of efficacy will be included as explanatory variables in the regression model. If there is extensive patient withdrawal following the initial 8-week dosing period, the regression analysis will be adjusted for potentially informative right censoring (e.g., Mori, Woodworth and Woolson, 1992; Follman and Wu, 1995).

(9). The following references were added to reference section

44. Gehan EA. The determination of the number of patients required in a preliminary and follow-up trial of a new chemotherapeutic agent. J. Chronic Diseases 13: 346-353, 1961.

45. Simon R, Wittes, RE and Ellenberg, SS. Randomized Phase II trials. Cancer Treatment Reports 69: 1375-1381, 1985.

46. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. Controlled Clinical Trials 2: 93-113, 1981.

47. Mori M, Woodworth GG and Woolson RF. Application of empirical Bayes inference to estimation of rate of change in the presence of informative right censoring. Statistics in Medicine 11: 621-631, 1992.

48. Follman D and Wu M. An approximate generalized linear model with random effects for informative missing data. Biometrics 51: 151-168, 1995.

(10). Delete appendix B.

(11) In the consent form under(description of research) , last paragraph, change total number of patients to 50.

(12) Item 12.4 first paragraph has been changed to:

The appearance of new lesions or an increase of at least 25% in the sum of the products of the longest perpendicular diameters of measurable lesions. A new bone scan lesion would only be considered progression if it is associated with appearance of a new or enlarging lytic lesion on plain bone radiography, CT scan or MRI.

A revised protocol and consent form incorporating all the above changes are attached. All the changes are highlighted for your convenience. If further information is needed, please feel free to contact me.

Core 1: Patient Accession Core

Appendix 1: CARE Flow of Activities
Appendix 2: Primary Care Clinic Advisory Board Meeting Minutes
Appendix 3: Key Informant Questionnaire
Appendix 4: Materials
Appendix 5: Strategic Plan

Appendix 1: CARE Flow of Activities

CARE Flow Of Activities

*Males are also eligible for CARE

1. Potential participant calls number from brochure or other advertisement source
   - a voice mail service is set up to instruct callers to leave their phone number and best time to call
   - within a few days, a return call is made and eligibility determined

2. At call back, questions are addressed and a RA administers the eligibility screen - 10 minutes → If not eligilble - referral made

   If eligible - RA conducts baseline survey - 15 minutes

3. Baseline completed, participants's name and number passed on to GC to set up visit.

4. Mail to participant
   - directions to appointment
   - copy of consent form
   - family history form
   - pre-counseling questionnaire
   - pre-stamped envelope to return family history form

5. Initial session, participant comes to Lombardi with consent forms, questionnaire and family history form, if not mailed beforehand

6. Session estimate time 1.5 - 2hr
   - review family history
   - medical history
   - concerns about risk
   - genetic information
   - cancer risk
   - cancer screening and prevention guidelines
   - risks, limitations and benefits of genetic testing

7. Participant is offer opportunity to get tested...

If Yes
- participant has blood drawn on site
- If known mutation in family = 4-8 wks
- If Jewish = 4-8 wks
- If not in above categories = 4wks -8 mos

If Unsure
- can take some time to think about it and may return for testing

If No
- may recommend to clinical trial

8. Disclosure
   - once test results are received, GC calls participant to set up appointment to disclose result
   - physician present @ disclosure

Positive + result
- 1 - 1.5 hr session
- discuss options & what results mean to participant and risk

Negative - result
- 30 minute session to reinforce the importance of screening

→ All participants receive 1, 6, and 12 month follow-up

RA = Research Assistant
GC = Genetic Counselor

Appendix 2: Primary Care Clinic Advisory Board Meeting Minutes

Lombardi Cancer Center
Breast Cancer Center's Patient Accession Core
Primary Care Clinic Advisory Board Meeting
Tuesday, August 12, 1997, 8:30AM to 10:30AM

MEETING NOTES

Present: Juan Romagoza (La Clinica del Pueblo), Sister Kay Koppes (Spanish Catholic Center), Randi Abramson (Zaccheaus Clinic), Catalina Sol (Washington Free Clinic), Ann O'Malley, Jon Kerner, Lenora Johnson, Anna Ryan-Robertson, Joscelyn Silsby (Lombardi Cancer Center)

A packet of materials was distributed at the meeting which included a roster of the Primary Care Clinic Advisory Board members, a flow chart of activities for the CARE study, brochures for CARE and CAB CAD, and "The Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research".

Dr. Romagoza asked about the time line for the advisory board to meet and the studies to be conducted. The timeline was reviewed and clarified in that we are coming up on the end of Year 01 in September, and this advisory board is now meeting for the second time. During Year 02 beginning October 1997, the board will meet quarterly.

CARE Study

The CARE flow chart of activities was reviewed and an update on accrual was provided. Approximately 400 women have participated in the study to date, the vast majority of whom have been referred from sources internal to Georgetown University Medical Center. Dr. Abramson reported that the brochure is being distributed to women with a family history of breast and ovarian cancer, but the initial message of the brochure may discourage them from calling because it appears as if it is directed primarily towards women who have had breast cancer, especially the green insert. Dr. Kerner suggested changing the order so that the first message is about family history. Dr. Abramson mentioned that many women do not know their family history of disease, and Dr. Romagoza added that those who do know are very worried about it and would benefit greatly from counseling. Dr Abramson shared that those women, who know they have a strong family history of breast cancer, are so frightened about it that they don't want to get mammograms. They don't want to know if a lump is there because they associate it with a fatal outcome. It was agreed that a family approach is very important, especially in the Latino community. There is already a framework for families to participate in CARE, but the recruitment messages need to focus more on the family. Catalina added that a good recruitment strategy is to get adult children involved in the recruitment of their elders, mothers and aunts.

The need to train clinic staff and volunteers to promote the studies was addressed. At Washington Free Clinic, training of Lay Health Promoters will begin on Saturday September 6 and continue for several weeks. Catalina Sol suggested we conduct a training session on cancer in general, and include orientation to the Breast Cancer Center's clinical trials (CARE and the CAB/CAD studies). At Zaccheaus Free Clinic, they have health educators who lead classes for patients while they wait for appointments. This may be a good opportunity to orient patients and family members to the CARE study. Sister Kay suggested that staff from the Spanish Catholic Center receive training, especially if the CARE study becomes open to Spanish speaking patients.

Cancer Genetics Network

Dr. Kerner discussed Lombardi's NCI proposal to become part of a national Cancer Genetics Network. He mentioned that the National Institutes of Health are concerned about people using commercial vendors for genetic testing and not receiving adequate education and counseling to understand what the results -- positive or negative -- mean. Therefore the NIH is calling for cancer genetic testing to be conducted within the _ context of research AND that it must always have counseling and education included as necessary components.

The proposal being submitted by Dr. Caryn Lerman, Director of the Cancer Genetics Program at Lombardi, includes a full-time Latino health educator, a bilingual genetic counselor, and the possibility of the health educator and genetic counselor providing services directly in community settings.

To justify the need for these resources, Dr. Kerner needs demographic data on the patient populations served by each clinic. Men and women should be included, because genetic testing may soon be available for colo-rectal cancer in addition to breast and ovarian cancer. Letters of support are also needed from each clinic demonstrating interest and commitment to participating in the work of the Cancer Genetics Network. Joscelyn Silsby will draft sample letters of support for each clinic that can be edited and re-typed on letterhead. The proposal is due September 12, 1997 and the project would begin in the Spring of 1998.

In the context of further discussions about issues in genetic counseling among Latinos, including the need for a family focus and the point that the issues for men and counseling for men should be approached differently, Catalina Sol pointed out that most Hispanic women in the prenatal clinic at Washington Free Clinic do not elect to receive the AFP test. Genetics issues are very sensitive in this community, and it is Catalina's perception that most people do not want to know about their genetic make up, whether the news is good or bad.

Primary Care and Regular Breast Cancer Screening in Under-served Minority Women, Ann O'Malley

Dr. O'Malley spent some time orienting the board to the study she will begin shortly in the clinics. The crux of the study is to determine what women see as barriers to obtaining regular breast cancer screening in the primary care setting. These are some of the research questions:
1) How do patients navigate the clinic?
2) How can the structure of primary care maximize regular breast cancer screening?
3) From the perspective of women, what will increase regular screening utilization over time?

Focus groups will be conducted to learn what women see as barriers to obtaining regular screening. Separate focus groups by site will be conducted for women clients and clinic providers. Based on results of these focus groups, a 30 minute survey will be developed and conducted using a sample from the four clinic sites. Results of focus groups will be presented to the Primary Care Clinic Advisory Committee. Dr. O'Malley would also like to include women who are not using the services of the clinics, but whom are eligible.

Dr. Randi pointed out that it's difficult to get people from her clinic to participate in focus groups. First, many people do not have phones, and secondly there are many languages spoken in addition to Spanish and English. At Zaccheaus Clinic, Korean, Vietnamese, Ethiopian and West African patients are being seen. It may not be possible to include all of these groups. Dr. Romagoza stressed the importance of following up focus group sessions with information coming back to participants in the form of an educational session. Once people are together talking about issues that raise awareness, concern and possible questions, they should have opportunities for education once the research part of the focus group is completed. Ms. Sol informed the group that at the Washington Free Clinic they do not allow studies to be done on their patient population without an educational component or without some other need getting accomplished at the same time. For example, the clinic would like to conduct focus groups with their patients to obtain certain feedback, but they have neither the staff time or monetary resources to undertake such a project.

CAB/CAD Study

So far 40 women have been accrued to this study from source internal to Georgetown University Medical Center. As soon as a woman finds out she needs a biopsy, she can enroll in the study and completes participation prior to getting the biopsy. It takes approximately four hours to get 4-5 less invasive diagnostic procedures, that may show efficacy for making accurate breast cancer diagnosis without the need for biopsy. *In*

response to the question of how patients are remunerated the $100 for participating, it was learned after the meeting that participants complete a W-9 form and are mailed a check for $100 (no taxes are deducted) within 4-6 weeks. It was also requested that the tests be explained in lay people's terms. Anna Robertson and Joscelyn Silsby will meet with staff conducting the study to get more information about each test and translate it into everyday language.

Materials Development Work Group

Anna Robertson offered to head up a working group of representatives from each clinic to review and adapt recruitment materials. This would begin with English speaking materials and eventually expand to Spanish speaking. Primary Care Advisory Board representatives will be contacted in the next month to designate staff or volunteers who could be part of this effort.

Next Meeting

Given that during Year 02 of the PAC (begining in September) the Advisory Board will be meeting on a quarterly basis, it was suggested that the next meeting take place in October. *However, there were several activities suggested at this meeting such as staff training and materials development. Therefore, the next meeting will be determined at a later date.*

Appendix 3: Key Informant Questionnaire

Lombardi Breast Cancer Center - Patient Accession Core
Health Maintenance Organization Advisory Board

Key Informant Questionnaire

Name: _____

Organization Name: _____

Address: _____

_____

_____

Telephone: _____ Facsimile: _____

HMO Model Type: ☐ IPA ☐ Network ☐ Group ☐ Staff

Plan Population:

1.) How many of your enrollees are District of Columbia residents? _____

2.) What percentage of your enrollees from DC is over the age of 50 years? _____

3.) Do you have any enrollees from DC whose premiums are paid by:

a.) Medicaid: _____ Yes _____ No

b.) Medicare: _____ Yes _____ No

Cancer:

4.) Please complete this grid for the period **01/01/94 through 12/31/94.**

Population	Number of New Cancer Cases	Number of Cancer Deaths	Number of New Breast Cancer Cases	Number of Breast Cancer Deaths
All Enrollees				
D.C. Enrollees				

5.) Please complete this grid for the **period 01/01/95 through 12/31/95.**

Population	Number of New Cancer Cases	Number of Cancer Deaths	Number of New Breast Cancer Cases	Number of Breast Cancer Deaths
All Enrollees				
D.C. Enrollees				

Screening Information:

6.) How many female enrollees from D.C. are over the age of 50? _____

7.) Approximately what percentage of these enrollees have had a mammogram in:
1994 _____ 1995 _____

Health Care Centers:

8.) Please list the names and addresses of your primary care facilities in the District of Columbia (please list all):

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____

Cancer Care Centers:

9.) Are you currently contracting out services for cancer screening, diagnosis, and treatment?
_____ Yes _____ No

If yes, please list the agencies to which you contract services and the types of services they provide.

Organization	Service Provided

10.) Does your plan have a policy or policies relating to members participation in clinical trials and specifically, cancer clinical trials?

_____ Yes _____ No

If yes, are you willing to provide Lombardi Cancer Center with a copy of the policy (ies)?

_____ Yes _____ No

If no, can you briefly give an overview of what the policies state?

_____

_____

_____

_____

11.) Does the plan have a disease management plan for cancer care?

_____ Yes _____ No

If yes, are you willing to provide Lombardi Cancer Center with a copy of the plan?

_____ Yes _____ No

If no, can you briefly give an overview of what the plan states?

_____

_____

_____

_____

Breast Cancer Education:

12.) Please describe the breast cancer education programs you provide to the population you serve (summarize narrative).

_____

_____

_____

_____

13.) Would you like assistance from Lombardi in developing a breast cancer education plan for members?

_____ Yes _____ No

14.) Have you partnered with other community entities to disseminate breast cancer awareness and education materials?

_____ Yes _____ No

If yes, please describe.

_____

_____

_____

_____

15.) Is there a health education/health promotion department within your organization?

_____ Yes _____ No

If yes, who is the contact person in that department?

Name: _____

Organization Name: _____

Address: _____

_____

_____

Telephone: _____ Facsimile: _____

Thank you for taking the time to complete this key informant survey. Please bring your completed survey to the first meeting of the LCC Breast Cancer Center HMO Advisory Board or fax it to Ms. Lenora Johnson at (202) 687-0651.

Appendix 4: Materials

A clinical trial is a systematic investigation of the effect of materials or methods, according to a formal study plan and generally in a human population with a particular disease or class of diseases.

How Clinical Trials for Cancer Work

In cancer research, a clinical trial generally refers to the evaluation of treatment methods, such as surgery, drugs, or radiation techniques. Methods of cancer prevention, detection, or diagnosis may also be the subject of such studies. Cancer clinical trials are conducted not only to decrease illness and death but also to improve the methods and procedures for cancer detection, to improve the quality of life of cancer patients during and after treatment, and to ultimately prevent cancer altogether.

Examples of Clinical Trials Protocols

Clinical trials are conducted to explore new drug developments for cancer. Protocols:

- examine the integration of multiple treatment modalities
- test new combinations of existing drugs or new dosing schedules and routes of administration
- assess new screening tests
- evaluate methods of supportive care
- teach and counsel individuals about lifestyle and behavior changes

Clinical Trial Categories

Clinical trials are generally categorized into four groups, Phase I, Phase II, Phase III and Phase IV trials.

Phase I studies generally establish whether a treatment is safe and which dosages may be most effective.

Phase II studies assess the efficacy of treatment, after their safety and feasibility has been established in Phase I studies.

Phase III studies compare effective treatments, from Phase II studies, with currently accepted treatments.

Phase IV studies collect and compare data on established treatments.

Additional Categories for Clinical Trials

Additional study categories that serve to evaluate treatments to prevent the recurrence of cancer after a patient has become clinically free of disease, and to evaluate treatments designed to reduce tumors to the point that they can be treated with standard therapies are considered adjuvant and neoadjuvant respectively.

Some clinical studies are designated Group C and Treatment Referral Center (TRC) protocols. Group C studies make accessible drugs that are not yet commercially available but have been submitted for or are close to approval by the Food and Drug Administration. Toxicities associated with Group C drugs are generally manageable at local hospitals, and the drug is provided by the National Cancer Institute to any qualified oncologist with an eligible patient. TRC protocols are a limited mechanism by which treatment on a clinical trial is provided at the NCI Clinical Center or at NCI-funded Cancer Centers to patients for whom no standard treatments are available and who do not qualify for existing clinical trials.

Clinical Trial Benefits to Patients

For each type of clinical trial there may be anticipated benefits. In Phase I trials, there is always the potential, albeit limited, for therapeutic benefit. In Phase II trials the therapeutic outcomes are unknown at the outset. However, the benefit for some patients is anticipated based on preclinical data. Ethical considerations require that investigators of Phase II trials terminate studies when severe toxicity without compelling efficacy is observed. For patients participating in Phase III trials, whether for primary treatment or supportive care, they are receiving the most up-to-date treatment for a given indication. Supportive care studies serve to improve the quality of life for patients and their families through decreased discomfort and anxiety.

Cancer Prevention & Early Detection Trials

Prevention and early detection studies assess prevention and screening techniques in people at increased risk for

developing cancer or for the population at large. These studies are designed to show that cancer incidence or mortality is reduced because of the intervention.

Prevention studies typically require long follow-up to assess the endpoints. Cancer prevention studies may involve drug intervention, prophylactic therapy, education and counseling for dietary or other life-style modification all aimed at reducing cancer incidence or delaying the onset of cancer. Cancer screening studies are designed to encourage participants to begin and continue screening on a regular basis. Overall the anticipated benefits are a decrease in cancer-related mortality and an increase in overall survival. For screening studies, the immediate outcome is a reduction in the incidence of advanced cancers.

Referring Patients for Participation in a Clinical Trial

In many cases clinical trials offer state-of-the-art therapeutics for persons diagnosed with cancer. Generally, the trial compares state-of-the-art with standard treatment. Also, this is a way that patients can contribute in a very important way to cancer research. The decision to participate is one that you and your patient should arrive at together. Some issues you may want to address in making this decision include:

- the purpose of the study
- type of tests or treatments involved
- advantages and disadvantages
- study's impact on the patient's life and daily routine
- costs, side effects (if any), and likely outcomes.

Payment for Clinical Trials

For the most part, clinical trials are paid for by the federal government and private industry (pharmaceutical companies). Physicians may sometimes be paid on a per-patient basis. Patients in a limited number of cancer prevention and early detection studies may also be paid a small fee to participate.

NCI CCC

Comprehensive Cancer Center Designated by the National Cancer Institute

GEORGETOWN

The Art of Medicine

Produced by the Department of External Affairs 9/97

The

Lombardi

Cancer

Center

Research

Education

Treatment

GEORGETOWN UNIVERSITY MEDICAL CENTER

LOMBARDI CANCER CENTER

NCI CCC®

A Comprehensive Cancer Center designated by the National Cancer Institute

Help us..

improve the diagnosis of Breast Cancer

What is "A Coordinated Approach to Breast Cancer Diagnosis"?

This is a study to determine whether some new diagnostic tests for breast cancer will reduce the number of breast biopsies and help in early diagnosis. It will involve 400 women from the Washington, DC area, ages 18 or older, for whom a breast biopsy has been recommended.
The study is sponsored by the Lombardi Cancer Center, an NCI designated Comprehensive Cancer Center, and the U.S. Army.

Why Is This Study Being Done?

Every year about 600,000 diagnostic breast biopsies are performed in the U.S. but 65-80% of these biopsies are shown *not* to be cancerous. Therefore, this study is designed to find out if these new tests are useful in ruling out breast cancer in women who would otherwise require a diagnostic biopsy.

Who Can Participate?

Any woman:

- who is over the age of 18
- for whom a breast biopsy has been recommended
- who is NOT pregnant or nursing
- who DOES NOT have a pacemaker

What Is Involved If You Decide To Join?

If you decide to join, the diagnostic tests will take place at a visit PRIOR to your scheduled biopsy. This visit can be scheduled by calling Miriam F. Mullins, our Project Coordinator, at (202) 784-3359. At the visit, you will fill out a detailed questionnaire along with undergoing these various diagnostic tests.

Is There Any Compensation or Cost?

There is no cost to you for these tests and they should be complete in about three to five hours. If you complete all the tests, you will receive $100 for participating and complementary free parking and lunch.

How Can I Participate?

Once you've been recommended for a breast biopsy, you may be eligible for the study. If you are interested in being a part of the study and need more information, you can call our Project Coordinator, Miriam F. Mullins, at (202) 784-3359. If you are eligible you will be given detailed information about what is involved in participating. You can then decide whether or not you want to participate. Participation in the study will not delay your biopsy in any way. All of the information collected will be kept in the strictest confidence.

Who is eligible for CARE?

Since eligibility for the CARE program is subject to change as research progresses, please see the insert for the current eligibility criteria.

Participants must be at least age 18 and have at least one living family member who has had breast or ovarian cancer. While the CARE program focuses on women, male relatives may also be eligible.

To learn more about the CARE Program and to find out if you are eligible to participate, please call (202) 687-1750

Produced by the Department of External Affairs, 1996

do you have a family history of breast or ovarian cancer

GEORGETOWN UNIVERSITY MEDICAL CENTER

You may have heard

or read in the news about breast and ovarian cancer susceptibility genes, such as BRCA1 and BRCA2. Here is your chance to find out more.

The **CARE** (Cancer Assessment and Risk Evaluation) Program is a genetic counseling and testing program offered by the Lombardi Cancer Center at Georgetown University Medical Center. Through the CARE Program, women receive information and counseling about their risks for breast and ovarian cancer—two cancers shown to be related to genes that are inherited, or passed down, in families.

This is a free program

that is supported by research grants from the National Institutes of Health, the Department of Defense, and the Susan G. Komen Foundation.

Why should I participate in the CARE Program?

By participating in the CARE Program, you may learn valuable information about your risk of developing breast and ovarian cancer that will help you in making decisions about your health care.

You also will be helping research efforts to learn more about the best ways to educate and counsel women who are at increased risk for breast and/or ovarian cancers. Ultimately, the goal is to reduce illness and death from these cancers.

What does the CARE Program involve?

Each participant in the CARE Program will meet with a genetic counselor for approximately 1 to 2 hours and will receive:

- a detailed family history and risk factor assessment
- genetic education and counseling
- guidelines for cancer prevention and screening
- option of genetic testing for cancer susceptibility, if eligible
- information regarding cancer screening services and prevention trials

Since the CARE Program is a clinical research program, all participants are asked to complete four telephone interviews over a one-year period to evaluate the benefits of the program and develop future genetic counseling and testing programs. All information is confidential.

If you had breast cancer,

you may be eligible for CARE if:

- You were diagnosed at age 40 or younger, and are of Jewish descent
- You were diagnosed before age 50 and you also have a first-degree relative (mother, sister, daughter) who had ovarian (any age) or breast cancer (before age 50)

If you had ovarian cancer,

you may be eligible for CARE if:

- You were diagnosed at age 50 or younger, and are of Jewish descent
- You also have a first-degree relative who had ovarian cancer (any age) or breast cancer (before age 50)

If you have not had breast or ovarian cancer,

you may be eligible for CARE if:

- You have a first-degree relative (mother, sister, daughter) who had breast cancer at age 30 or younger, OR
- You have two first-degree relatives who had early-onset breast cancer (age 50 or younger) and/or ovarian cancer (any age), OR
- You have three relatives on the same side of the family with early-onset breast cancer and/or ovarian cancer

CARE

Cancer Assessment and Risk Evaluation

Lombardi
Cancer
Center

Research
Education
Treatment

GEORGETOWN
UNIVERSITY
MEDICAL CENTER

This material will introduce you to a free genetic counseling and testing program. There is now a genetic test that can help you learn more about cancer risks for you and your family. If you want to learn more about genetic testing, please take a few moments to read through this information.

What is the CARE program?

The CARE (Cancer Assessment and Risk Evaluation) program is a free genetic counseling and testing program offered by the Lombardi Cancer Center at Georgetown University Medical Center. This program is supported by research grants from the National Institutes of Health, the Department of Defense, and the Susan G. Komen Foundation.

Participation in CARE

Through the CARE program, each participant meets with a genetic counselor to discuss:

- *a detailed family history and risk factor assessment*
- *the genetics and inheritance of breast and ovarian cancer*
- *personalized guidelines for cancer prevention and screening*
- *the options available for genetic testing for cancer susceptibility, including the pros and cons of testing (genetic testing is offered to all eligible individuals)*

CARE is a clinical research program. Therefore, all participants are asked to complete telephone and in-person interviews and questionnaires before and after participation. These assessments allow us to evaluate the benefits of the program and learn more about how people make decisions about genetic testing. We also hope to learn how these decisions affect their lives. Even if you decide that you are not interested in testing, we would like to interview you briefly on the telephone. This is a critical part of our research.

The clinical staff of CARE includes two master's-level genetic counselors and a medical director—a physician trained in medical oncology. The program's principal investigator is a behavioral scientist and clinical psychologist. These individuals work closely with other oncologists, surgeons, nurses, and psychologists at Georgetown University Medical Center to provide services and information to CARE participants.

For more information about CARE, or to find out how to enroll, please call (202) 687-1750.

What is the significance of breast cancer susceptibility genes?

It is estimated that hereditary breast cancer accounts for approximately 5 percent to 10 percent of all breast cancer cases. BReast CAncer 1 (BRCA1) and BReast CAncer 2 (BRCA2) are the two major breast cancer susceptibility genes that have been identified to date. Alterations in these genes are thought to account for the majority of inherited breast and ovarian cancers. The frequency of these altered genes in the general population is not known. One estimate suggests that BRCA1 alterations occur in about 1 of every 800 individuals.

The BRCA1 and BRCA2 genes are thought to act as "tumor suppressor" genes when they function properly. Tumor suppressor genes prevent cells in our body from growing out of control; however, alterations of these genes can change their usual function. This change can increase the chance of developing breast, ovarian, and other cancers.

Because the BRCA1 and BRCA2 genes are very large, there are many places within each gene where an alteration (mutation) can occur. Thus far, more than 100 alterations have been detected in these genes and some mutations occur much more frequently than others. A few mutations have been found with increased frequency in specific populations.

A specific alteration in one of these genes has been identified in your family. Research is under way to learn more about this and other mutations in BRCA1 and BRCA2. This research will improve our understanding of the cancer risks associated with these alterations and will provide more information about the function of these genes. Ultimately, these discoveries may lead to improved prevention, early detection, and treatment of cancer.

What are the risks associated with BRCA1 and BRCA2 alterations?

Cancer risks associated with BRCA1 and BRCA2 alterations must be evaluated in the context of your medical and family history. In general, a woman with an alteration in the BRCA1 gene has a 55 percent to 85 percent chance of developing breast cancer, and a 15 percent to 60 percent chance of developing ovarian cancer. There may also be an increased risk of prostate cancer for men, as well as an increased risk of colon cancer for men and women.

Identification of the BRCA2 gene took place more recently. We know less about the cancer risks associated with alterations in this gene. When a BRCA2 alteration is present, the risk of breast cancer is estimated to be from 55 percent to 80 percent. The risk of ovarian cancer is thought to be between 15 percent and 20 percent. BRCA2 alterations also are associated with other cancers, such as breast and prostate cancer in men, pancreatic cancer, and possibly other cancers.

Research is in progress to better define these risks. As more information becomes available, these estimates may change. It is important to remember that risk varies from individual to individual and from family to family. We cannot predict with certainty the type of cancer to which an individual is most susceptible, or the age at which cancer may develop.

What is my chance of having the BRCA1 or BRCA2 alteration which is present in my family?

The genetic counselor can discuss your individual risk based upon your position in your family tree. An individual with a BRCA1 or BRCA2 alteration has a 50 percent chance of passing it down to his or her children. This happens because eggs and sperm each carry only one copy of each gene pair. Each child of a parent with an altered gene and each full brother or sister of an individual with an altered gene has a 50 percent chance of inheriting it. Individuals also have a 50 percent chance of inheriting the functioning gene. The risk is not affected by the sex of the child or the affected parent, or by the child's birth order. It cannot be predicted based on how much a child resembles either parent.

How is genetic testing performed?

As an alteration in BRCA1 or BRCA2 has already been identified in your family, it is a simple process to test you. A small blood sample is drawn. From it, genetic material (DNA) is obtained and analyzed for the specific alteration previously identified in your relative. This testing can be completed in a relatively short period of time. It is very accurate and provides results that are clearly positive or negative for a particular alteration.

What are the pros and cons of testing?

There are potential benefits to being genetically tested. There also are potential risks and limits to the information that can be obtained. Each individual needs to consider whether the potential benefits outweigh the risks in order to decide whether or not to be tested. All individuals who decide to provide a blood sample for genetic testing must sign a consent form. The form contains additional information about the benefits, limitations, and risks of genetic testing.

Increased knowledge:

Genetic tests may provide you with more information about your risk of getting cancer. It may also provide insight as to why cancer developed in your family.

Health care decisions:

Information about cancer risk can facilitate decisions about whether certain screening tests should be considered. It may help women decide about risk-reducing surgery.

Emotional implications:

Learning the test results may produce a sense of relief. It may reduce uncertainty about cancer risk. People whose test results are negative may feel a sense of reassurance. However, those who learn their test results are positive may feel sad, angry, or anxious. Given its impact on relatives or children, this information may strain relationships. Individuals may feel guilty regarding the outcome or possible outcome of testing. Each person responds differently to information about risk. Sometimes, psychological counseling and support may be helpful.

Possible discrimination:

Genetic testing may place individuals at risk for discrimination by health, life, and disability insurers, as well as employers. Knowledge that you have a genetic predisposition to cancer may compromise your ability to obtain or maintain insurance coverage. Today, fewer than half the states restrict the extent to which health insurers may use genetic information. Almost all states allow life and disability insurers to ask questions about genetic predisposition to cancer, and then use the answers in their underwriting decisions. Recently enacted federal legislation may help protect those individuals who decide to undergo genetic testing. In August 1996, President Clinton signed The Health Insurance Portability and Accountability Act of 1996. It recognizes "genetic information" as protected medical information. It forbids those who provide health care coverage from using such information to deny access to individuals who must change health plans when they change jobs.

The act also states that, based on genetic information, a group medical plan cannot require an individual to pay a premium or contribution (to join the plan or stay in it) that is greater than that for a "similarly situated" enrollee. The term "similarly situated" means that a plan or coverage could vary benefits available to different groups of employees, such as full-time versus part-time, or employees in different geographic locations. A limitation of the act is that it does not restrict the premiums charged for individual health insurance. Such premiums need only comply with state law. These insurance reform provisions went into effect on July 1, 1997.

The Health Insurance Portability and Accountability Act of 1996 is a major step toward protecting individuals who undergo genetic tests; however, it does not address the issue of confidentiality, nor does it require an individual's permission to release genetic information. There has been no federal legislation passed regarding medical record privacy, employment, and other forms of insurance, such as life and disability. The Senate and the House are reviewing bills that would offer additional federal protection from genetic discrimination.

The staff of the CARE program will do everything possible to maintain the privacy of genetic test results. Each participant is identified by a unique number, and no information about him or her is released to third parties without that participant's consent. Our research program received a Certificate of Confidentiality from the Department of Health and Human Services. This allows CARE to withhold information about participants from any outside sources, unless an individual has given written consent.

How do I get more information?

If you are interested in participating in CARE, you are eligible to come to Georgetown University Medical Center and receive free genetic counseling and testing. Even if you are not interested in genetic counseling or testing, we would appreciate your participation in a few brief telephone interviews. If you are interested in genetic testing, but cannot travel to Georgetown, one of our research assistants can provide information about referrals in your local area. Many of these referral programs charge a fee for genetic counseling and testing.

Please feel free to contact us at (202) 687-1750 for more information.

NCI
CCC

A Comprehensive Cancer
Center Designated by the
National Cancer Institute

GEORGETOWN

The Art of Medicine

Produced by the Department of External Affairs 8/97

lombardi

care

Cancer Assessment and Risk Evaluation

information packet

LOMBARDI
CANCER
CENTER

RESEARCH •
EDUCATION •
TREATMENT •

GEORGETOWN
UNIVERSITY
MEDICAL CENTER

GEORGETOWN

The Art of Medicine

NCI CCC

A Comprehensive Cancer Center Designated by the National Cancer Institute

CARE Program Overview

The CARE (Cancer Assessment and Risk Evaluation) Program is a genetic counseling and testing program offered by the Lombardi Cancer Center at Georgetown University Medical Center. This is a free program that is supported by research grants from the National Institutes of Health, the Department of Defense, and the Susan G. Komen Foundation.

Participation in CARE

Through the CARE Program, each participant meets with a genetic counselor to discuss:

- *a detailed family history and risk factor assessment*
- *the genetics and inheritance of breast and ovarian cancer*
- *personalized guidelines for cancer prevention and screening*
- *the options available for genetic testing for cancer susceptibility, including the pros and cons of testing (genetic testing is offered to all eligible individuals)*

The CARE program is a clinical research program. Therefore, all participants are asked to complete telephone and in-person interviews and questionnaires both before and after participation. These assessments are important to evaluate the benefits of the program, and will help us learn more about how people make decisions about genetic testing and about the impact of these decisions on their lives.

CARE Staff

The clinical staff of the CARE program includes two master's level genetic counselors and a medical director—a physician trained in medical oncology. The principal investigator of the CARE program is a behavioral scientist and clinical psychologist. These individuals work closely with other oncologists, surgeons, nurses, and psychologists at Georgetown University Medical Center to provide services and information to CARE participants.

Care *info sheet*

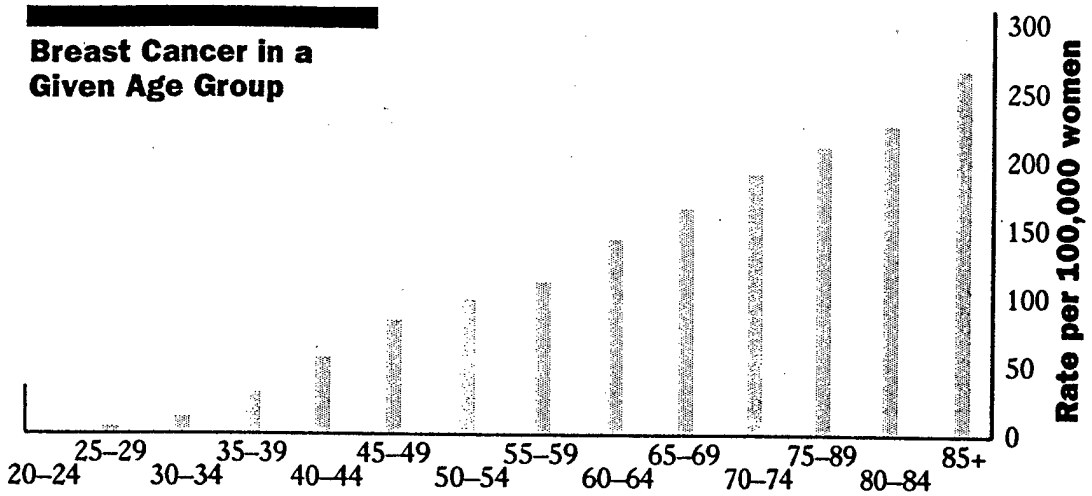
Major Risk Factors for Breast and Ovarian Cancer

All women have a risk of developing breast and ovarian cancer over their lifetimes. Breast cancer is a common disease, with over 180,000 women diagnosed every year in the United States. Ovarian cancer is a much rarer disease, which is newly diagnosed in about 24,000 women annually.

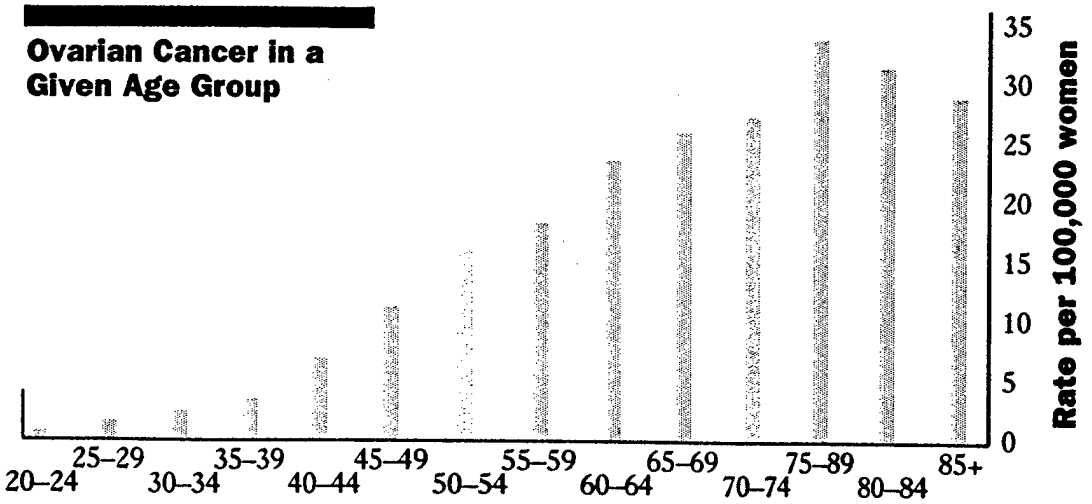
The cause of these diseases cannot be pinpointed to a single factor. Breast and ovarian cancers result from a combination of genetic (inherited) and environmental (non-inherited) factors. Key risk factors for breast and ovarian cancer are summarized below:

Age: A woman's age is the most significant risk factor for getting breast or ovarian cancer. The older a woman is, the higher her risk of developing breast or ovarian cancer. At least three-fourths of breast and ovarian cancers are diagnosed in women over the age of 50. However, women with an inherited predisposition to breast and ovarian cancer face an increased risk of developing these cancers at younger ages, such as in their 30s and 40s.

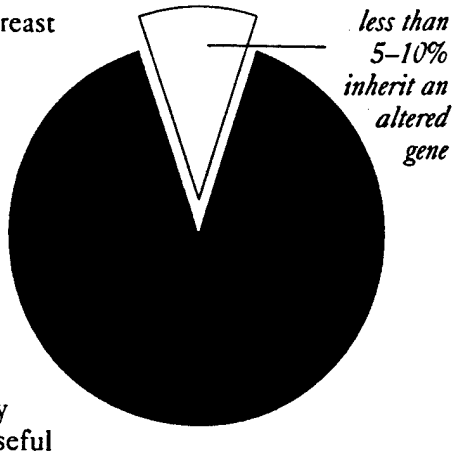
Breast Cancer in a Given Age Group



Ovarian Cancer in a Given Age Group



Family history: The risk of developing breast or ovarian cancer is higher among women who have one or more close relatives with these cancers. The risk may be further increased if the cancers were diagnosed at a young age, especially before menopause, or if breast cancer occurred in both breasts. Although many women with breast cancer have a close relative with this disease, only about 5–10% of women are thought to have inherited a cancer susceptibility gene, such as the BRCA1 or BRCA2 gene. Because ovarian cancer is much rarer, familial clusters are less common. A family tree constructed by the genetic counselor is a useful tool to help determine whether an individual's family history is suggestive of an inherited pattern of cancer predisposition.



Biopsy history: Most breast lumps, often called "fibrocystic disease," are benign (not cancerous). However, a breast biopsy that shows the growth of altered cells (known as atypical hyperplasia) is associated with an increased risk of developing breast cancer. This risk is further increased if a woman has a close relative with breast cancer.

Prior cancer history: Any woman who has a prior history of breast cancer has an increased risk of developing a second breast cancer (for example, in her opposite breast after a mastectomy). Women with a prior history of breast cancer also have a slight increased risk for ovarian cancer. These risks are significantly higher if a woman is found to have an alteration in a gene such as BRCA1.

Other Risk Factors for Breast and Ovarian Cancer

In addition to a woman's age, history of breast biopsies or cancer, and family history, other factors may contribute to a woman's risk for developing breast or ovarian cancer. It is important to understand that for women with an inherited predisposition to breast or ovarian cancer, it is not known to what extent the risk factors listed below may affect risk. Studies are underway to address these issues.

Reproductive factors:

Hormonal changes related to menstruation and pregnancy may increase a woman's risk for breast cancer. These include having menstrual periods before age 12, menopause after age 55, never having children, or giving birth to a first child after age 30. A woman who has never given birth also has a somewhat increased risk for ovarian cancer.

Hormone use:

The use of birth control pills (BCPs) is not associated with a significantly elevated risk of breast cancer, although long-term use of BCPs in women under age 25 may be associated with a slight increase in the risk of developing breast cancer at a young age. However, even short-term (i.e., 6 month) use of BCPs may reduce the risk of ovarian cancer. The effect of BCPs in women with a family history of cancer suggestive of an inherited predisposition to breast or ovarian cancer is unknown. Some studies have demonstrated that long-term hormone replacement therapy (HRT), with estrogen alone or estrogen and progesterone, slightly increases breast cancer risk. It is important to remember, however, that estrogen replacement therapy may also provide other health benefits such as relief of menopausal symptoms, and protection from cardiac and bone disease (i.e., osteoporosis).

Other factors:

Based on current information, it is not clear whether high amounts of fat in the diet increase the chance of developing breast cancer; however, reducing fat in the diet can reduce the risk of other diseases and cancers. Alcohol consumption is also associated with a slight increase in breast cancer risk, and appears to be related to the amount consumed over a period of years.

Inheritance of Cancer Susceptibility

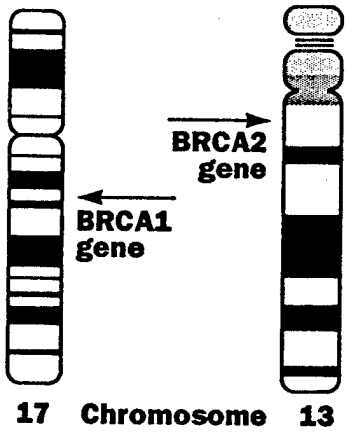
In order to better understand how an individual may inherit a susceptibility to cancer, it is helpful to know some basic concepts in genetics.

Chromosomes:

Chromosomes are found in the nucleus or control center of a human cell and are the structures on which genes are located. There are 46 individual chromosomes, or 23 different pairs, in each cell. The chromosomes are passed down, or inherited, randomly from parent to child; 23 chromosomes are passed down from the mother and 23 chromosomes are passed down from the father. Since our chromosomes are found in pairs, the genes they contain are also found in pairs.

Genes:

There are approximately 50,000 to 100,000 genes in a human cell. Genes are the blueprints or instructions that control the growth, development, and normal function of the body. Only a small proportion of our genes is associated with cancer susceptibility. When genes are working properly, our bodies are able to develop and function smoothly. However, when a gene is altered (e.g., by the addition, deletion, or rearrangement of genetic material), a normal cell function, such as cell growth, may be impaired or changed. Thus, in some instances, altered genes may result in a deformity or the development of disease. An altered gene may also result in very subtle effects. In fact, it is estimated that each individual has between 4 to 8 altered genes that have no harmful effects.

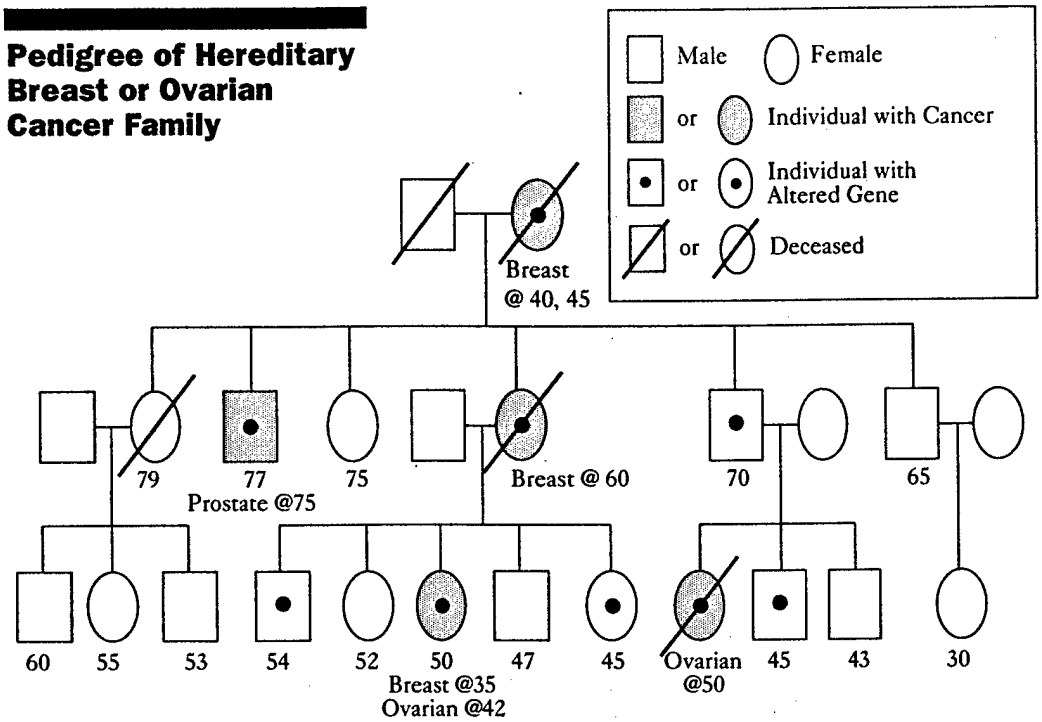


Dominant Inheritance:

The way that cancer susceptibility may be passed down in families is by dominant inheritance. People have two copies of every gene (one copy from each parent). Both copies of a gene pair control the same function but may vary in form from each other, since each copy is received from a different parent. An alteration or change in one copy of a gene pair can affect how the body functions even though the other copy of that gene may not be altered. In this situation, the altered gene has a dominant effect on a specific body function. Alterations in BRCA1 and BRCA2 are inherited in a dominant fashion.

In large families, this inheritance pattern may be observed clearly because there are multiple individuals in several generations affected with breast and/or ovarian cancer, often at young ages. The family tree on the following page depicts dominant inheritance of a cancer susceptibility gene, showing individuals who have inherited the altered gene, and whether they have developed cancer.

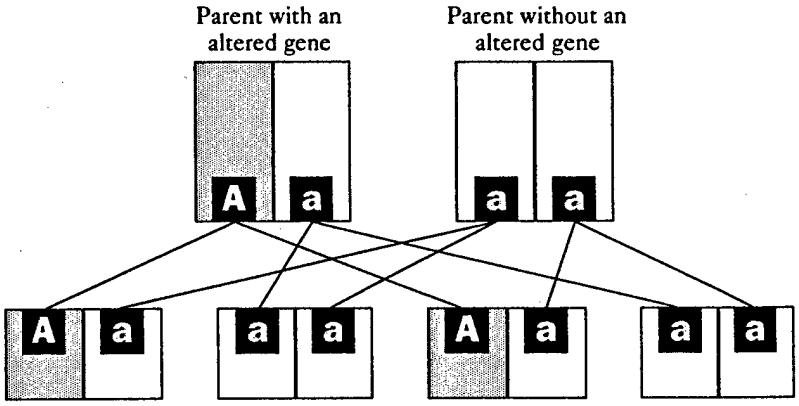
Pedigree of Hereditary Breast or Ovarian Cancer Family



An individual with a BRCA1 or BRCA2 alteration has a 50% chance of passing down that alteration to his or her children. This happens because eggs and sperm each carry only one copy of each gene pair. Thus, each child of a parent with an altered gene has a 50% chance of inheriting the altered gene and a 50% chance of inheriting the functioning gene (see below). The risk is not affected by the sex of the child or the affected parent, or by the child's birth order, and cannot be predicted based on how much a child may resemble one or the other parent.

Inheritance of a Dominant Breast Cancer Susceptibility Gene

A = Altered copy of breast cancer susceptibility gene
a = Working copy of breast cancer susceptibility gene



50% chance for each child to inherit the altered copy of the gene

Care *info sheet*

Breast Cancer Susceptibility Genes

BReast CAncer-1 (BRCA1) and BReast CAncer-2 (BRCA2) are the two major breast cancer susceptibility genes that have been identified to date. Alterations in these genes are thought to account for the majority of inherited breast and ovarian cancers. The frequency of these altered genes in the general population is not known, but one estimate suggests that BRCA1 alterations occur in up to 1 of every 800 individuals in the general population and BRCA2 alterations appear to be even more rare.

The BRCA1 and BRCA2 genes are thought to act as "tumor suppressor" genes when they are functioning properly. Tumor suppressor genes prevent cells in our body from growing out of control. However, alterations of these genes can change their usual function. This change in function can increase a person's chance of developing breast, ovarian, and some other cancers.

Hundreds of alterations have been detected in these genes. The BRCA1 and BRCA2 genes are very large. Therefore, there are many places within each gene where an alteration (mutation) can occur. However, some mutations occur much more frequently than others.

A few mutations have been found with increased frequency in specific populations. For example, a study of over 5000 Ashkenazi (Central or Eastern European) Jewish individuals in the Washington DC area revealed that about 1 in 44, or 2.3%, of the participants carried one of three alterations in the BRCA1 or BRCA2 genes. Specifically, the alterations are referred to as 185delAG and 5382insC in the BRCA1 gene and 6174delT in the BRCA2 gene. The notion refers to the place in the gene where some material was *del*eted or *ins*erted. Preliminary studies suggest that the 185delAG alteration may account for a significant proportion of breast and ovarian cancer in young Jewish women, especially breast cancer in women diagnosed at or before age 40, and ovarian cancer in women diagnosed less than age 50. Many of these women may not have a strong family history of breast/ovarian cancer. While these mutations occur mostly in Jewish families, they have also been observed in families with no known Jewish ancestry.

Research is underway to identify and characterize mutations in BRCA1 and BRCA2. This research will lead to more rapid and efficient means of genetic testing, an improved understanding of the cancer risks associated with these alterations, and more information about the function of these genes. Ultimately, these discoveries may lead to improved prevention, early detection, and treatment of cancer.

Care *info sheet*

Estimated Cancer Risks Associated with BRCA1 and BRCA2 Alterations

The risks for cancer associated with BRCA1 or BRCA2 alterations, summarized below, are based on several disease-conferring mutations. As the BRCA2 gene was identified more recently than the BRCA1 gene, there is less information about the cancer risks associated with BRCA2 alterations.

The available risks are cumulative (lifetime) and are only estimates, derived in part from studies of large families in which multiple women developed breast and ovarian cancer. However, some of the risks are derived from studies in which individuals who were tested were not selected because of a strong family history of breast or ovarian cancer. It is therefore important to note that as additional families are studied, these risks may be modified. However, it is unclear by how much these cancer risks may change.

The table on the next page summarizes estimated lifetime risks for different cancers for individuals with a BRCA1 or BRCA2 alteration as compared to the general population.

As more information becomes available, these estimates may be modified and better defined. It is also important to remember that risk varies from individual to individual and from family to family, so it is not possible to predict with certainty the type of cancer to which an individual is most susceptible or the age at which cancer may develop.

Estimated Cancer Risks Associated with BRCA1 and BRCA2 Alterations

Updated July1997

Type of Cancer	Estimated lifetime risk in BRCA1 mutation carriers	Estimated lifetime risk in BRCA2 mutation carriers	Lifetime risk in general population
Breast cancer (female)[1]	55%-85%	55%-80%	12%
2nd breast cancer (in opposite breast)[1]	Up to 65%	Probably elevated over general population	0.5-1% a year (up to about 25%)
Ovarian cancer [1]	15%-60%	15%-20%	1.4%
Ovarian cancer after breast cancer [1]	Up to 30%-55%	Probably elevated over general population	2-3% (about twice the average risk)
Colon cancer[2]	Possible 4-fold increased risk	Possible increased risk	About 6%
Prostate cancer[3]	Increased risk, possibly up to 3-fold	Possible increased risk	Up to 19%, but includes cancers that are not clinically evident
Male breast cancer	A few reported cases	About 6%	Extremely rare
Pancreatic cancer[4]	Not increased	Associations noted	Less than 1%

[1] Early ages of onset for breast and ovarian cancer have been reported to occur frequently in women with BRCA1 or BRCA2 alterations. Whereas women in the general population often develop breast or ovarian cancer after age 50, women with BRCA1 or BRCA2 alterations have an increased risk of developing breast cancer before age 50 and throughout their lifetimes.

[2] When colon cancer has been reported in individuals with a BRCA1 or BRCA2 alteration, the ages of onset do not appear to be significantly younger than those found in the general population. The peak incidence of colon cancer occurs in men and women over age 60.

[3] Although early ages of onset for prostate cancer has been reported occasionally, in general, the ages at diagnosis do not appear to differ significantly from those noted in the general population. Prostate cancer occurs most often in men over age 60.

[4] Early ages of onset have been reported in association with pancreatic cancer; however, additional research is needed to confirm these findings. The median age of diagnosis for pancreatic cancer is age 70.

Care *info sheet*

Cancer Screening

At present, there are no long term studies that have demonstrated the best methods to screen for or prevent cancer in an individual with an alteration in the BRCA1 or BRCA2 gene. Participants in the CARE program receive individualized guidelines for cancer risk management that should be discussed with personal physicians. The following summarizes the general approaches that are now suggested.

Breast Cancer Screening:

Monitoring for breast cancer includes:
- *monthly breast self-examination*
- *frequent clinician breast exams*
- *mammography*

Women at increased risk for breast cancer may choose to undergo exams at a younger age and more frequently than women in the general population.

Ovarian Cancer Screening:

Women in the general population do not undergo routine screening to detect ovarian cancer. An annual gynecological exam, which should be a part of every woman's care, includes a Pap smear, a test used to detect cancer of the cervix, and a pelvic exam. A pelvic exam is important for detecting some problems, but it is not a sensitive method to detect ovarian cancer. Therefore, for women at increased risk of ovarian cancer, screening involves two tests in addition to pelvic exams: a CA-125 blood test and a pelvic ultrasound with color Doppler enhancement. Although these additional screening tests are available, they have not been proven to detect ovarian cancer in its early stages, when treatment is most effective. In other words, these tests can be abnormal even when no cancer is present, or can be normal when cancer is present.

Colon Screening:

All individuals (men and women) are encouraged to undergo routine screening for colon cancer beginning at age 50. Such exams include digital rectal exams and fecal (stool) blood test annually, in addition to sigmoidoscopy (an exam of the lower colon) every 3-5 years. If you have other medical conditions which might increase your risk for colon cancer, a family history of colon cancer, or an alteration in the BRCA1 or BRCA2 gene (which may also increase the risk of colon cancer), then a colonoscopy could be considered. A colonoscopy is a more extensive exam of the whole colon and enables the physician to remove polyps (growths) at the time of the exam. Your physician can help determine which procedure(s) is right for you.

Prostate Screening:

Men should have regular screening for prostate cancer, beginning at age 50, or earlier if certain risk factors exist, such as a family history of prostate cancer. Screening tests for prostate cancer include a PSA (prostate specific antigen) blood test and a digital rectal exam.

Prevention for Breast and Ovarian Cancer

Prophylactic Surgery:

Some women at increased risk for breast cancer may consider having their breast(s) removed preventively, a procedure known as prophylactic mastectomy. This procedure involves the removal of the entire breast, including the skin overlying the breast and the nipple. However, because some breast tissue remains after this surgery, there is still a small chance for a woman to develop breast cancer after having prophylactic mastectomy.

Due to the limitations of ovarian screening, women at high risk for ovarian cancer may consider having their ovaries removed, especially after childbearing is completed. This procedure is known as prophylactic oophorectomy. While this surgery significantly reduces the risk of ovarian cancer, there is still a small chance of developing an ovarian-like cancer after the ovaries are removed. Women who have had this surgery generally do not undergo screening tests for ovarian cancer, but are closely followed by their physicians.

It is important to remember that there is no right or wrong decision about getting prophylactic surgery. We know that women who undergo preventive surgery still have residual risks for cancer, and it is possible that women with an inherited susceptibility to breast or ovarian cancer may face a higher remaining risk than women without a genetic predisposition to cancer. There are many other factors to be considered before undergoing surgery, such as the effectiveness of currently available screening procedures, the type and extent of surgery that would be performed, the emotional impact of surgery, other medical implications, and financial costs. Before deciding whether to have surgery, all of these issues should be discussed in more detail with your physicians.

Chemoprevention:

Some women may be eligible to participate in studies evaluating the effectiveness of a medicine, nutritional supplement, or other substance to reduce cancer risk. For example, researchers are evaluating whether Tamoxifen, a drug used to treat breast cancer, may reduce the risk of breast cancer in healthy high risk women. As with any drug, there are possible side effects from Tamoxifen. Results pooled from several collaborating centers are expected to take a few years to obtain. It is also not known whether Tamoxifen reduces the risk of breast cancer in women with a genetic susceptibility to breast cancer. The National Institutes of Health has begun a study to determine whether a combination of Tamoxifen and a vitamin A derivative reduces the risk of breast cancer in high-risk women who have no prior history of cancer. This study is not randomized; thus all participants are guaranteed to receive the medications. Additional information about this study may be obtained through the CARE program. Other chemoprevention studies are expected to become available in the future.

Other Screening and Prevention Issues

Hormone Use:

As with every important medical decision, the relative pros and cons of using birth control pills (BCPs) or hormone replacement therapy (HRT) must be weighed very carefully. There are no data on the effects of these medications in women with a genetic susceptibility to cancer. It is therefore a good idea to consider with physicians a range of options that may provide benefits similar to those provided by taking BCPs or HRT. For example, it is important to consider what other forms of birth control may be acceptable; what non-hormonal methods are available to reduce the symptoms of menopause; what other medications or interventions may provide similar health benefits to HRT in reducing risk of heart disease and osteoporosis. Each woman must make a informed decision with which she and her doctor are comfortable.

Risk Avoidance:

All individuals are encouraged to minimize their intake of alcohol and dietary fat, refrain from tobacco smoking, and minimize sun exposure. While these measures may not reduce the risk of breast or ovarian cancer, they do have proven benefits in maintaining general good health and in reducing the risk of other cancers.

Care *info sheet*

The Process of Genetic Testing

The process of genetic testing is different from most other medical tests. A genetic test for cancer susceptibility is not diagnostic; that is, it does not reveal the presence or absence of cancer, but whether an individual has an inherited tendency or predisposition to cancer. Also, the methods used in performing genetic analysis are very complex and time consuming. Unlike most routine lab work, results from genetic testing may take several weeks or months to obtain and sometimes results may be difficult to interpret. Another difference is that most of the risks associated with genetic testing are not physical risks, but involve risks associated with how one may feel or how others, including family members, may react after learning about a genetic test result. For this reason, education and counseling before and after testing are offered as part of the CARE program.

A small blood sample is needed in order to perform genetic testing. Genetic material (DNA) is then obtained from your blood and analyzed for alterations (mutations). For a family in which a mutation has not been previously found, it is helpful to first test a blood sample from a woman with breast and/or ovarian cancer who was diagnosed at a young age. Scientists have a number of ways of looking for genetic mutations. In some instances, testing is performed in steps, whereby common mutations in a gene are looked for first. If these are ruled out, then more complete analysis of the gene is usually undertaken. The most complex type of genetic analysis is called sequencing, which means that the "chemical alphabet" of an individual's DNA is obtained and compared to DNA that is known to be "normal." The process of sequencing is comparable to looking for a single spelling mistake in a several thousand page book—a very difficult and time consuming process. Alterations include those in which some genetic material is missing, substituted, or inserted. In very rare instances, an alteration may be identified that is of questionable clinical significance (in other words, the alteration may represent a normal variation in DNA as opposed to an alteration known to be associated with increased cancer risks). Interpretation of such results is handled on a case by case basis.

Once a clinically significant alteration in the BRCA1 or BRCA2 gene has been identified in a close relative, it is easier to test other individuals in the family. Because the specific alteration in the gene is known, other individuals in the family are usually tested only for the presence or absence of that mutation. This testing can be completed in a relatively short period of time and is very accurate, providing results that are clearly positive or negative for a particular alteration.

If an alteration is not identified in a family member who has had cancer, relatives are usually not tested. This is because testing would not be expected to provide further information about their cancer risks. For example, it may be determined that the first woman to be tested within a family who has a prior history of breast cancer does not have a BRCA1 or BRCA2 alteration. This test result may be due to one of the following possibilities:

- Current methods may not be sensitive enough to detect a mutation in the BRCA1 or BRCA2 gene (e.g., the mutation may be in a part of the gene that is difficult to analyze).
- A mutation is present in a different cancer susceptibility gene for which testing was not performed.
- The individual(s) tested does not have an inherited susceptibility to cancer due to an alteration in a single gene such as BRCA1 or BRCA2.

Care *info sheet*

Genetic Testing: Pro and Cons

There are potential benefits to having genetic testing, as well as potential risks of testing and limitations to the information that is obtained. Each individual needs to consider whether the potential benefits outweigh the potential risks in order to make his or her own decision about whether or not to be tested. All individuals who decide to provide a blood sample for genetic testing must sign a consent form which contains additional information about the benefits, limitations, and risks of genetic testing. Some of the major points are highlighted below.

PROS:

There are potential benefits of testing which may lead some individuals to decide to have testing for alterations in cancer susceptibility genes.

Increased knowledge: Genetic testing may provide individuals with more information about their risk for getting cancer and provide insight as to why cancer developed in themselves or their family.

Health care decisions: Information about cancer risk can facilitate decisions about whether certain screening tests should be considered and may help women decide about prophylactic surgery.

Information for other relatives: Testing may provide information about cancer risk for children, siblings, and other family members.

Emotional benefits: Learning the results of testing may produce a sense of psychological relief because uncertainty about cancer risk may be reduced.

Contribution to research: Participation in genetic counseling and testing programs will help further understanding about inherited cancer.

CONS:

There are limitations and potential risks of testing which may lead some individuals to decide they do not wish to have testing.

Difficulties in test result interpretation: Because genetic testing for BRCA1 and BRCA2 alterations is investigational, it is possible that test results will be uninformative or difficult to interpret. Genetic testing does not provide a definitive answer about an individual's risk for getting cancer.

Length of time to receive results: There is a possibility that test results will take a long time to acquire. Such a delay may make it more difficult to make decisions about cancer prevention and screening.

Discrimination: Genetic testing may place individuals at risk for discrimination by health, life, and disability insurers, as well as employers. Knowledge that you have a genetic predisposition to cancer may compromise your ability to obtain or maintain insurance coverage. At the present time, fewer than half of the states have laws restricting the extent to which genetic information may be used by health insurers. Almost all states allow life and disability insurers to ask questions about genetic predisposition to cancer and use the answers in their underwriting decisions. However, recently enacted federal legislation may help to protect those individuals who decide to undergo genetic testing. In August 1996, President Clinton signed The Health Insurance Portability and Accountability Act of 1996, which recognizes "genetic information" as protected medical information, and forbids those who provide health care coverage from using such information to deny access to individuals who must change health plans when they change jobs.

The Act also states that, based on genetic information, a group medical plan cannot require an individual to pay a premium or contribution (to get into the plan or to stay in the plan) that is greater than that for a "similarly situated" individual enrolled in that plan. The term "similarly situated" means that a plan or coverage would be permitted to vary benefits available to different groups of employees, such as full-time vs part-time or employees in different geographic locations. A limitation of the Act is that the premiums charged for individual health insurance are not restricted by the Act, and need only comply with state law. These insurance reform provisions of the Act went into effect on July 1, 1997.

The Health Insurance Portability and Accountability Act of 1996 is a major step toward gaining protection for individuals who undergo genetic testing. However, it does not address the issue of confidentiality and does not require the individual's permission to release genetic information. Although there has been no federal legislation passed regarding the areas of medical record privacy, employment, and other forms of insurance, such as life and disability, both the Senate and the House are reviewing bills that would offer additional federal protection from genetic discrimination.

The staff of the CARE program will do everything possible to protect the privacy of genetic testing results for participants in the CARE program. Each individual is identified by a unique ID number and no information about a participant of the program is released to third parties without the consent of that individual. Likewise, our research program has been issued a Certificate of Confidentiality from the Department of Health and Human Services, which allows the CARE program to withhold information about CARE participants from any outside sources, unless that individual has given written consent.

Emotional implications: Individuals who learn their test results may feel sad, angry, or anxious. Particularly when the impact on relatives or children is considered, relationships may become strained and individuals may feel guilty regarding the outcome or possible outcome of testing. Each person responds differently to information about risk and in some circumstances, psychological counseling and support may be helpful.

Family information: The correct interpretation of the test results is based on the family history provided by each participant. In gathering this information and pursuing genetic testing, it is possible that you may learn unanticipated information, such as information regarding adoption or non-paternity (i.e., that someone is not the biological father of a child).

Resources

Many resources for information and support are available at Georgetown University Medical Center and in the surrounding community, as listed below:

Physicians/Professional Services at GUMC:

Lombardi Cancer Center's Comprehensive Breast Center (202) 687-2122

Offers women the keystones of breast health: instruction in monthly breast self-examination, breast examinations by a health care professional, and regular mammograms.

Lombardi Cancer Center Helplink (202) 784-4000

Cancer Information and Referral
A toll-free hotline with a registered nurse, who is certified in oncology, and will answer questions about cancer screening, diagnosis, and treatment.

Other referrals to specific physicians, nutritionists, or psychologists are provided upon request.

Other Organizations:

American Cancer Society 1-800-ACS-2345

Web page: http://www.cancer.org
A nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives from cancer, and diminishing suffering from cancer through research, education, and service.

National Alliance of Breast Cancer Organizations (212) 719-0154

Web page: http://www.nabco.org
A network of breast cancer organizations that provides information, assistance, and referrals to anyone with questions about breast cancer, and acts as a voice for the interests and concerns of breast cancer survivors and women at risk.

National Breast Cancer Coalition (202) 296-7477

Web page: http://www.natlbcc.org
A national advocacy group concerned with furthering research about breast cancer. The group is also involved in lobbying efforts for issues such as legislation to protect against genetic discrimination.

National Cancer Institute's Cancer Information Service 1-800-4CANCER

Web page: http://www.nci.nih.gov
A nationwide telephone service for cancer patients and their families, the public, and health care professionals providing up-to-date and understandable information about cancer screening, diagnosis, and treatment. Many publications are available free of charge.

Gilda's Club (212) 647-9700

Web page: http://www.jocularity.com/gilda1.html
Education and support for people with cancer and their families.

Y-ME National Breast Cancer Organization 1-800-221-2141

Web page: http://www.yme.org
National support hotline for breast cancer survivors. A large, comprehensive breast cancer support program founded in 1978 by two breast cancer patients.

Books/Publications:

Krause, C. **How Healthy is Your Family Tree? A Complete Guide to Tracing Your Family's Medical and Behavioral History.** New York: Simon and Schuster. 1995. A helpful guide to gaining vital information about your family history.

What You Need to Know Series: Breast, Ovarian, Colon, and Prostate Cancer. Free publications from the National Cancer Institute's Cancer Information Service explaining the symptoms, diagnosis, and treatment of these cancers.

Understanding Genetic Testing. Free booklet by the National Cancer Institute providing information about gene testing. This booklet also provides answers to frequently asked questions about the potential risks and benefits of genetic testing.

Web Sites:

Breast Cancer Information Clearinghouse
http://nysernet.org/bcic
The purpose of this webserver is to provide information for breast cancer patients and their families. It is maintained as a partnership of organizations which provides information about cancer to the public.

The Breast Gene and BRCA123 Information Directory
http://www.ncgr.org/gpi/bc_pg_front.html
The National Center for Genome Resources' Genetic and Public Issues Program has complied this page to help people understand recent developments in genetic testing related to breast cancer.

Cancer Net
http://cancernet.nci.nih.gov
A service of the National Cancer Institute's International Cancer Information Center which provides current information on cancer.

Oncolink
http://www.oncolink.upenn.edu
A multimedia cancer information resource developed and maintained by the University of Pennsylvania Cancer Center.

The Gene Letter
http://www.geneletter.org
The U.S. Department of Energy has awarded the Shriver Center a 2 year grant to develop and generate an electronic newsletter about genetics and public policy. The major purpose of the Gene Letter is to inform consumers and professionals about advances in genetics and to encourage discourse about emerging policy dilemmas.

Legislative Information on the Internet
A service of the Congress through its library
http://www.thomas.loc.gov

Phase II Evaluation of Thalidomide in Patients with Metastatic Breast Cancer

Principal Investigator: Said Baidas, MD 202-687-2198

Background:
Thalidomide is felt to have anti-angiogenic activity. It has been given to thousands of women in the 1950's and 60's as a sleep aid and anti-emetic for pregnant women but was found to have teratogenic effects which may be linked to its anti-angiogenic action. Studies in cancer patients have shown this to be well tolerated and suggest potential anti-cancer activity. This study is designed to look at thalidomide's anti-cancer activity using 2 different dose levels in breast cancer patients.

Eligibility:

- Advanced breast cancer
- Objective progression
- 18 years or older
- ECOG 0,1,2
- HIV negative
- No major surgery within 21 days
- No chemo, hormone, XRT in 4 wks
- No pregnant or lactating women
- No other cancer
- Evaluable or Measurable Disease
- No more than 3 prior chemo regimens
- Able to give informed consent
- Recovered from side effects of prior Tx
- BHCG negative
- Frequent vomiting or anorexia
- No brain mets or cardiomyopathy
- No serious or intercurrent illness
- No grade 2 neurotoxicity

WBC ≥ 3000, Hgb ≥ 8 g/Dl, platelet ≥ 75,000, PT, PTT ≤ 1.25 normal, Bili, SGOT, SGPT, Alk. Phos ≤ 1.5 X ULN (2.5 X if hep mets), Mg ≥ 1.8 (may be supplemented), creatinine≤ 1.5 X ULN (or Cr.. Cl ≥ 60 mL/min)

Treatment:
Thalidomide is administered orally at one of two randomized doses:
200 mg/d qhs 9 pm or
800 mg/day qhs 9 pm (Increase by 200 mg/day q 2 weeks up to 1200 mg/day)

Potential toxicity:
Constipation (rec. Routine laxative use), somnolence, nausea, dry mouth and skin, increase appetite, headache, urticaria, erythema, altered menstrual cycles, hypothyroidism, lower extremity edema, teratogenicity, peripheral neuropathy.

Evaluation:
tumor assessment q 8 weeks. Bioassays (TNF, VEGF, bFGF, MMP-9, urinary bFGF baseline, weeks 2,4,6,8 and then monthly). Pharmacokinetics on day 1 at 1/2, 1, 1.5, 2, 3, 4, 5, 6, 7, hours after 1st dose and 9 am and 1 pm on day 2. Serum levels then q 2 weeks for the first 8 weeks then monthly.

Off study:
Progressive disease or unacceptable toxicity

Phase II Evaluation of Thalidomide in Patients with Metastatic Breast Cancer.

STUDY SCHEMA

Parameter	**On Study	Day One	Week 2	Week 4	Week 6	Week 8	Monthly, After Cycle 1
History/Physical NeuroExam Vital Signs	X	X	X	X	X	X	X
Height	X						
Weight	X		X	X	X	X	X
Performance Status	X		X	X	X	X	X
CBC, Diff, Platlets	X		X	X	X	X	X
Mg, PT, PTT	X		X	X	X	X	X
Chemistry Survey[1]	X[1]		X[1]	X[1]	X[1]	X[1]	X[1]
Thyroid Function Tests[3]	X[3]						
Urinalysis	X						X
Chest X-Ray[5]	X[5]					X[5]	
Bone Scan[5]	X[5]					X[5]	
Abdominal CT[5]	X[5]					X[5]	
Growth Factors, MMP and TNF Assay[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Tumor Assessment[4]	X[4]					X[4]	
EKG	X						
Pregnancy test[2]	X[2]		X[2]	X[2]	X[2]	X[2]	X[2]
HIV	X						
PK	X	X	X	X	X	X	X
CEA	X		X	X	X	X	X

**** On study laboratory tests and X-rays must be obtained within 2 weeks of starting on study.**

[1] Includes: BUN, creatinine, glucose, SGOT/SGPT, alkaline phosphatase, total bilirubin, LDH, calcium, and uric acid.
[2] For fertile women in whom pregnancy cannot otherwise be ruled out pregnancy tests must be negative prior to starting treatment. Beta HCG.
[3] At 12 weeks or another time point only if clinically indicated. [4] Any other studies required to assess tumor size/extent.
[5] If required to assess tumor size/extent.
[6] Growth Factors and MMP assay to be done before enrollment, every 2 weeks during the 1st cycle then monthly.

A Comparison of Standard Therapies for Metastatic Breast Cancer and the Protocol A Phase II Evaluation of Thalidomide In Patient with Metastatic Breast Cancer

	Standard Treatment			*Study Arms*	
Test or Exam Administered	**5FU 425mg/m2 IV Leucovorin 20mg/m2 day 1-5 every 28 days evaluate every 8-12 weeks**	**Navelbine IV 20mg/m2 weekly evaluate every8-12 weeks**	**VP-16 PO 50mg/m2 day 1-21 every 28 days evaluate every 8-12 weeks**	**Thalidomide PO cycle 1 evaluate at 8 weeks** *Arm 1*	**Thalidomide PO all subsequent cyles evaluate every 8 weeks** *Arm 2*
Common Tests and Examinations					
Drug and Administration Cost	$	$	$	Free	Free
History andPhysical Exam	2-3	4-6	2-3	5	2
CBC,Diff, Platelets	8-12	8-12	8-12	5	2
Chem 18	2-3	4-6	4-6	5	2
Pregnancy Test	1	1	1	1	
Tumor Assessment (1)	2	2	2	2	1
Bone Scan (2)				1	
Abdominal CT (2)				1	
Chest X-ray (2)				1	
Tumor markers (2)				3	2
Research Related Tests					
Mg				5	2
PT/PTT, FVIII				5	2
TFTs				1	
Urinalysis				1	2
HIV				1	
ECG				1	

1. Any test required to assess tumor size/extent.
2. Required pre-treatment for Thalidomide patients,to become part of standard tumor assessment if abnormal. Required for standard therapies only if part of tumor assessment.

Lombardi Cancer Center
Study Profile Sheet

Study Title: **Outcomes of Genetic Testing for Breast Cancer Susceptibility (CARE)**

Principal Investigator: Caryn Lerman, Ph.D.
Co-Investigator: Claudine Isaacs, MD

Funding Agency: Department of Defense, Susan G. Komen Foundation

Study Period: October 1, 1996 through September 30, 2000

Accession Period: October 1, 1996 through September 30, 1999 (600 women)

Specific Aims (Hypotheses) of Study:
Breast Cancer affects 1 in 9 women in the United States. Studies suggest that up to 10% of all women with breast cancer have inherited an altered gene the increases risk of this disease. This study proposes to evaluate the psychosocial and medical impact of genetic testing for female members of hereditary breast-ovarian (HBOC) families. The specific aims are:

1. To evaluate the short and long-term impact of genetic testing for BRCA1 and BRCA2 mutations on adoption of cancer prevention and control practices,

2. To evaluate the impact of genetic testing on quality of life (cancer-specific distress, depression, sexual functioning, and/or sleep disturbance), and

3. To identify early predictors of psychological morbidity and non-adherence among participants.

Subject Eligibility Criteria (subject to change):
- Greater than 18 years of age
- Must have one living family member with breast or ovarian cancer
- Personal history or first degree relative with breast or ovarian cancer diagnosed $\leq$ age 30, or
- Two first degree relatives diagnosed with breast or ovarian cancer < age 50, or
- Three first degree relatives on the same side of the family with breast or ovarian (one diagnosed < 50)
- If of Ashkenazi Jewish descent, criteria may be lessened

Accession Support Needs:
- strategies for accrual of patients receiving services through managed care organization
- in-reach strategies (physician/provider referrals/cancer registries)

Clinical Services Provided for Study Participants:
- genetic counseling
- genetic testing for BRCA1 and BRCA2 genes

Study Site: Lombardi Cancer Center

Subject Accrual Site (if different from Study Site): None

Lombardi Cancer Center
Breast Cancer Center
funded by the Department of Defense
Outcomes of Genetic Testing for Breast Cancer Susceptibility (CARE)
Eligibility Criteria

If your patient had breast cancer, she may be eligible for CARE if:

- Her cancer was diagnosed before age 50 and she also has a first-degree relative (mother, sister, daughter) who had breast cancer (before age 50) Y/N
- Her cancer was diagnosed at age 40 or younger, and she is of Jewish descent Y/N

If your patient had ovarian cancer, she may be eligible for CARE if:

- She has a first-degree relative (mother, sister, daughter) who had ovarian cancer (before age 50) Y/N
- Her cancer was diagnosed at age 50 or younger, and she is of Jewish descent Y/N

If your patient has not had breast or ovarian cancer, she may be eligible for CARE if:

- She has a first-degree relative (mother, sister, daughter) who had breast cancer at age 30 or younger, OR Y/N
- She has two first-degree relatives who had early-onset breast cancer (age 50 or younger) and/or ovarian cancer (any age) Y/N
- She has three relatives on the same side of the family with early-onset breast cancer and/or ovarian cancer Y/N

"Outcomes of Genetic Testing for Breast Cancer Susceptibility (CARE)"

Recommendations Administered During Disclosure Session of Genetic Testing

During the disclosure session, the genetic counselor will review options for cancer prevention and surveillance. These recommendations are based on Cancer Genetics Studies Consortium (CGSC) guidelines. All women are informed about the benefits, limitations and risks of these strategies, and encouraged to make autonomous decisions.

Recommendations for Carriers of Mutations

Breast Surveillance:
- monthly breast self examinations (BSE) beginning at age 18
- biannual clinical breast exams at ages 18-25
- clinical breast exams three to four times a year after age of 25
- annual mammograms between ages 25 and 35

Ovarian Surveillance:
- annual pelvic exam beginning at age 18
- biannual transvaginal ultrasound with color enhancement and CA-125 tests after age 25

Oral Contraceptives:
- explore potential risks and potential benefits along with other birth control methods

Prophylactic Mastectomy:
- raised as an issue with understanding that residual risks for cancer exist
- refer interested women to a breast and plastic surgeon for consultation

Prophylactic Oophorectomy:
- informed about considering this issue, especially after age 35 and if childbearing is completed
- informed about risks for intra-abdominal carcinomatosis after surgery
- refer interested women to a gynecologic oncologist and endocrinologist for consultation

Recommendations for Noncarriers of Mutations

Advised to follow the National Cancer Institute's age-specific breast cancer screening guidelines. Such include:
- annual mammogram after age 50
- annual clinical breast examination
- monthly breast self examinations (BSE)

Women are also advised to discuss with their physician the role that mammography plays for them personally between the ages of 40 and 50.

Recommendations for All Study Participants

- annual digital rectal examinations after age 40
- annual fecal occult blood testing after age 50
- sigmoidoscopy every 3-5 years beginning at age 50
- annual pelvic examination and biennial Pap smears

Lombardi Cancer Center
Study Profile Sheet

Study Title: A Coordinated Approach to Breast Cancer Diagnosis (CABCAD)

Principal Investigator(s): Matthew Freedman, MD
Bruce Trock, PhD

Funding Agency: Department of Defense

Study Period: October 1, 1996 through September 30, 2000

Accession Period: October 1, 1996 through September 30, 2000 (400 women)

Specific Aims of Study:
The majority of diagnostic breast biopsies that are performed show that the woman does not have breast cancer. Thus, development of more sensitive and specific *noninvasive* tests would allow many women to be spared the anxiety, pain, and cost of a breast biopsy. In this study, a multidisciplinary team of radiologists, epidemiologists, molecular biologists and health services researchers will evaluate new strategies for breast cancer diagnosis, to determine whether any may be used instead of a breast biopsy (and in what circumstances this may be done). The specific aims are:

1. To enroll a cohort of at least 400 white and African American women (for whom a diagnostic breast biopsy has already been recommended) over four years to participate in each of the proposed imaging (digital mammography, sono-elastography, breast magnetic resonance imaging, Tc-99m sestamibi imaging) and molecular biolgic (nipple aspirate fluid cytology) tests.

2. To compare the proposed diagnostic imaging methods to the pathology results from the biopsy to determine their diagnostic sensitivity and specificity, and whether these methods represent improvements over conventional mammography and sonography.

3. To analyze the imaging data from Aim 2 in order to discern preferred pathways for the evaluation of specific types of abnormalities found on screening mammogram and/or physical examination.

4. To correlate the prevalence of genetic abnormalities in breast epithelial cells derived from nipple aspirate fluid with pathology results from breast biopsy, and with the results of imaging studies.

5. To perform a comprehensive economic evaluation of each of the methods used, and to develop a decision analysis model for hypothetical cohorts of women comparing the costs and outcomes of alternative diagnostic tests to surgical biopsy.

6. To create a core resource for the conduct of this and future studies. This resource will consist of a common database and serve as an important standard training set that can be made available to other institutions for training in these new imaging methods.

Subject Eligibility Criteria:
- women 18 years of age and older (white and African American) for whom a breast biopsy has been recommended
- women cannot be pregnant or nursing, and must use effective birth control
- women must not have pacemakers

Appendix 5: Strategic Plan

Patient Accession Core
Working Accrual Strategic Plan

Introduction

The overall goal of the Patient Accession Core (PAC) is to promote and facilitate increased participation, in current and proposed Lombardi Cancer Center Breast Center research protocols, by patients and high-risk women who have historically had difficulty accessing and benefiting from cancer prevention, diagnostic and treatment trials. Two particular groups of patients and high-risk women will be the focus of these outreach efforts: 1) medically underserved populations, particularly African-Americans and the elderly patients and 2) high-risk individuals who are members of health maintenance organizations (HMOs).

The specific aims of the PAC are as follows:

Expand Lombardi's links with local and national Health Maintenance Organizations (HMO) serving the greater Washington D.C. area. This will be done by forming an HMO advisory board to the Lombardi Breast Cancer Center to review HMO member education, protocol promotion and clinical referral mechanisms and to participate in evaluating cost-effectiveness data from HMO members participating in breast cancer diagnosis and treatment trials at the Lombardi Center.

Expand Lombardi's established links with the community-based Washington D.C. clinics already serving the primary care needs of the area's medically underserved. This will be done by forming a Community Advisory Board to the Lombardi Breast Cancer Center in order to review community-based education, protocol promotion, clinical referral, and patient transportation mechanisms. This will ensure that, while efforts are made to increase medically underserved patient participation in Lombardi clinical trials, continuity of primary care is maintained for illnesses and health problems unrelated to breast cancer.

Expand Lombardi's existing breast cancer education materials and health promotion programs by making them available through the information superhighway (e.g. the Internet) for HMO members and by basing these materials and programs in medically underserved community settings. All messages, materials and programs will be made culturally and educationally appropriate for different racial/ethnic, age and socioeconomic breast cancer patient and high-risk groups.

Provide cultural awareness and sensitivity training to Lombardi Breast Cancer Center clinicians involved with prevention, diagnostic and treatment research protocols to ensure supportive patient care for all patients on clinical trials.

Provide free transportation, with the Lombardi Cancer Center van, for medically underserved patients for whom transportation to, and/or parking in, Georgetown may represent a barrier.

Health Maintenance Organizations

PAC has been working with HMOs since January 1996. Several have expressed an interest in working collaboratively to enable plan members to access clinical trials. Some of the hurdles that PAC is experiencing have to do with the ongoing changes in the leadership of local managed care organizations. For example:

- Senior Medical Director at Capital Care-BC/BS has resigned. We have made contact with the new Medical Director to express the gains made toward partnership with his predecessor.

- Kaiser Permanente has expressed that they are interested but the recent acquisition of Humana is overwhelming them to the point that they are unable to discuss partnership for the purpose of accrual until things calm down (Summer 1997).

- PHN-HMO,Inc. has just undergone new leadership changes (President, CEO, and Medical Director).

After two meetings, PAC has categorized HMOs into two accrual prospect levels, first and second rung. Almost all plans are experiencing a great deal of difficulty in completing the HMO Key Informant Questionnaire, which was designed to provide specific information relating to plan cancer statistics and demographics. Without these data, selection and placement of plan in PAC's accrual strategy begins with what are believed to be the most stable plans with the greatest diversity in membership. Two plans, both Medicaid populations, do not provide a membership base that is likely to be eligible for any of the DOD studies because of the age of their membership. The majority of the members are very young; children and women under 25 years of age.

Phase I - First Rung Accrual

Capitol Care - Blue Cross/Blue Shield of the National Capitol Area
Kaiser Permanente Health Plan - Mid-Atlantic Region
MAMSI (M.D. - IPA)

Phase II - Second Rung Accrual

NYLCare, Inc.
Prudential Health Plan
PHN-HMO, Inc.

Table 1 - HMO Contacts and Expected Accrual

HMO	Contact	Expected Accrual to Begin
Capital Care Blue Cross & Blue Shield of the National Cap. Area 550 12th Street, SW Washington, D.C. 20065	Dr. Raymond Turner Senior Medical Director	June/July 1997
Kaiser Permanente Health Plan 2101 East Jefferson Street Rockville, MD 20849	Dr. Stephen Staal Chief of Oncology	August 1997
MAMSI 4 Taft Court Rockville, MD 20850	Nancy Bivens Vice President Dr. Vera Dvorak Medical Director	July 1997
Prudential Health Care Plan 2800 North Charles Street Baltimore, MD 21218	Dr. David Yalowitz Medical Director	September 1997
NYL Care, Inc. 7601 Ora Glen Dr., Suite 200 Greenbelt, MD 20770	Dr. Stephen Bandeian Associate Medical Director	Spring, 1998
PHN-HMO, Inc. 1099 Winterson Road Linthicum, MD 21090	Alan Silverstone President Dr. Gregory Alexander Medical Director	Spring 1998

It is expected that the next meeting of the HMO Advisory Board will be convened in early summer, 1997. The strategy is to have one or two HMOs set up to refer members to studies prior to the next meeting of the full committee. PAC staff is currently working to set up meetings with individual HMOs targeted for the first rung accrual level. A meeting with MAMSI took place in May, 1997.

Community Representatives

Representatives that currently serve on the PAC Community Advisory Board (CAB) as well as others that have been invited to serve on that board have expressed much interest in the area of genetic testing and its applicability to the populations they represent. These populations are, for the most part, comprised of women of color and women that are under represented in clinical trials. For this reason, a genetic counselor, Jeri Reutenauer, was invited to address this group at their meeting on May 28, 1997.

The accrual strategies for this group will be one of education first and accrual second. While the representatives of the CAB recognize the value of participation into clinical trial, they also recognize the perceptions of their constituents and the negative connotations that have previously accompanied participation in clinical research. Despite the perceived barriers, many of the representative are excited about being involved in recruitment.

Accrual strategy for this group is targeted toward the CARE program in that it is not appropriate for these organizations to be determining eligibility of patients for the other DOD studies. However, it is also important for them to fully understand the eligibility criteria for CARE so that inappropriate referrals do not lead to CARE's unacceptance.

The groups currently represented on the Community Advisory Board are found in Table 2.

Table 2 - Current Organizations Represented on Community Advisory Board

Organization	Population Served
American Association of Retired Persons	Women over 55
Breast Cancer Resource Committee	African American Breast Cancer Survivors
Delta Sigma Theta Sorority	African American Women
Greater Southeast Community Hospital Education and Outreach	Individuals participating in outreach services
Greater Washington Urban League	Residence in Senior Centers throughout D.C.
Health Insurance Counseling Project	
Links, Inc. Health & Wellness Programs	African American professional women
Maryland State Council on Cancer Control	participants of state funded cancer services (screening and treatment)
Montgomery County Health Department	County residents utilizing Health Services
National Association of Health Service Execs.	Health Service Executive Interested in African American Participation in Clinical Trials
National Black Leadership Initiative on Cancer Metropolitan Area Chapter	Organizations serving African Americans
National Black Women's Health Project	African American women
National Caucus on Black Aged	African American Elderly
National Council of Negro Women, Inc.	African American Women
Sharing & Caring Support Group GSECH	African American & Underserved Women
Washington Seniors Wellness Center	Seniors Wellness Program Participants

Primary Care Clinics

Because the issues for primary care clinics differ significantly from those of representatives from community organizations, the individuals representing primary care clinics will meet separate from the full Community Advisory Board. The representatives of primary care clinics convened on May 20, 1997. At that meeting a discussion of existing barriers to accrual began. Given that such barriers can be adequately addressed, PAC is predicting that accrual from primary care clinics will begin in the fall of 1997 if not earlier. The clinics represented on the Community Clinic Advisory Board include;

Zacchaeus Free Clinic/Bread for the World
1525 Seventh Street, NW
Washington, D.C. 20001

La Clinica del Pueblo
1470 Irving Street, NW
Washington, D.C. 20010

Woodridge Neighborhood Health Center
2146 24th Place, NE
Washington, D.C. 20018

Spanish Catholic Center
3055 Mt. Pleasant Street, NW
Washington, D.C. 20009

Washington Free Clinic
16th & Newton Streets, NW
Washington, D.C. 20010

Additional Accrual Strategies

1. Practices

While not originally planned or budgeted, oncologists and oncology surgeons as well as community hospitals have been incorporated into the accrual strategies. A merge file that includes the names, addresses and telephone numbers of oncologist and surgeons in the D.C. metropolitan area has been created in preparation for a mass mailing. This file will be extended into a more comprehensive database when resources permit (program design and data input). Currently, over 150 practices have been placed into the file. Initial practices that PAC will focus upon at the request of Thalidomide/TNP470 trial are Wilkinson practice and a K Street practice, which responded favorable in a first meeting with investigators.

Materials that explain clinical trials and the responsibilities that practices and hospital take on when agreeing to partner for the purposes of clinical trial participation. This material is currently under review by Clinical Research Management Organization (CRMO). It includes study eligibility check sheets (CABCAD not yet developed), study profile sheets, and information on clinical trial and partner/LCC responsibility sharing. Once approved, this material will be mailed to individual on the mailing list.

2. Hospitals

Area hospital will also be contacted for partnering for the purpose of clinical trials accrual. Thus far, four hospitals have been identified, three contacted and one with which meetings have been held. The first hospital with which a formal arrangement will be explored is Providence Hospital. Providence Hospital has a Cancer Committee that meets once a month. PAC staff met with members of that committee to begin discussions on collaboration. Members of the committee are listed below. The asterisk (*) indicates those represented in the meeting with PAC staff.

As part of the ACoS program approval requirements, Providence Hospital will require that 3% of their patients be on a clinical research protocol. For this reason, they are very interested in moving forward for the purpose of research partnerships.

Providence Hospital Cancer Committee

*Edwarda Buda, MD - Chair
Michael Brancaccio, MD - Pathology
Vani Padmanabha, MD - Pathology
*Robert Simmons, MD - VP Med Affairs
Robert Hamm, MD - Radiology
Francisco Correa-Paz, MD - Radiology
Luther Virgil, MD - Int Med/Inf Dis
Alexander Fangonil, MD - Urology
Gerald Batipps, MD - Urology
Alfred Goldson, MD - Rad Onc
Ebrahim Ashayeri, MD - Rad Onc
Michael Richardson, MD - Pulmonary
*Sonja Jennings - Tumor Registrar
*Deborah Gill, RN - Asst., VP Medical Affairs
Mary Lesster - Dir., Discharge Planning
Heidi Brancatelli - Discharge Planning
*Michael Thompson - Dir., Planning/Administration
Gail Aaron, RN - Palliative Care
Palma Berardi, RN - Oncology Nurse Manager
Teresa McLaughin, RN - Hem/Onc
William Funderburk, MD - General Surgery
John Butler, MD - General Surgery
Delores Clair, RN - Dir., Med/Surg Nursing
Morris Fitts, RPh - Pharmacy
*Pearl Garcia Warren - Dir., Health Info Mngmt

PAC will continue to explore community hospitals. The strategy is to begin with Providence Hospital and continue with others as systems fall into place with Providence. The strategic plan for hospitals and expected accrual dates are listed in Table 4.

Table 4 - Community Hospital Accrual Strategy

Hospital	Contact	Expected Accrual to Begin
Providence Hospital (Washington, D.C.)	Michael Thompson	Fall 1997
Doctors Community Hospital (Lanham, MD)	Susan Breslin Dir., Oncology	Spring 1998
Prince George's County	Nate Boring	Summer 1998

Hospital	Contact	Expected Accrual to Begin
Hospital (Cheverly, MD)	V.P., Professional Svcs.	
Holy Cross Hospital (Silver Spring, MD)	unidentified	Summer 1998

Expected Accrual Summary

Site	Contact	Expected Accrual to Begin
Capital Care Blue Cross & Blue Shield of the National Cap. Area 550 12th Street, SW Washington, D.C. 20065	Dr. Raymond Turner Senior Medical Director	June/July 1997
Kaiser Permanente Health Plan 2101 East Jefferson Street Rockville, MD 20849	Dr. Stephen Staal Chief of Oncology	August 1997
MAMSI 4 Taft Court Rockville, MD 20850	Nancy Bivens Vice President Dr. Vera Dvorak Medical Director	July 1997
Prudential Health Care Plan 2800 North Charles Street Baltimore, MD 21218	Dr. David Yalowitz Medical Director	September 1997
NYL Care, Inc. 7601 Ora Glen Dr., Suite 200 Greenbelt, MD 20770	Dr. Stephen Bandeian Associate Medical Director	Spring, 1998
PHN-HMO, Inc. 1099 Winterson Road Linthicum, MD 21090	Alan Silverstone President Dr. Gregory Alexander Medical Director	Spring 1998
Providence Hospital (Washington, D.C.)	Michael Thompson	Fall 1997
Doctors Community Hospital (Lanham, MD)	Susan Breslin Dir., Oncology	Spring 1998
Prince George's County Hospital (Cheverly, MD)	Nate Boring V.P., Professional Svcs.	Summer 1998
Holy Cross Hospital (Silver Spring, MD)	unidentified	Summer 1998
Zacchaeus Free Clinic	Randi Abrahamson, MD	TBD
Woodridge Neighborhood Health Center	Cheryl Williams, MD	TBD
Washington Free Clinic	Judith Krones, CNM	TBD
Spanish Catholic Center	Sister Kate Coppes, OSF, RN, FNP	TBD
La Clinica del Pueblo	Juan Romagaza, MD	TBD
Community Agencies/Organizations	CAB	Fall, 1997
Oncology Practices/Surgeons		Fall, 1997

Patient Accession Core
Working Accrual Strategic Plan

Study Specific Accrual Summary

Study	Anticipated Recruitment Source	Anticipated Accession Timeline*
CARE	MAMSI	July 1997
	Kaiser Permanente	Begun - Surge Summer 1997
	Blue Cross & Blue Shield	July 1997
	Zacchaeus Free Clinic	Charting Pts. June-Aug. Fall, 1997
	Woodridge Neighborhood Health Center	Summer, 1997
	Greater Southeast Comm. Hosp.	August, 1997
	Providence Hospital	Summer, 1997
	Delta Sigma Theta Sorority	August, 1997
	National Black Leadership Initiative on Cancer	Fall, 1997
	Breast Cancer Resource Committee	Fall, 1997
	Physicians Practices	August, 1997
CABCAD	Providence Hospital	Fall, 1997
	Zacchaeus Free Clinic	August, 1997
	Spanish Catholic Center	August, 1997
	Woodridge Neighborhood Clinic	Fall, 1997
Thalidomide	Providence Hospital	Fall, 1997
	Physicians' Practices	Summer, 1997

* Staff working to confirm accession deadlines week of June 2nd.

Core 2: Cancer Clinical and Economic Outcomes Evaluations Core

Appendix 1: Project 1 Survey Instruments
Appendix 2: Core 1 Cost Data Collection Instrument
Appendix 3: Project 2 Survey Instrument
Appendix 4: Novel Palliative Treatments of Metastatic Breast Cancer - Survey Instruments
Appendix 5: Core Advisory Committee Meeting Agenda
Appendix 6: Quality of Life Library Contents
Appendix 7: Core Consultants
Appendix 8: Core Publications and Grants

CORE #2: CANCER CLINICAL AND ECONOMIC OUTCOMES EVALUATIONS CORE

APPENDIX 1:
(PROJECT #1) GENETIC TESTING FOR BREAST CANCER SUSCEPTIBILITY SURVEY INSTRUMENTS

ID #:_____

Interviewer Initials: _____ Date: ____ / ____ / _____

Breast Cancer Health-Related Quality of Life Survey

My name is _____. I am calling from CARE (Cancer Assessment and Risk Evaluation) program at Georgetown University. We are doing a survey to see how women think about different issues related to breast cancer. Your answers will help us to understand how women would feel about living with and without breast cancer. Do you have 10 to 15 minutes to complete the survey now? All of your answers will be confidential, and we will not use your name. You do not have to answer the questions. Your decision to participate will not affect your care here. Do you have any questions?

I am going to read you several hypothetical stories about women at risk for, or affected with, breast cancer who are being asked to make decisions about their health. After reading the story, I will ask you to discuss the choices you think that the woman in the story should make. While some of these women may resemble you, remember that all of these stories are purely hypothetical. There are no right or wrong answers, only the choices you prefer. Before I ask you about the choices, I will ask you if you have any questions about the scenario. Remember, these are situations that women might face. They are not about your situation. Do you have any questions before we begin?

****

Before I ask you about the stories, I would like to give you an example. I would like you to imagine for a moment a woman who is completely blind, but otherwise completely healthy. I would also like you to imagine that this woman is faced with a choice:

She could choose to live 30 years completely blind, but otherwise healthy,

or

she could choose to live 30 years in excellent health, including having excellent vision.

If she had to make this choice, which option do you think she should choose, or do both choices seem about the same to you?

[Let the participant respond]

[If choosing blindness, ask the following question to make sure the participant understands the question.]
Why did you choose complete blindness rather than excellent health?

Record verbatim response: _____

Thank you. Remember, there are no right or wrong answers -- we want to know what you think. Are you ready to start the stories?
So, let's start the first story.

ID #:_____

[Case 1: Mastectomy]

A 41 year old mother of two was diagnosed with early stage breast cancer six months ago, and she chose to have a mastectomy. The mastectomy involved surgery to remove the whole breast and the lymph nodes under the arm. She is now completely recovered from the surgery. She has a 6-inch scar on her chest from the surgery, and may get some swelling in her arm on the side of the surgery. That arm is somewhat stiff, but she is doing exercise to help the arm move well.

She has been using a prosthesis (bra filler) in her bra since her breast was removed, but she can have a breast implant placed later if she wants.

She is free of known cancer, although from time to time she worries about the breast cancer coming back. Other than the breast cancer, she is healthy.

So, in summary, this woman has:

- her breast removed,
- a 6-inch scar on the chest, and
- possible arm swelling or stiffness.
- She is free of known cancer, but
- worries about the return of the breast cancer.

Do you have any questions about what she has?

I would like you to imagine that this woman is faced with a choice: she, or anyone in her situation, could either live 30 years with her health as it is after the mastectomy, or, she could choose to live 30 years in excellent health. Excellent health would mean that she no longer had the breast cancer or the surgery, and she would be completely healthy.

If she had to make this choice, which do you think she should choose, or do both choices seem about the same to you?

[IF chooses Excellent Health]
If she could choose between living one month in excellent health or 30 years with a mastectomy, which do you think she should choose, or do they seem about the same to you?

[IF chooses Mastectomy]
If she could choose between living 15 years in excellent health or 30 years with a mastectomy, which do you think she should choose, or do they seem about the same to you?

[If the respondent chooses excellent health, repeat making the years for excellent smaller; if they choose mastectomy, repeat making the years for excellent health larger.]

[The confirmatory question asked at the end when a range of time is given:]
Is that fair to say somewhere between [28] and [29] years both options seem about the same to you?

ID #:_____

Now, I would like to ask you a different question about the same woman. Again, this 41-year-old woman has:

- her breast removed,
- a 6-inch scar on the chest and
- possible arm swelling or stiffness.
- She is free of known cancer, but
- worries about the return of the breast cancer.

I would like you to rate her health on a scale ranging from 0, representing death, to 100, representing the best state of health you can imagine. What number do you think best describes her health?

[If not finished]
Now, on to the next story.

ID #:_____

[Case 2: BCS]

A 41 year old mother of two was diagnosed with early stage breast cancer six months ago. She decided to have breast conserving surgery (known as a lumpectomy), and six weeks of daily radiation therapy to the remaining breast. The surgery removed the cancer, leaving a 2-inch scar on the breast, and the rest of her breast has been preserved. She also had the lymph nodes removed from under the arm. She is now completely recovered from the surgery and radiation. She may get some swelling in her arm on the side of the surgery. That arm is somewhat stiff, but she is doing exercise to help the arm move well. She may have some changes in her breast after radiation, such as shrinkage, swelling, or firmness.

She is now free of known cancer, although from time to time she still worries about the breast cancer coming back. Other than the breast cancer, she is healthy.

So, in summary, this woman has:

- her cancer removed, her breast preserved,
- a 2-inch scar on the breast, which may get shrinkage, swelling, or firmness, and
- possible arm swelling or stiffness.
- She is free of known cancer, but
- worries about the return of the breast cancer.

Do you have any questions about what she has?

I would like you to imagine that this woman is faced with a choice: she, or anyone in her situation, could either live 30 years with her health as it is after the lumpectomy, or, she could choose to live 30 years in excellent health. Excellent health would mean that she no longer had the breast cancer or the surgery, and she would be completely healthy.

If she had to make this choice, which do you think she should choose, or do both choices seem about the same to you?

[IF chooses Excellent Health]
If she could choose between living one month in excellent health or 30 years with a lumpectomy, which do you think she should choose, or do they seem about the same to you?

[IF chooses lumpectomy]
If she could choose between living 15 years in excellent health or 30 years with a lumpectomy, which do you think she should choose, or they choices seem about the same to you?

[If the respondent chooses excellent health, repeat making the years for excellent smaller; if they choose lumpectomy, repeat making the years for excellent health larger.]

[The confirmatory question asked at the end when a range of time is given:]
Is that fair to say somewhere between [28] and [29] years both options seem about the same to you?

ID #:_____

Now, I would like to ask you a different question about the same woman. Again, this 41-year-old woman has:

- her cancer removed, her breast preserved,
- a 2-inch scar on the breast, which may get shrinkage, swelling, or firmness, and
- possible arm swelling or stiffness.
- She is free of known cancer, but
- worries about the return of the breast cancer.

I would like you to rate her health on a scale ranging from 0, representing death, to 100, representing the best state of health you can imagine. What number do you think best describes her health?

[If not finished]
Now, on to the next story.

ID #:_____

[Case 3: Prophylactic mastectomy]

A 41 year old mother of two was diagnosed with early stage breast cancer. Due to a high chance of getting a new, second breast cancer in the future, she decided to have both breasts removed (a bilateral mastectomy) to treat her current cancer.

The surgery involved removing both breasts, and removing lymph nodes under the arm on the side that had the cancer. She is now completely recovered from surgery. She has 6-inch scars on her chest from the surgery, and may get some swelling in her arm on the side of the surgery. That arm is somewhat stiff, but she is doing exercise to help the arm move well.

She is currently using two prostheses in her bra, but she can have breast implants later if she wants.

She is now free of known cancer, although from time to time she still worries about the breast cancer coming back. Other than the breast cancer, she is healthy.

So, in summary, this woman has:

- both breasts removed,
- 6-inch scars on her chest, and
- possible arm swelling or stiffness.
- She is free of known cancer, but
- worries about the return of the breast cancer.

Do you have any questions about what she has?

I would like you to imagine that this woman is faced with a choice: she, or anyone in her situation, could either live 30 years with her health as it is after the mastectomy, or, she could choose to live 30 years in excellent health. Excellent health would mean that she no longer had the breast cancer or the surgery, and she would be completely healthy.

If she had to make this choice, which do you think she should choose, or do both choices seem about the same to you?

[IF chooses Excellent Health]
If she could choose between living one month in excellent health or 30 years with a mastectomy, which do you think she should choose, or do they seem about the same to you?

[IF chooses Mastectomy]
If she could choose between living 15 years in excellent health or 30 years with a mastectomy, which do you think she should choose, or do they seem about the same to you?

[If the respondent chooses excellent health, repeat making the years for excellent smaller; if they choose lumpectomy, repeat making the years for excellent health larger.]

[The confirmatory question asked at the end when a range of time is given:]
Is that fair to say somewhere between [28] and [29] years both options seem about the same to you?

Now, I would like to ask you a different question about the same woman. Again, this 41-year-old woman has:

- both breasts removed,
- 6-inch scars on her chest, and
- possible arm swelling or stiffness.
- She is free of known cancer, but
- worries about the return of the breast cancer.

I would like you to rate her health on a scale ranging from 0, representing death, to 100, representing the best state of health you can imagine. What number do you think best describes her health?

[If not finished]
Now, on to the next story.

ID #:_____

[Case 4: prophylactic oophorectomy - finished childbearing]

A 41 year old woman, who has finished childbearing, was diagnosed with early stage breast cancer and has completed her breast cancer treatment. She has also decided to have surgery to remove both ovaries, due to a high chance of getting ovarian cancer in the future. After the ovarian surgery she went through early menopause. Early menopause may lead to hot flashes, vaginal dryness, and a higher chance of osteoporosis and heart disease. There are some hormonal and some non-hormonal treatments for those menopausal symptoms, but her doctor told her she could not take hormones because of her breast cancer.

She is now free of known cancer, although from time to time she still worries about the breast cancer coming back. Her health is otherwise excellent.

So, in summary, this woman has:

- treated the early breast cancer, and
- both of the ovaries are removed.
- She goes through menopause.
- She is free of known cancer, but
- worries about the return of the breast cancer.

Do you have any questions about what she has?

I would like you to imagine that this woman is faced with a choice: she, or anyone in her situation, could either live 30 years with her health as it is after a removal of both ovaries, or, she could choose to live 30 years in excellent health. Excellent health would mean that she no longer had the breast cancer or the surgery, and she would be completely healthy.

If she had to make this choice, which do you think she should choose, or do both choices seem about the same to you?

[IF chooses Excellent Health]
If she could choose between living one month in excellent health or 30 years with a removal of both ovaries, which do you think she should choose, or do they seem about the same to you?

[IF chooses oophorectomy]
If she could choose between living 15 years in excellent health or 30 years with a removal of both ovaries, which do you think she should choose, or do they seem about the same to you?

[If the respondent chooses excellent health, repeat making the years for excellent smaller; if they choose lumpectomy, repeat making the years for excellent health larger.]

[The confirmatory question asked at the end when a range of time is given:]
Is that fair to say somewhere between [28] and [29] years both options seem about the same to you?

ID #:_____

Now, I would like to ask you a different question about the same woman. Again, this 41-year-old woman has:

- treated the early breast cancer, and
- both of the ovaries are removed.
- She goes through menopause.
- She is free of known cancer, but
- worries about the return of the breast cancer.

I would like you to rate her health on a scale ranging from 0, representing death, to 100, representing the best state of health you can imagine. What number do you think best describes her health?

[If not finished]
Now, on to the next story.

ID #:_____

[Case 5: In-breast recurrence / 2nd primary]

This 41 year old woman was diagnosed with breast cancer five years ago. At that time she had a lumpectomy followed by six weeks of radiation therapy. Recently, she went in for a routine follow-up mammogram and her doctor found a lump in the same area as the original tumor. A biopsy was done and it was found to be a recurrence of her cancer. To treat this recurrence, she had a mastectomy and chemotherapy. The mastectomy involved surgery to remove the whole breast and lymph nodes under the arm. The other unaffected breast remained intact. She has a 6-inch scar on her chest from the surgery, and may get some swelling in her arm on the side of the surgery. That arm is somewhat stiff, but she is doing exercise to help the arm move well.

The chemotherapy lasted for several months, and required her to come to the outpatient clinic and receive chemotherapy through a vein in her arm. She lost most of her hair for the time that she was on treatment and experienced some mild nausea. Her hair will eventually grow back. She was tired during the several months of therapy. She may go into early menopause from the chemotherapy.

She has been using a prosthesis (bra filler) in her bra since her breast was removed, but she can have reconstruction with a breast implant placed later if she wants.

After all the treatment, she is free of known cancer. Although from time to time she still worries about the cancer coming back. Other than the breast cancer, she is healthy.

So, in summary, this woman has:

- her breast removed,
- a 6-inch scar on the chest,
- possible arm swelling or stiffness, and
- possible early menopause.
- She is free of known cancer, but
- worries about the return of the breast cancer.

Do you have any questions about what she has?

I would like you to imagine that this woman is faced with a choice: she, or anyone in her situation, could either live 30 years with her health as it is after treatment of recurrence, or, she could choose to live 30 years in excellent health. Excellent health would mean that she no longer had the breast cancer or the surgery, and she would be completely healthy.

If she had to make this choice, which do you think she should choose, or do both choices seem about the same to you?

[IF chooses Excellent Health]

If she could choose between living one month in excellent health or 30 years after treatment of recurrence, which do you think she should choose, or do they seem about the same to you?

[IF chooses recurrence]

If she could choose between living 15 years in excellent health or 30 years after treatment of recurrence, which do you think she should choose, or do they seem about the same to you?

[If the respondent chooses excellent health, repeat making the years for excellent smaller; if they chose recurrence, repeat making the years for excellent health larger.]

[The confirmatory question asked at the end when a range of time is given:]
Is that fair to say somewhere between [28] and [29] years both options seem about the same to you?

ID #:_____

Now, I would like to ask you a different question about the same woman. Again, this 41-year-old woman has:

- her breast removed,
- a 6-inch scar on the chest,
- possible arm swelling or stiffness, and
- possible early menopause.
- She is free of known cancer, but
- worries about the return of the breast cancer.

I would like you to rate her health on a scale ranging from 0, representing death, to 100, representing the best state of health you can imagine. What number do you think best describes her health?

[If not finished]
Now, on to the next story.

ID #:_____

[Case 6: Metastatic Disease]

This 41 year old woman was diagnosed with breast cancer seven years ago. She had a lumpectomy and radiation therapy at that time. On a routine follow-up visit with her doctor, based on lab tests her doctor found that her cancer had spread elsewhere in her body (metastases).

To treat the spread of her cancer, the oncologist recommended chemotherapy. She received her chemotherapy through a vein each month. She lost most of her hair, and occasionally required medication for nausea and diarrhea. Her hair might grow back in the future. Most of the time she can do her usual activities if she does not try to exert herself too much, but from time to time, she needs another person to help her with her usual daily activities. Occasionally she takes pain medications, which control any pain she has, but the medications make her feel "less sharp". She may feel somewhat anxious or depressed about her cancer. The therapy does not cure her cancer; it only helps to keep the cancer under control.

So, in summary, this woman has:

- her breast removed, a 2-inch scar on the chest, and
- possible arm swelling or stiffness.
- She loses most of her hair, and
- has nausea, diarrhea, and pain requiring medication that makes her "less sharp".
- Occasionally she feels tired and needs help.
- She may be anxious and depressed about the control of her current cancer.

Do you have any questions about what she has?

I would like you to imagine that this woman is faced with a choice: she, or anyone in her situation, could either live 5 years with her health as it is with metastases, or, she could choose to live 5 years in excellent health. Excellent health would mean that she no longer had the breast cancer or the surgery, and she would be completely healthy.

If she had to make this choice, which do you think she should choose, or do both choices seem about the same to you?

[IF chooses Excellent Health]
If she could choose between living one month in excellent health or 5 years with metastases, which do you think she should choose, or do they seem about the same to you?

[IF chooses Metastases]
If she could choose between living 2 and ½ years in excellent health or 5 years with metastases, which do you think she should choose, or do they seem about the same to you?

[If the respondent chooses excellent health, repeat making the years for excellent smaller; if they choose metastases, repeat making the years for excellent health larger.]

[The confirmatory question asked at the end when a range of time is given:]
Is that fair to say somewhere between [3.5] and [4] years both options seem about the same to you?

ID #:_____

Now, I would like to ask you a different question about the same woman. Again, this 41-year-old woman has:

- her breast removed, a 2-inch scar on the chest, and
- possible arm swelling or stiffness.
- She loses most of her hair, and
- has nausea, diarrhea, and pain requiring medication that makes her "less sharp".
- Occasionally she feels tired and needs help.
- She may be anxious and depressed about the control of her current cancer.

I would like you to rate her health on a scale ranging from 0, representing death, to 100, representing the best state of health you can imagine. What number do you think best describes her health?

[If not finished]
Now, on to the next story.

ID #:_____

[Case 7: Current health vs excellent]

Let's consider your current health. Compared to how you function every day now,

if you could choose between living for 30 years in excellent health, which would mean that you are free of any diseases and completely healthy, or 30 years with your current health, which would you choose, or do they seem to be about the same to you?

If you could choose between living one month in excellent health or 30 years with your current health, which would you choose, or do they seem about the same to you?

If you could choose between living 15 years in excellent health or 30 years with your current health, which would you choose, or do they seem about the same to you?

[If the patient chooses excellent health, repeat making the years for excellent lower; if they choose current health, repeat making the years for excellent health higher.]

[The confirmatory question asked at the end when a range of time is given:]
Is that fair to say somewhere between [28] and [29] years both options seem about the same to you?

Now, I would like you to rate your current health on a scale of health ranging from 0, representing death, to 100, representing the best state of health you can imagine. What number do you think best describes how good or bad living with your own health is?

I..D. _____

I would like to ask you some questions about your day to day health during the *past four weeks*. Some of these questions may not apply to you, but it is important that we ask the same questions of everyone. For some of the questions, I want you to tell me which statement *most closely describes* how you felt. Please **circle** the most appropriate answer for each of the questions.

1.[HUI_1] Are you able to see well enough *without* glasses or contact lenses to read the newspaper?

Yes 1
No 2

2.[HUI_2] Are you able to see well enough *without* glasses or contact lenses to recognize a friend on the other side of the street?

Yes 1
No 2

3.[HUI_3] Are you able to hear what is said in a group conversation with at least three other people *without* a hearing aid?

Yes 1
No 2

4.[HUI_4] Are you able to hear what is said in a conversation with one other person in a quiet room without a hearing aid?

Yes 1
No 2

5.[HUI_7] Which *one* of the following best describes how you usually feel? Would you say you are...

Happy and interested in life? 1
Somewhat happy? 2
Somewhat unhappy? 3
Very unhappy? 4
So unhappy that life is not worthwhile? 5

6.[HUI_8] Are you free of pain and discomfort?

Yes . . . . . 1 (SKIP TO 7)
No 2

6a.[HUI_8a] Which *one* of the following best describes your usual level of pain and discomfort during the past four weeks? Would you say you...

Have mild to moderate pain or discomfort
that prevents no activities? 1
Have moderate pain or discomfort
that prevents a few activities? 2
Have moderate to severe pain or discomfort
that prevents some activities? 3
Have severe pain or discomfort
that prevents most activities? 4

7.[HUI_9] Are you able to walk around the neighborhood without difficulty and without walking equipment (such as a cane or walker)?

Yes 1
No 2

8.[HUI_10] Do you have full use of two hands and ten fingers?

Yes . . . . . 1 (SKIP TO 9)
No 2

8a.[HUI_10a] Which *one* of the following best describes your usual ability during the past four weeks to use your hands and fingers? (NOTE: SPECIAL TOOLS REFER TO HOOKS FOR BUTTONING CLOTHES, TOOLS FOR OPENING JARS OR LIFTING SMALL ITEMS) Would you say you have..

Limited use of hands or fingers, but do
not require special tools or the help
of another person? 1
Limited use of hands or fingers,
independent with use of special tools
(do not require the help of another person)? 2
Limited use of hands or fingers,
require the help of another person for
some tasks (not independent even with
the use of special tools)? 3
Limited use of hands or fingers,
require the help of another person for
most tasks (not independent even with
the use of special tools)? 4
Limited use of hands or fingers,
require the help of another person for
all tasks (not independent even with
the use of special tools)? 5

I..D. _____

9.[HUI_11] Are you able to remember most things?

Yes . . . . . 1 (SKIP TO 10)
No 2

9a.[HUI_11a] Which *one* of the following best describes your usual ability during the past four weeks to remember things? Would you say you are...

Somewhat forgetful? 1
Very forgetful? 2
Unable to remember anything at all? 3

10.[HUI_12] Are you able to think clearly and solve day to day problems?

Yes . . . . . 1 (SKIP TO 11)
No 2

10a.[HUI_12a] Which *one* of the following best describes your usual ability during the past four weeks to think and solve day to day problems? Would you say you...

Have a little difficulty when trying to think
and solve day to day problems? 1
Have some difficulty when trying to think
and solve day to day problems? 2
Have a great deal of difficulty when trying
to think and solve day to day problems? 3
Are unable to think or solve day to day problems? 4

11.[HUI_13] Do you eat, bathe, dress and use the toilet normally?

Yes 1
No 2

12.[HUI_14] Are you generally happy and free from worry?

Yes . . . . . 1 (SKIP TO 13)
No 2

12a.[HUI_14a] Which *one* of the following best describes how you usually feel during the past four weeks? Would you say you are...

Occasionally fretful, angry, irritable, anxious or depressed? 1
Often fretful, angry, irritable, anxious or depressed? 2
Almost always fretful, angry, irritable, anxious or depressed? 3
Extremely fretful, angry, irritable, anxious or depressed, usually requiring hospitalization or psychiatric institutional care? 4

13.[HUI_15] Are you free of pain and discomfort?

Yes . . . . . 1 (SKIP TO 14)
No 2

13a.[HUI_15a] Which *one* of the following best describes your usual level of pain during the past four weeks? Would you say you...

Have occasional pain, with discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities? 1
Have frequent pain, with discomfort relieved by oral medicines with occasional disruption of normal activities? 2
Have frequent pain, with frequent disruption of normal activities, and discomfort that requires prescription narcotics for relief? 3
Have severe pain, that is not relieved by drugs and constantly disrupts normal activities? 4

14. How do you describe your level of fertility, or ability to reproduce in the future?

Able to have children with a fertile spouse 1
Difficulty having children with a fertile spouse 2
Unable to have children with a fertile spouse 3
Being infertile due to age 4
Being infertile due to having chosen to be "fixed" because of life-style considerations 5
Being infertile due to having been "fixed" because of health problems or other considerations that do not imply free choice 6
Of "unknown" fertility status 8
Do not want to answer 9

Thank you again for participating the study. We'd like to ask you some questions about how coming for the study affects you. Your answers will help us understand what you and other participants need, so that we can better serve you in the future. Remember, answering these questions does not affect the care that you will receive here at Georgetown or your regular doctor. You do not have to answer any question you do not want to. All of your answers will be confidential, and we will not use your name. If you have any question about how to fill out this survey, the genetic counselor would be happy to help you.

Please **circle the one** most appropriate answer
For each of the following questions.

1. How did you get to Georgetown for the genetic counseling? (Circle one)

Personal car, either drove self or brought by friend or relative	1
Taxi cab	2
Public transportation (bus, train, Metro subway; etc.)	3
Hospital/clinic supplied transportation	4
Walked	5
Community-based organization supplied transportation (including church, shelter, senior citizens center; etc.)	6
Other (Please write in what this was):	77
Do not want to answer	99

2. Are you employed outside of the home? (Circle one)

Yes **(PLEASE GO TO QUESTION 3.)**	1
No **(PLEASE GO TO QUESTION 5.)**	2
Do not want to answer	99

3. Did you take off from work to participate in the genetic counseling? (Circle one)

Yes **(PLEASE GO TO QUESTION 4.)**	1
No **(PLEASE GO TO QUESTION 5.)**	2
Do not want to answer	99

4. Will you receive compensation for your time off work, such as personal leave, sick time, or vacation time? (Circle one)

Yes	1
No	2
Do not want to answer	99

5. Did you need to arrange for child care / spouse or parent care while here for the genetic counseling? (Circle one)

Yes	1
No	2
Do not want to answer	99

6. How much total time did you spend traveling from your home to Georgetown for the genetic counseling? (Circle one)

<10 minutes	1
10-29 minutes	2
30-59 minutes	3
1-2 hours	4
2 hours or more	5
Don't know / unsure	88
Do not want to answer	99

Thank you for taking your time to complete the survey.
Please give this completed survey to the genetic counselor.

CORE #2: CANCER CLINICAL AND ECONOMIC OUTCOMES EVALUATIONS CORE

APPENDIX 2:
(CORE #1) PATIENT ACCESSION CORE
COST DATA COLLECTION INSTRUMENT

PATIENT ACCESSION CORE COST ASSESSMENT SHEET

Date:_____

Data recorded for Start Date:_____ to End date:_____

Data recorded by:_____

Personnel:	
Jon Kerner	hrs:
Lenora Johnson	hrs:
Anna Ryan Robertson	hrs:
Research Assistant	hrs:
Administrative Assistant	hrs:
Other (NAME:)	hrs:
Equipment	
Item:	$
Item:	$
Supplies and Materials	
Impact of Genetic Testing for Breast CA	
Recruitment tools - development	$
Recruitment tools - purchasing/duplicating	$
Educ. Tools - development	$
Educ. Tools - purchasing/duplicating	$
Other ( )	$
Breast Cancer Diagnosis	
Recruitment tools - development	$
Recruitment tools - purchasing/duplicating	$
Educ. Tools - development	$

Educ. Tools - purchasing/duplicating	$
Other ( )	$
Novel Antiangiogenic Therapies	
Recruitment tools - development	$
Recruitment tools - purchasing/duplicating	$
Educ. Tools - development	$
Educ. Tools - purchasing/duplicating	$
Other ( )	$
General	
Office supplies	$
Advisory committee materials	$
Other ( )	$
Travel	
Professional Travel	$
Patient transportation	$
Patient parking	$
Personnel mileage	$
Consultants	
Trainer	$
Breast CA Resource Committee	$
Other ( )	$
Other Resources (Please list)	

CORE #2: CANCER CLINICAL AND ECONOMIC OUTCOMES EVALUATIONS CORE

APPENDIX 3:
(PROJECT #2) NEW COORDINATED BREAST CANCER DIAGNOSTIC TECHNOLOGIES
SURVEY INSTRUMENT

ID #: _____

Patient Satisfaction Survey

Georgetown University Medical Center
Lombardi Cancer Center/ Radiology Department

We would like to thank you again for participating in our program. Now that you have had the tests, we would like to ask some questions to help us understand how you felt about the tests. Your opinion is important to us. Your answers will help us to improve things for future women like yourself. Remember, answering these questions does not affect the care that you will receive here at Georgetown, or from your regular health care provider. You do not have to answer any question you do not want to. All of your answers will be confidential, and we will not use your name. If you have any questions about how to fill out this survey, Miriam Mullins would be happy to help you.

Please **circle the one** most appropriate answer
for each of the following questions.

First, we'd like to ask you some questions about how coming for these tests affects you.

1. How did you get to Georgetown for the tests? (Circle one)

Personal car, either drove self or brought by friend or relative	1
Taxi cab	2
Public transportation (bus, train, Metro subway; etc.)	3
Hospital/clinic supplied transportation	4
Walked	5
Community-based organization supplied transportation (including church, shelter, senior citizens center; etc.)	6
Other (Please write in what this was):	77
Do not want to answer	99

2. Are you employed outside of the home? (Circle one)

Yes **(PLEASE GO TO QUESTION 3.)**	1
No **(PLEASE GO TO QUESTION 5.)**	2
Do not want to answer	99

ID #: _____

3. Did you take off from work to participate in this study? (Circle one)

Yes **(PLEASE GO TO QUESTION 4.)**	1
No **(PLEASE GO TO QUESTION 5.)**	2
Do not want to answer	99

4. Will you receive compensation for your time off work, such as personal leave, sick time, or vacation time? (Circle one)

Yes	1
No	2
Do not want to answer	99

5. Did you need to arrange for child care / spouse or parent care while here taking the tests? (Circle one)

Yes	1
No	2
Do not want to answer	99

6. How much total time did you spend traveling from your home to Georgetown for the tests? (Circle one)

<10 minutes	1
10-29 minutes	2
30-59 minutes	3
One hour or more	4
Don't know / unsure	88
Do not want to answer	99

ID #: _____

7. Once you got here, how much time did you spend getting all of the tests today, including waiting time? (Circle one)

0 to just under 2 hrs	1
2 to just under 4 hrs	2
4 to just under 6 hrs	3
6 to just under 8 hrs	4
> 8 hrs	5
Don't know / unsure	88
Do not want to answer	99

8. We would like a general estimate of the total family income during the last month for you and all family members living with you. About how much money do you have coming into your household in each month (from jobs, interest, retirement plans, social security, investments, and social services)? (Circle one)

Less than $ 1,000	1
$1,000 to $1,999	2
$2,000 to $2,999	3
$3,000 to $3,999	4
$4,000 to $4,999	5
$5,000 or more	6
Don't know / unsure	88
Do not want to answer	99

ID #: _____

Here are some questions about your visit to Georgetown today, and the tests that you had. In terms of your **satisfaction**, how would you rate each of the following:

9. The tests you received at Georgetown today **overall**? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

10. The **technical skills** (thoroughness, carefulness, competence) of the radiology staff? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

11. The **personal manner** (courtesy, respect, sensitivity, friendliness) of the radiology staff? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

ID #: _____

12. **Convenience** of getting the tests at Georgetown? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

13. Length of **time spent waiting** for the tests / in between tests? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

14. **Explanation** of what was done for you? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

ID #: _____

Now, we'd like to know the degree of **discomfort** and **embarrassment** that you have experienced in the routine mammogram you have received before today's visit.

15. a) How would you rate the level of **discomfort** that you experienced from **a routine mammogram?** (Circle one)

Extremely uncomfortable	1
Very uncomfortable	2
Somewhat uncomfortable	3
Mildly uncomfortable	4
Not uncomfortable at all	5
Don't know / unsure	88
Do not want to answer	99

b) How **embarrassing** was it for you to have a **routine mammogram?** (Circle one)

Extremely embarrassing	1
Somewhat embarrassing	2
Mildly embarrassing	3
Not embarrassing at all	4
Don't know / unsure	88
Do not want to answer	99

ID #: _____

These next questions are about the **tests** themselves. We'd like to know the degree of **discomfort** and **embarrassment** you experienced in each of the tests you received today.

16. a) Compared to a **routine mammogram** how would you rate the level of **discomfort** that you experienced from the **ultrasound test (sonogram**, breast covered with jelly and checked in the mammography machine)? (Circle one)

A lot less	1
A little less	2
No different	3
A little more	4
A lot more	5
Did not receive the ultrasound test	77
Don't know / unsure	88
Do not want to answer	99

b) How **embarrassing** was it for you to have the **ultrasound test**? (Circle one)

Extremely embarrassing	1
Somewhat embarrassing	2
Mildly embarrassing	3
Not embarrassing at all	4
Did not receive the ultrasound test	77
Don't know / unsure	88
Do not want to answer	99

ID #: _____

17. a) Compared to a **routine mammogram** how would you rate the level of **discomfort** that you experienced from the **MRI test** (breast pictures taken while you lay on a table for 15 to 20 minutes)? (Circle one)

A lot less	1
A little less	2
No different	3
A little more	4
A lot more	5
Did not receive the MRI test	77
Don't know / unsure	88
Do not want to answer	99

b) How **embarrassing** was it for you to have the **MRI test**? (Circle one)

Extremely embarrassing	1
Somewhat embarrassing	2
Mildly embarrassing	3
Not embarrassing at all	4
Did not receive the MRI test	77
Don't know / unsure	88
Do not want to answer	99

ID #: _____

18. a) Compared to a **routine mammogram** how would you rate the level of **discomfort** that you experienced from the **digital mammography test** (the procedure similar to a routine mammogram)? (Circle one)

A lot less	1
A little less	2
No different	3
A little more	4
A lot more	5
Did not receive the digital mammography test	77
Don't know / unsure	88
Do not want to answer	99

b) How **embarrassing** was it for you to have the **digital mammography test?** (Circle one)

Extremely embarrassing	1
Somewhat embarrassing	2
Mildly embarrassing	3
Not embarrassing at all	4
Did not receive the digital mammography test	77
Don't know / unsure	88
Do not want to answer	99

ID #: _____

19. a) Compared to a **routine mammogram** how would you rate the level of **discomfort** that you experienced from the **Sestamibi test (Nuclear image,** breast pictures obtained on two different machines following a single injection of a trace amount of radioactive medicine)? (Circle one)

A lot less	1
A little less	2
No different	3
A little more	4
A lot more	5
Did not receive the Sestamibi test	77
Don't know / unsure	88
Do not want to answer	99

b) How **embarrassing** was it for you to have the **Sestamibi test?** (Circle one)

Extremely embarrassing	1
Somewhat embarrassing	2
Mildly embarrassing	3
Not embarrassing at all	4
Did not receive the Sestamibi test	77
Don't know / unsure	88
Do not want to answer	99

ID #: _____

20. a) Compared to a **routine mammogram** how would you rate the level of **discomfort** that you experienced from the **nipple aspirate test** (using a breast pump to extract a small amount of the fluid from the nipple) ? (Circle one)

A lot less	1
A little less	2
No different	3
A little more	4
A lot more	5
Did not receive the nipple aspirate test	77
Don't know / unsure	88
Do not want to answer	99

b) How **embarrassing** was it for you to have the **nipple aspirate test?** (Circle one)

Extremely embarrassing	1
Somewhat embarrassing	2
Mildly embarrassing	3
Not embarrassing at all	4
Did not receive the nipple aspirate test	77
Don't know / unsure	88
Do not want to answer	99

ID #: _____

These next questions are hypothetical questions about having to pay for tests. These questions will NOT affect your bills for health care services. All tests in the project are provided at NO COST TO YOU. Your answers to these questions will help us understand how women like you might feel about the tests you had today.

Imagine for a moment that a woman who has had a problem on her mammogram could have a test, like one of the tests that you had today, **instead** of a surgical biopsy. If the test was **equally (100%) as good** at telling whether or not she had breast cancer, how much do you think a woman like her would be willing to pay out of her own pocket to have the test **instead of a biopsy?**

$_____.00 (21)

(If you do not think she would be willing to pay anything, please put zero (0) in the space above.)

Now, again imagine for a moment that a woman who has had a problem on her mammogram could have a test, like one of the tests that you had today, **instead** of a surgical biopsy. If the test was **nearly (95%) as good** at telling whether or not she had breast cancer, how much do you think a woman like her would be willing to pay out of her own pocket to have the test **instead of a biopsy?**

$_____.00 (22)

(If you do not think she would be willing to pay anything, please put zero (0) in the space above.)

Now, please turn to the next page for the last questions.

ID #: _____

23. In your opinion, compared to other women your age, what are your chances of getting breast cancer some day? Would you say they are ... (Circle one)

Much higher	1
A little higher	2
The same	3
A little less	4
Much Less	5
Don't know / not sure	88
Do not want to answer	99

24. Is there anything that we have not asked about that you would like to tell us about? We appreciate any comments you may have about your experience today.

_____

_____

_____

_____

_____

Thank you for taking your time to complete the study today. Please give your completed survey to Miriam Mullins. If you have any further questions about the project, please feel free to contact Miriam Mullins at (202)784-3359.

CORE #2: CANCER CLINICAL AND ECONOMIC OUTCOMES EVALUATIONS CORE

APPENDIX 4:
(PROJECT #3) NOVEL PALLIATIVE TREATMENTS OF METASTATIC BREAST CANCER
SURVEY INSTRUMENTS

Quality of Life Survey

Georgetown University Medical Center
Lombardi Cancer Center / Oncology Department

Patient I.D. # _____

Date of interview: _____ / _____ / _____

Inteviewer initials: _____

INTRODUCTION

Thank you again for participating in our project. We would like to ask some questions to help us understand how you feel about your current health and the quality of your life. Your answers will help us to improve cares for future women like yourself. Remember, answering these questions does not affect the care that you will receive here at Georgetown or at your regular doctor. You do not have to answer any question you do not want to. All of your answers will be confidential, and we will not use your name.

This survey consists of four sets of questions: The first set of questions ask about your day to day health; the second set asks you to rate your health; the third set asks about your feeling of various statements that other people with illness have said are important; and the last set of questions ask about your current symptoms. It will take approximately 10 minutes to complete the survey. The study coordinator will assist you in answering all the questions. Please feel free to ask any question about the survey questions.

Now, let's go to the first section.

I.D. _____

INTRODUCTION: This set of questions asks about your day to day health **during the past four weeks**. Some of these questions may not apply to you, but it is important that we ask the same questions of everyone. PLEASE **CIRCLE** THE STATEMENT WHICH MOST CLOSELY DESCRIBES HOW YOU FELT.

1.[HUI] Are you able to see well enough *without* glasses or contact lenses to read the newspaper?

Yes . . . . . 1 (SKIP TO 2)
No 2

1a.[HUI] Which of the following best describes your usual ability to see well enough to read the newspaper? Are you...

Able to see well enough, *but with* glasses
or contact lenses? 1
Unable to see well enough, *even with* glasses
or contact lenses? 2
Unable to see at all? 3

2.[HUI] Are you able to see well enough *without* glasses or contact lenses to recognize a friend on the other side of the street?

Yes . . . . . 1 (SKIP TO 3)
No 2

2a.[HUI] Which *one* of the following best describes your usual ability during the past four weeks to see well enough to recognize a friend on the other side of the street? Would you say you...

Can see well enough with glasses or
contact lenses? 1
Cannot see well enough even with glasses
or contact lenses? 2
Cannot see at all? 3

I.D. _____

3.[HUI] Are you able to hear what is said in a group conversation with at least three other people *without* a hearing aid?

Yes . . . . . 1 (SKIP TO 4)
No 2

3a.[HUI] Which *one* of the following best describes your usual ability during the past four weeks to hear what is said in a group conversation with at least three other people? Would you say you...

Can hear what is said with a hearing aid? 1
Cannot hear what is said even with a hearing aid? 2
Cannot hear what is said, but don't wear a hearing aid? . . . 3
Cannot hear at all? 4

4.[HUI] Are you able to hear what is said in a conversation with one other person in a quiet room without a hearing aid?

Yes . . . . . 1 (SKIP TO 5)
No 2

4a.[HUI] Which *one* of the following best describes your usual ability during the past four weeks to hear what is said in a conversation with one other person in a quiet room? Would you say you...

Can hear what is said with a hearing aid? 1
Cannot hear what is said even with a hearing aid? 2
Cannot hear what is said, but don't wear a hearing aid? . . . 3
Cannot hear at all? 4

5.[HUI] Are you able to be understood when speaking the same language with strangers?

Yes . . . . . 1 (SKIP TO 6)
No 2

5a.[HUI] Which *one* of the following best describes your usual ability during the past four weeks to be understood when speaking the same language with strangers? Would you say you are...

Able to be understood partially? 1
Unable to be understood? 2
Unable to speak at all? 3

I.D. _____

6.[HUI] Are you able to be understood when speaking the same language with people who know you well?

Yes . . . . . 1 (SKIP TO 7)
No 2

6a.[HUI] Which *one* of the following best describes your usual ability during the past four weeks to be understood when speaking with people who know you well? Would you say you are...

Able to be understood completely? 1
Able to be understood partially? 2
Unable to be understood? 3
Unable to speak at all? 4

7.[HUI] Which *one* of the following best describes how you usually feel? Would you say you are...

Happy and interested in life? 1
Somewhat happy? 2
Somewhat unhappy? 3
Very unhappy? 4
So unhappy that life is not worthwhile? 5

8.[HUI] Are you free of pain and discomfort?

Yes . . . . . 1 (SKIP TO 9)
No 2

8a.[HUI] Which *one* of the following best describes your usual level of pain and discomfort during the past four weeks? Would you say you...

Have mild to moderate pain or discomfort
that prevents no activities? 1
Have moderate pain or discomfort that prevents
a few activities? 2
Have moderate to severe pain or discomfort
that prevents some activities? 3
Have severe pain or discomfort that prevents
most activities? 4

I.D. _____

9.[HUI] Are you able to walk around the neighborhood without difficulty and without walking equipment (such as a cane or walker)?

Yes . . . . . 1 (SKIP TO 10)
No 2

9a.[HUI] Which of the following best describes your usual ability during the past four weeks to walk? Would you say you are...

Able to walk around the neighborhood with difficulty, but without walking equipment or a helper? 1
Able to walk around the neighborhood with walking equipment, but without a helper? 2
Able to walk only short distances with walking equipment, and require a wheelchair to get around the neighborhood? 3
Unable to walk alone, even with walking equipment; able to walk short distances with a helper, and require a wheelchair to get around the neighborhood? 4
Cannot walk at all 5

I.D. _____

10.[HUI] Do you have full use of two hands and ten fingers?

Yes . . . . . 1 (SKIP TO 11)
No 2

10a.[HUI] Which *one* of the following best describes your usual ability during the past four weeks to use your hands and fingers? (NOTE: SPECIAL TOOLS REFER TO HOOKS FOR BUTTONING CLOTHES, TOOLS FOR OPENING JARS OR LIFTING SMALL ITEMS) Would you say you have..

Limited use of hands or fingers, but do not require special tools or the help of another person? 1
Limited use of hands or fingers, independent with use of special tools (do not require the help of another person)? 2
Limited use of hands or fingers, require the help of another person for some tasks (not independent even with the use of special tools)? 3
Limited use of hands or fingers, require the help of another person for most tasks (not independent even with the use of special tools)? 4
Limited use of hands or fingers, require the help of another person for all tasks (not independent even with the use of special tools)? 5

11.[HUI] Are you able to remember most things?

Yes . . . . . 1 (SKIP TO 12)
No 2

11a.[HUI] Which *one* of the following best describes your usual ability during the past four weeks to remember things? Would you say you are...

Somewhat forgetful? 1
Very forgetful? 2
Unable to remember anything at all? 3

I.D. _____

12.[HUI] Are you able to think clearly and solve day to day problems?

Yes . . . . . 1 (SKIP TO 13)
No 2

12a.[HUI] Which *one* of the following best describes your usual ability during the past four weeks to think and solve day to day problems? Would you say you...

Have a little difficulty when trying to think
and solve day to day problems? 1
Have some difficulty when trying to think
and solve day to day problems? 2
Have a great deal of difficulty when trying
to think and solve day to day problems? 3
Are unable to think or solve day to day problems? 4

13.[HUI] Do you eat, bathe, dress and use the toilet normally?

Yes . . . . . 1 (SKIP TO 14)
No 2

13a.[HUI] Which *one* of the following best describes your ability during the past four weeks to perform these basic activities? Would you say you...

Eat, bathe, dress and use the toilet independently
with difficulty? 1
Require mechanical equipment to eat, bathe,
dress or use the toilet independently? 2
Require the help of another person to eat, bathe,
dress or use the toilet? 3

I.D. _____

14.[HUI] Are you generally happy and free from worry?

Yes . . . . . 1 (SKIP TO 15)
No 2

14a.[HUI] Which *one* of the following best describes how you usually feel during the past four weeks? Would you say you are...

Occasionally fretful, angry, irritable, anxious or depressed? 1
Often fretful, angry, irritable, anxious or depressed? 2
Almost always fretful, angry, irritable, anxious or depressed? 3
Extremely fretful, angry, irritable, anxious or depressed, usually requiring hospitalization or psychiatric institutional care? 4

15.[HUI] Are you free of pain and discomfort?

Yes . . . . . 1 (SKIP TO 16)
No 2

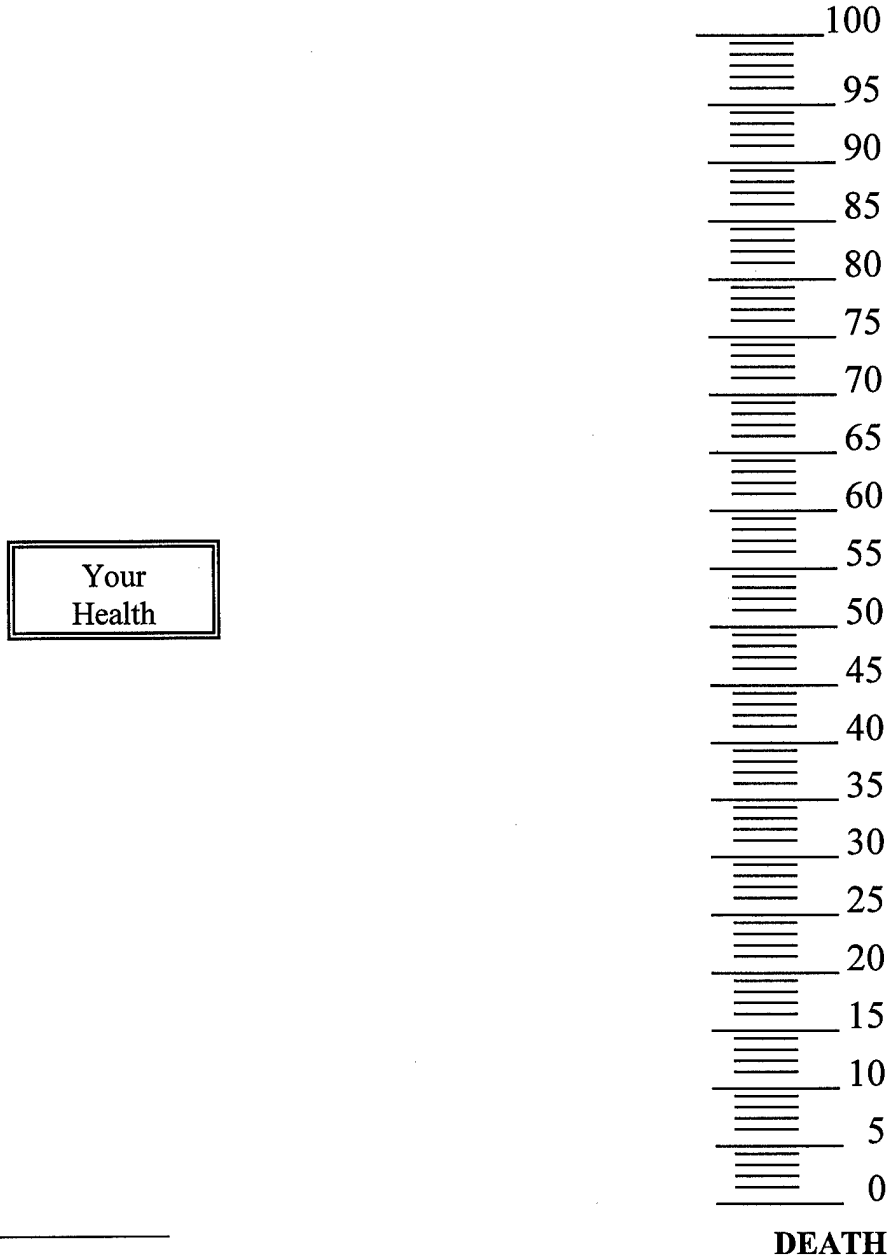
15a.[HUI] Which *one* of the following best describes your usual level of pain during the past four weeks? Would you say you...

Have occasional pain, with discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities? 1
Have frequent pain, with discomfort relieved by oral medicines with occasional disruption of normal activities? 2
Have frequent pain, with frequent disruption of normal activities, and discomfort that requires prescription narcotics for relief? 3
Have severe pain, that is not relieved by drugs and constantly disrupts normal activities? 4

I.D. _____

Now I would like you to indicate on this scale how good or how bad you consider your own state of health to be. Please do this by drawing a line from the box to whichever point on the scale indicates how good or bad living with your own health is.

BEST IMAGINABLE HEALTH STATE



DEATH

Number _____

I.D. _____

Below is a list of statements that other people with your illness have said are important. By circling one number per line, please indicate how true each statement has been for you **during the past 7 days.** PLEASE **CIRCLE ONE NUMBER** FOR EACH STATEMENT.

PHYSICAL WELL-BEING

Statement	*Not at all*	*A little bit*	*Some-what*	*Quite a bit*	*Very much*
1. I have a lack of energy	0	1	2	3	4
2. I have nausea	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4. I have pain	0	1	2	3	4
5. I am bothered by side effects of treatment	0	1	2	3	4
6. I feel sick	0	1	2	3	4
7. I am forced to spend time in bed	0	1	2	3	4

8. Looking at the above 7 questions, how much would you say your **PHYSICAL WELL-BEING** affects your quality of life? . . . . . .
(Circle one number)

1 2 3 4 5 6 7 8 9 10

Not at all <----------> Very much so

SOCIAL/FAMILY WELL-BEING

Statement	*Not at all*	*A little bit*	*Some-what*	*Quite a bit*	*Very much*
9. I feel distant from my family	0	1	2	3	4
10. I get emotional support from my family	0	1	2	3	4
11. I get support from my friends and neighbors	0	1	2	3	4
12. My family has accepted my illness	0	1	2	3	4
13. Family communication about my illness is poor	0	1	2	3	4
14. I feel close to my partner (or the person who is my main support)	0	1	2	3	4
15. Have you been sexually active during the past year? No___ Yes___ If yes: I am satisfied with my sex life	0	1	2	3	4

16. Looking at the above 7 questions, how much would you say your **SOCIAL/FAMILY WELL-BEING** affects your quality of life? . . . . . .
(Circle one number)

1 2 3 4 5 6 7 8 9 10

Not at all <----------> Very much so

I.D. _____

Please indicate how true each statement has been for you **during the past 7 days**.

RELATIONSHIP WITH DOCTOR

Statement	*Not at all*	*A little bit*	*Some-what*	*Quite a bit*	*Very much*
17. I have confidence in my doctor	0	1	2	3	4
18. My doctor is available to answer my questions	0	1	2	3	4

19. Looking at the above 2 questions, how much would you say your **RELATIONSHIP WITH DOCTOR** affects your quality of life?
(Circle one number)

1 2 3 4 5 6 7 8 9 10

Not at all <----------> Very much so

EMOTIONAL WELL-BEING

Statement	*Not at all*	*A little bit*	*Some-what*	*Quite a bit*	*Very much*
20. I feel sad	0	1	2	3	4
21. I am proud of how I'm coping with my illness	0	1	2	3	4
22. I am losing hope in the fight against my illness	0	1	2	3	4
23. I feel nervous	0	1	2	3	4
24. I worry about dying	0	1	2	3	4
25. I worry that my condition will get worse	0	1	2	3	4

26. Looking at the above 6 questions, how much would you say your **EMOTIONAL WELL-BEING** affects your quality of life?
(Circle one number)

1 2 3 4 5 6 7 8 9 10

Not at all <----------> Very much so

I.D. _____

Please indicate how true each statement has been for you **during the past 7 days**.

FUNCTIONAL WELL-BEING

Statement	*Not at all*	*A little bit*	*Some-what*	*Quite a bit*	*Very much*
27. I am able to work (include work in home)	0	1	2	3	4
28. My work (include work in home) is fulfilling	0	1	2	3	4
29. I am able to enjoy life	0	1	2	3	4
30. I have accepted my illness	0	1	2	3	4
31. I am sleeping well	0	1	2	3	4
32. I am enjoying the things I usually do for fun	0	1	2	3	4
33. I am content with the quality of my life right now	0	1	2	3	4

34. Looking at the above 7 questions, how much would you say your **FUNCTIONAL WELL-BEING** affects your quality of life?
(Circle one number)

1 2 3 4 5 6 7 8 9 10

Not at all <----------> Very much so

ADDITIONAL CONCERNS

Statement	*Not at all*	*A little bit*	*Some-what*	*Quite a bit*	*Very much*
35. I have been short of breath	0	1	2	3	4
36. I am self-conscious about the way I dress	0	1	2	3	4
37. My arms are swollen or tender	0	1	2	3	4
38. I feel sexually attractive	0	1	2	3	4
39. I have been bothered by hair loss	0	1	2	3	4
40. I worry about the risk of cancer in other family members	0	1	2	3	4
41. I worry about the effect of stress on my illness	0	1	2	3	4
42. I am bothered by a change in weight	0	1	2	3	4
43. I am able to feel like a woman	0	1	2	3	4

44. Looking at the above 9 questions, how much would you say your **ADDITIONAL CONCERNS** affects your quality of life? . . . . . .
(Circle one number)

1 2 3 4 5 6 7 8 9 10

Not at all <----------> Very much so

I.D. _____

In this section you will be asked about your **symptoms**. Please indicate to what extent you have been bothered by each of the symptoms **during the past week**, by **CIRCLING** THE ANSWER MOST APPLICABLE TO YOU.

Have you, during the past week, been bothered by

lack of appetite	not at all	a little	quite a bit	very much
irritability	not at all	a little	quite a bit	very much
tiredness	not at all	a little	quite a bit	very much
worrying	not at all	a little	quite a bit	very much
sore muscles	not at all	a little	quite a bit	very much
depressed mood	not at all	a little	quite a bit	very much
lack of energy	not at all	a little	quite a bit	very much
low back pain	not at all	a little	quite a bit	very much
nervousness	not at all	a little	quite a bit	very much
nausea	not at all	a little	quite a bit	very much
desperate feelings about the future	not at all	a little	quite a bit	very much
difficulty sleeping	not at all	a little	quite a bit	very much
headaches	not at all	a little	quite a bit	very much
vomiting	not at all	a little	quite a bit	very much
dizziness	not at all	a little	quite a bit	very much
decreased sexual interest	not at all	a little	quite a bit	very much
tension	not at all	a little	quite a bit	very much
abdominal aches	not at all	a little	quite a bit	very much
anxiety	not at all	a little	quite a bit	very much
constipation	not at all	a little	quite a bit	very much
diarrhea	not at all	a little	quite a bit	very much
heartburn/belching	not at all	a little	quite a bit	very much
shivers	not at all	a little	quite a bit	very much
tingling hands or feet	not at all	a little	quite a bit	very much
difficulty concentrating	not at all	a little	quite a bit	very much
sore mouth/pain when swallowing	not at all	a little	quite a bit	very much
loss of hair	not at all	a little	quite a bit	very much
brining/sore eyes	not at all	a little	quite a bit	very much
shortness of breath	not at all	a little	quite a bit	very much
dry mouth	not at all	a little	quite a bit	very much

ID #: _____

Now we'd like to ask you about how coming to Georgetown for chemotherapy affects you.

Please **circle the one** most appropriate answer
for each of the following questions.

1. How did you get to Georgetown for your chemotherapy? (Circle one)

Personal car, either drove self or brought by friend or relative	1
Taxi cab	2
Public transportation (bus, train, Metro subway; etc.)	3
Hospital/clinic supplied transportation	4
Walked	5
Community-based organization supplied transportation (including church, shelter, senior citizens center; etc.)	6
Other (Please write in what this was):	77
Do not want to answer	99

2. Are you employed outside of the home? (Circle one)

Yes **(PLEASE GO TO QUESTION 3.)**	1
No **(PLEASE GO TO QUESTION 5.)**	2
Do not want to answer	99

3. Did you take off from work to come to Georgetown for your chemotherapy infusion? (Circle one)

Yes **(PLEASE GO TO QUESTION 4.)**	1
No **(PLEASE GO TO QUESTION 5.)**	2
Do not want to answer	99

4. Will you receive compensation for your time off work, such as personal leave, sick time, or vacation time? (Circle one)

Yes	1
No	2
Do not want to answer	99

ID #: _____

5. Did you need to arrange for child care / spouse or parent care while here getting your chemotherapy? (Circle one)

Yes	1
No	2
Do not want to answer	99

6. How much total time did you spend traveling from your home to Georgetown for your chemotherapy? (Circle one)

<10 minutes	1
10-29 minutes	2
30-59 minutes	3
One hour or more	4
Don't know / unsure	88
Do not want to answer	99

7. Once you got here, how much time did you spend getting your chemotherapy, including waiting time? (Circle one)

0 to just under 2 hrs	1
2 to just under 4 hrs	2
4 to just under 6 hrs	3
6 to just under 8 hrs	4
> 8 hrs	5
Don't know / unsure	88
Do not want to answer	99

ID #: _____

Here are some questions about your visit(s) to the Georgetown chemotherapy infusion clinic, and the treatment you received here. In terms of your **satisfaction**, how would you rate each of the following:

8. Your visit(s) to the Georgetown chemotherapy infusion clinic **overall**? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

9. The **technical skills** (thoroughness, carefulness, competence) of the clinic staff? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

10. The **personal manner** (courtesy, respect, sensitivity, friendliness) of the clinic staff? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

ID #: _____

11. **Convenience** of getting your chemotherapy at Georgetown? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

12. Length of **time spent waiting for and getting** your chemotherapy? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

13. **Explanation** of what was done for you? (Circle one)

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5
Don't know / unsure	88
Do not want to answer	99

ID#: _____

Georgetown University Medical Center
Lombardi Cancer Center

Resource Utilization Survey - Outpatient

We would like to ask you a few questions about any outpatient visits that you had since your last visit here.

Since your last visit, have had an outpatient visit to a hospital, clinic, or emergency room?
Yes ☐ No ☐

If yes, please complete the following for **each** visit. If you need additional forms, the study coordinator (Barbara Brogran) would be happy to get them for you.

Facility Name: _____

City, State: _____

Date of Visit (MM/DD/YY): _____

What was the reason or diagnosis for your visit? _____

_____

STUDY COORDINATOR USE ONLY - PLEASE LEAVE BLANK

Visit Diagnosis: _____

DRG Code: _____

ICD-9 Code: _____

Non-Admitted Emergency Room: Yes ☐ No ☐ # Visits_____

Physician Visits: Yes ☐ No ☐
- Oncologist # Visits_____
- Surgeon # Visits_____
- GP # Visits_____
- Other (specify)_____ # Visits_____

ID#: _____

OUTPATIENT VISITS - CONTINUED

Other Professional Services: Yes ☐ No ☐

- Physical Therapist # Visits_____
- Psychologist/Social Worker # Visits_____
- Other (specify)_____ # Visits_____

Diagnostic Tests: Yes ☐ No ☐

- EKG # Times_____
- CT Scan # Times_____
- Bone Scan # Times_____
- MRI # Times_____
- Other (specify)_____ # Times_____

Procedures: Yes ☐ No ☐

- Chemotherapy # Times_____
- Transfusion # Times_____

Other Therapy (medications, etc.)

_____

_____

_____

ID#: _____

Georgetown University Medical Center
Lombardi Cancer Center

Resource Utilization Survey - Inpatient

We would like to ask you a few questions about any hospitalizations you had since your last visit here.

Since your last visit, have you been admitted to a hospital? Yes ☐ No ☐

If yes, please complete the following for **each** hospitalization. If you need additional forms, the study coordinator (Barbara Brogran) would be happy to get them for you.

Hospital Name: _____

City, State: _____

Date of Admission (MM/DD/YY): _____

Date of Discharge (MM/DD/YY): _____

What was the reason or diagnosis for your admission? _____

_____

STUDY COORDINATOR USE ONLY - PLEASE LEAVE BLANK

Transportation to Hospital: Ambulance ☐ Other (specify) _____ ☐

Discharge Diagnosis: _____ Length of Stay (days): _____

DRG Code: _____

ICD-9 Code: _____

ID#: _____

INPATIENT HOSPITALIZATION - CONTINUED

Services

Emergency Room (# hours): _____

Medical/Surgical unit (# days): _____

Intensive Care (#days): _____

Intermediate Care (# days): _____

Other (specify):_____ _____

Surgical Procedures:

_____

_____

_____

Physician Services:

Oncologist (# visits): _____

Surgeon (# visits): _____

Other (specify)_____ _____

Other Institutional Admission:

Rehab/Recuperative: Yes ☐ No ☐

Nursing Home: Yes ☐ No ☐

Other (specify)_____ Yes ☐ No ☐

If yes to above: Admission Date (MM/DD/YY): _____

Discharge Date (MM/DD/YY): _____

CORE #2: CANCER CLINICAL AND ECONOMIC OUTCOMES EVALUATIONS CORE

APPENDIX 5:
CORE ADVISORY COMMITTEE MEETING AGENDA

GEORGETOWN UNIVERSITY MEDICAL CENTER
LOMBARDI CANCER CENTER

CANCER CLINICAL AND ECONOMICS OUTCOMES CORE

ADVISORY COMMITTEE MEETING

MONDAY, MARCH 17, 1997

Funded by the Department of Defense Breast Cancer Center Support Grant

DOD ADVISORY COMMITTEE MEETING
MARCH 17, 1997

Agenda

10:00 - 10:15	Welcome
10:15 - 10:30	Introduction
10:30 - 10:45	Overview of Mission and Role of Advisors
10:45 - 11:45	Project Review: BRCA1/2 Testing PI Summary Core Role in Project Discussion Issues
11:45 - 12:30	Lunch
12:30 - 1:15	Project Review: Antioangiogenic Therapies in Metastatic Breast Cancer PI Summary Core Role in Project Discussion Issues
1:15 - 2:00	Project Review: Coordinated Approach to Diagnosing Breast Cancer PI Summary Core Role in Project Discussion Issues
2:00 - 2:15	Break
2:15 - 2:45	Core Outcomes Library
2:45 - 3:00	Wrap-Up

CORE #2: CANCER CLINICAL AND ECONOMIC OUTCOMES EVALUATIONS CORE

APPENDIX 6:
QUALITY OF LIFE LIBRARY CONTENTS

Core #2: Cancer Clinical and Economic Outcomes Core:
Core Library Titles:

Bodenheimer TS, Grumbach K. *Understanding Health Policy - A Clinical Approach.* Appleton & Lange: Stamford, Connecticut, 1995.

Breitbart W, Holland JC, eds. *Handbook of Measures for Psychological, Social and Physical Function in Cancer. Volume II: Cognitive Impairment Disorders.* Memorial Sloan-Kettering Cancer Center, New York, NY, 1996.

Drummond MF, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes.* Oxford University Press, 1987.

Duggar B, DeLozier J, Goldenberg D, et al. *Understanding and Choosing Clinical Performance Measures for Quality Improvement: Development of a Typology.* Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, January 1995.

Feasley JC, ed. *Health Outcomes for Older People: Questions for the Coming Decade.* National Academy Press, Washington, D.C., 1996.

Fowler FJ, Jr. *Improving Survey Questions. Design and Evaluation.* Applied Social Research Methods Series, Vol. 38. Sage Publications, 1995.

Gold MR, Siegel JE, Russell LB, Weinstein MC, eds.. Cost-Effectiveness in Health and Medicine. Oxford University Press: New York, 1996

Goldberg HI, Cummings MA, co-eds. *Conducting Medical Effectiveness Research: A Report From the Inter-PORT Work Groups.* Medical Care, July 1994, Vol. 32, No. 7. J.B. Lippincott Company, Philadelphia.

Haddix A, Teutsch S, Shaffer P, Duriet D, Churchill E, eds.. *A Practical Guide to Prevention Effectiveness: Decision and Economic Analyses.* U.S. Department of Health and Human Services, U.S. Public Health Service, Center for Disease Control and Prevention: Atlanta, GA, 1993.

Hadorn DC. Outcomes Management and Resource Allocation: *How Should Quality of Life be Measured?* HPRU 93:7D; Centre for Health Services and Policy Research: Vancouver, B.C. Canada, July 1993.

Luce BR, Simpson K. *Methods of Cost Effectiveness Analysis: Areas of Consensus and Debate.* Battelle Medical Technology Assessment and Policy (MEDTAP) Research Center: Washington, D.C., 1993

Kamlet MS. *The Comparative Benefits Modeling Project. A Framework for Cost-Utility Analysis of Government Health Care Programs*. U.S. Department of Health and Human Services, Public Health Service, 1992.

Keeney RL, Raiffa H. *Decisions with Multiple Objectives. Preferences and Value Tradeoffs*. Cambridge University Press, 1993.

Kornblith AB, Holland JC, eds. *Handbook of Measures for Psychological, Social and Physical Function in Cancer. Volume I: Quality of Life*. Memorial Sloan-Kettering Cancer Center, NewYork, New York, 1994.

McCormick KA, Moore SR, Siegel RA, eds. *Clinical Practice Guideline Development. Methodology Perspectives*. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, November 1994.

McDowell I, Newell C. *Measuring Health. A Guide to Rating Scales and Questionnaires.* Oxford University Press: New York, 1996.

Patrick DL, Erickson P. *Health Status and Health Policy. Allocating Resources to Health Care*. Oxford University Press, 1993.

Petitti DB. *Meta-Analysis Decision Analysis and Cost-Effectiveness Analysis. Methods for Quantitative Synthesis in Medicine*. Oxford University Press, 1994.

Plous S. *The Psychology of Judgment and Decision Making*. McGraw-Hill, Inc., 1993.

Schoenbaum SC, Sundwall DN, Bergman D, et al. *Using Clinical Practice Guidelines to Evaluate Quality of Care, Volume 2 Methods*. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, March 1995.

Spilker B, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*. Lippincott-Raven: Philadelphia, 1996.

Stewart AL, Ware JE, Jr., eds. *Measuring Functioning and Well-Being. The Medical Outcomes Study Approach*. Duke University Press, 1992.

Streiner DL, Norman GR. *Health Measurement Scales. A Practical Guide to Their Development and Use*. Oxford University Press, 1995.

Tchekmedyian NS, Cella DF, Winn RJ. *Economic and Quality of Life Outcomes in Oncology*. Oncology November 1995, Vol. 9, No. 11(Supplement).

U.S. Congress, Office of Technology Assessment, *Tools for Evaluating Health Technologies: Five Background Papers*, BP-H-142 (Washington, D.C.: Government Printing Office, February 1995).

Ware JE, Jr., Snow KK, Kosinski M, Gandek B. *SF-36 Health Survey. Manual and Interpretation Guide*. Nimrod Press, Boston, Massachusetts, 1993.

CD-ROMs

Center for Cost and Financing Studies (CCFS) and Agency for Health Care Policy and Research (AHCPR). *Projected NMES Data/1995*. Issued May 1996

National Cancer Institute. SEER 1973-1993 Public Use CD-ROM Revised. U.S. Department of Health and Human Services: Bethesda, MD, 1997.

Tamburini M. *Quality of Life Assessment in Medicine*. GLAMM Interactive, 1997.

U.S. Congress, Office of Technology Assessment. *OTA Legacy 1972 through 1995*.

Journals: Present and Planned

American Journal of Public Health
Health Economics
JAMA
Journal of Clinical Epidemiology
Medical Care
Medical Decision Making
Quality of Life Research

CORE #2: CANCER CLINICAL AND ECONOMIC OUTCOMES EVALUATIONS CORE

APPENDIX 7:
CORE CONSULTATIONS

CCEOC CONSULT REPORT

Consultant(s): Caroline B. Burnett, RN, ScD

Investigators(s): Barbara Brogan, RN, MS, (Research Nurse, Lombardi)

Date: 8/21/97 --1 hour

Funding mechanism: none

Reason for consultation: assist with development of pilot study

Service provided: design and development of research questions; preliminary discussions on how to approach topic of decision-making for breast cancer patients to have or not to have newly FDA approved biomarkers.

Time required: available to assist in future should she decide to pursue this study

Other resources:

Potential for funding for investigator:n/a

Potential for future grant support for core: possible if we get a group of interested individuals together as a working group on issues related to decision-making

Comments:

CCEOC CONSULT REPORT

Consultant(s): Caroline B. Burnett, RN, ScD

Investigators(s): Dan Hayes, MD

Date: 7/18, 8/4, 9/8

Funding mechanism: none

Reason for consultation: explore mutual interest in decision-making and QOL for patients with breast cancer

Service provided: Contacted Dr Nancy Avis, New England Research Institute for possible collaboration in projects related to patient decision-making and entering clinical trials.

Time required: Three phone calls (approximately 5-15 minutes in length) review of materials (approximately 1 hour) and subsequent discussions with Dr. Hayes (30 minutes, in addition to above meetings)

Other resources: discussions with Dr. Bill Lawrence concerning "Core" response to these external requests.

Potential for funding for investigator: none at present

Potential for future grant support for core: future possibilities

Comments: believe that this contact provided Core with the opportunity to discuss how it might better position itself to be responsive to requests for collaboration both within LCC and externally.

CCEOC CONSULT REPORT

Consultant(s): Caroline B. Burnett, RN, ScD

Investigators(s): Jane Ingham, MD

Date: Meetings: 7/24 (1 hour), 7/30 (2 hours), 7/31 (½ hour), 8/1 (1 hour), 8/7 (1 hour), 8/20 (1 hour), 8/21 1 hour). Background work (5 hours); Reviewing letter of intent (3 hours); Total = 15 ½ hours)

Funding mechanism: Robert Wood Johnson Foundation

Reason for consultation: proposal development

Service provided: Contact community parties, provide background work on community-based models; review letter of intent drafts, organizational meetings to develop approaches to project

Time required: 15 ½ hours

Other resources: Consult with Dr. Bill Lawrence about cost effectiveness aspect for project

Potential for funding for investigator: none

Potential for future grant support for core: possible if invited by Robert Wood Johnson to submit proposal based on review of letter of intent

Comments: While this was a labor intensive effort, the possibility for future core involvement is strong and is an interest of CPC and investigators.

CCEOC CONSULT REPORT

Consultant(s): Caroline B. Burnett, RN, SCD

Investigators(s): Kate McGuire, RN, MS, OCN, Clinical Nurse Specialist, BMT

Date: 6/17, 7/23, 8/6 (1& ½ hour meetings)

Funding mechanism: Oncology Nursing Foundation

Reason for consultation: Research proposal development

Service provided: Advise on how to write proposal, methodology, instrumentation, analyses and possible funding opportunities

Time required: probable 3-5 hours additional to review proposal prior to submission

Other resources:

Potential for funding for investigator: no

Potential for future grant support for core: possible

Comments: Topic: exercise in the BMT patient; outcomes QOL, decreased length of stay; possible cost-effectiveness

CCEOC CONSULT REPORT

Consultant(s): Caroline B. Burnett, RN, ScD

Investigators(s): Ruth Foelber, RN, MS, OCN (Research Nurse---Lombardi)

Date: August , 1997 to date

Funding mechanism: I have assisted her in the submission of 2 School of Nursing "Seed" grants to study Decision-making Process in Patients Choosing (1 grant) and Not Choosing (2nd) to undergo BMT.

Reason for consultation: Grant, manuscript, and abstract preparation

Service provided: Assistance with study design, instrument development, pilot testing, focus groups

Time required: over past 12 months - average out 2-4 hours/month

Other resources:

Potential for funding for investigator: We are targeting a grant submission for 1998. Possible co-investigator **(although, I can't take salary at this time)**

Potential for future grant support for core: Since I envision that this exploratory work will lead to an intervention study, outcomes will be QOL, coping and possible some cost-effectiveness analyses. Considering either Oncology Nursing Foundation grant submission or responding to PA from National Institutes of Nursing Research.

Comments:

CCEOC CONSULT REPORT

Consultant(s): WF Lawrence

Investigators(s): Jane Ingham MD

Date: 8/97

Funding mechanism: Robert Wood Johnson Foundation Palliative Care Program

Reason for consultation: Assistance with providing economic evaluation for a trial of a community-based palliative care program.

Service provided: Assistance with study design, consideration of QOL measurement. Helped put study in a framework amenable to cost-utility evaluation.

Time required: 1 hour consult.

Other resources:

Potential for funding for investigator: for letter of intent to RWJ. Could get a proposal out of it

Potential for future grant support for core: Same

Comments:

CCEOC CONSULT REPORT

Consultant(s): WF Lawrence

Investigators(s): Vered Stearns, MD, Oncology Fellow

Date: 6-7/97

Funding mechanism: Internal GUMC

Reason for consultation: Assistance in measuring QOL and hot-flash symptoms in a trial of Paxil for hot flashes in women with breast cancer.

Service provided: Assistance with study design, participant inclusion criteria. Refined hot flash questionnaire. Provided QOL measures including rating scale, CESD, Julia's post-menopausal sx index (Julia - does this have a name?), MOS sleep and sexual function scales. Some advice on statistical analysis.

Time required: WFL - 7 hours, as of 7/7/97
Julia Rowland - ?

Other resources:

Potential for funding for investigator: Pilot study. Could be future R01 if pilot successful.

Potential for future grant support for core: Same

Comments:

CCEOC CONSULT REPORT

Consultant(s): Julia Rowland

Investigators(s): Site PI: Daniel Hayes, M.D.

Date: 2/8/97 - 9/12/97

Funding mechanism: CALGB Cooperative Trial

Reason for consultation: Review of protocol designed to assess the Long Term Psychological Adaptation of Survivors of Breast Cancer Treatment by Adjuvant Chemotherpy Fifteen Years Ago

Service provided: Protocol was reviewed with respect to how the QOL assessments would be done and, if needed, for whom and how referrals for additional psychological intervention would be handled in general, and in particular at this site. In addition, followup was provided to ensure that all questions raised had been answered by the study investigators and that the protocol was approved and activated at Georgetown.

Time required: Julia Rowland - 4 hours as of 9/12/97

Other resources:

Potential for funding for investigator: Our ability to participate in this study supports the center's ability to maintain full membership in CALGB.

Potential for future grant support for core:

Comments:

CCEOC CONSULT REPORT

Consultant(s): Julia Rowland, WFL ?

Investigators(s): PI: Ken Meehan, M.D., Bone Marrow Transplant Oncologist; Co-Investigators: Ashraf Badros, M.D., Stanley Frankel, M.D., Daniel Hayes, M.D., Marc Lippman, M.D.

Date: 7/11-28/97

Funding mechanism: Phase III Multicenter Trial (Bill check the funding on this; cooperative group??)

Reason for consultation: Recommendations for QOL and cost components that could be incorporated in a Phase III Clinical Trial designed to compare STAMP V with or without IL-2 activated PSCT plus parenteral IL-2 for the Treatment of Breast Cancer.

Service provided: Review and recommendation of instruments and the timing of their assessment that might be used to collect demographic information and measure overall quality of life (FACT-B plus 2 EORTC summary QOL questions) , symptoms (Memorial Symptom Assessment Scale and/or BCPT Symptom Checklist) and support systems (MOS-Social support scale or the ISEL: Interpersonal Support Evaluation List).

Time required: Julia Rowland - 3 hours as of 7/28/97

Other resources:

Potential for funding for investigator: ???

Potential for future grant support for core: ???

Comments:

CCEOC CONSULT REPORT

Consultant(s): WFL, Julia Rowland

Investigators(s): Vered Stearns, Oncology Fellow

Date: 6-7/97

Funding mechanism: Internal GUMC

Reason for consultation: Assistance in measuring QOL and hot-flash symptoms in a trial of Paxil for hot flashes in women with breast cancer.

Service provided: Assistance with study design, participant inclusion criteria. Refined hot flash questionnaire. Provided QOL measures including rating scale, CESD, Julia's post-menopausal sx index (Julia - does this have a name?), MOS sleep and sexual function scales. Some advice on statistical analysis.

Time required: WFL - 7 hours, as of 7/7/97
Julia Rowland - ?

Other resources:

Potential for funding for investigator: Pilot study. Could be future R01 if pilot successful.

Potential for future grant support for core: Same

Comments:

CORE #2: CANCER CLINICAL AND ECONOMIC OUTCOMES EVALUATIONS CORE

APPENDIX 8:
CORE PUBLICATIONS AND GRANTS

Dollars May Not Buy as Many QALYs as We Think:

A Problem with Defining Quality-of-life Adjustments

DENNIS G. FRYBACK, PhD, WILLIAM F. LAWRENCE, Jr., MD

The scale of health state quality that should be used to compute quality-adjusted life years (QALYs) ranges from 0 (death) to 1.0 (excellent health); this is called the "Q" scale. But many cost–utility analyses (CUAs) in the literature use the upper anchor of the scale to denote only the *absence* of the particular health condition under investigation, and weight the disease state proportional to this endpoint; these are called "*q*" scales. Computations using *q*-scale health-state weights ignore the fact that the average patient is still subject to chronic and acute conditions comorbid with the condition being analyzed; the absence of a particular condition is *not* in general the same as excellent health, i.e., the Q scale is longer than a *q* scale. CUAs based on *q* scales yield 'qALYs." Incremental $/qALY ratios are generally lower than $/QALY ratios; in the example presented, $/qALY must be inflated by about 15% to yield $/QALY. Other CUAs correctly weight disease states using the Q scale, but erroneously assign a quality weight of 1.0 to absence of the disease in the CUA computations. The results of such analyses are called "NP-QALYs," as the correction factor to compute QALYs is not a simple proportional adjustment. The authors suggest that analysts doing cost–utility analyses without access to primary data from treated patients use average age-specific health-related quality-of-life weights from population-based studies to represent the state of not having a particular disease. Consumers of CUAs should closely examine the nature of the QALYs in any published analyses before making decisions based on their results. *Key words*: QALY; quality-adjusted life years; utility; quality-of-life assessment; cost–utility analysis; cost–effectiveness methodology. **(Med Decis Making 1997;17:276–284)**

Investigators performing cost–utility analyses typically report their primary results in terms of a ratio of incremental benefit of an intervention divided by its incremental cost. This ratio is denominated in dollars per quality-adjusted life year ($/QALY). Knowing the incremental $/QALY for a particular intervention can allow comparison with other medical interventions to understand relative cost-efficiencies of alternative uses for health care resources. For example, Goldman et al., discussing interventions to modify serum cholesterol levels, note:

> An incremental cost–effectiveness ratio below about $20,000 per additional quality-adjusted year of life is very attractive. . . . [R]atios between $20,000 and about $40,000 . . . are consistent with other currently funded programs, such as hemodialysis or the treatment of mild hypertension with diuretics or propranolol. . . . Incremental cost–effectiveness ratios between about $60,000 and $100,000 per additional quality-adjusted year of life are clearly higher than most currently accepted programs, whereas ratios above $100,000 are generally agreed to be unattractive.[1]

The special importance of cost–utility analysis (CUA) lies in the ability to make broad comparisons of the $/QALY ratio across a range of interventions for different conditions and in differing types of people, in order to infer whether the intervention at hand is a particularly expensive or an inexpensive way to "produce" health.

But we believe there is a methodologic problem with the way many investigators have computed

Received January 1, 1996, from the Department of Preventive Medicine (DGF) and the Department of Medicine (WFL Jr.), University of Wisconsin–Madison, Madison, Wisconsin. Revision accepted for publication September 5, 1996. Dr. Lawrence is now with the Department of Medicine, Georgetown University. Supported by grant HS-06491 from the Agency for Health Care Policy and Research.

Address correspondence and reprint requests to Dr. Fryback: Department of Preventive Medicine, 1300 University Avenue, Madison, WI 53706. e-mail: ⟨dfryback@facstaff.wisc.edu⟩.

Predicting Quality of Well-being Scores from the SF-36:

Results from the Beaver Dam Health Outcomes Study

DENNIS G. FRYBACK, PhD, WILLIAM F. LAWRENCE, MD, MSIE, PATRICIA A. MARTIN, MA, RONALD KLEIN, MD, MPH, BARBARA E. K. KLEIN, MD, MPH

Background. The SF-36 and the Quality of Well-being index (QWB) both quantify health status, yet have very different methodologic etiologies. The authors sought to develop an empirical equation allowing prediction of the QWB from the SF-36. *Data.* They used empirical observations of SF-36 profiles and QWB scores collected in interviews of 1,430 persons during the Beaver Dam Health Outcomes Study, a community-based population study of health status, and 57 persons from a renal dialysis clinic. *Method.* The eight scales of the SF-36, their squares, and all pairwise cross-products, were used as candidate variables in stepwise and best-subsets regressions to predict QWB scores using 1,356 interviews reported in a previous paper. The resulting equation was cross-validated on the remaining 74 cases and using the renal dialysis patients. *Results.* A six-variable regression equation drawing on five of the SF-36 components predicted 56.9% of the observed QWB variance. The equation achieved an R^2 of 49.5% on cross-validation using Beaver Dam participants and an R^2 of 58.7% with the renal dialysis patients. An approximation for computing confidence intervals for predicted QWB mean scores is given. *Conclusion.* SF-36 data may be used to predict mean QWB scores for groups of patients, and thus may be useful to modelers who are secondary users of health status profile data. The equation may also be used to provide an overall health utility summary score to represent SF-36 profile data so long as the profiles are not severely limited by floor or ceiling effects of the SF-36 scales. The results of this study provide a quantitative link between two important measures of health status. *Key words*: health status; SF-36; Quality of Well-being index; quality of life; health-state utility; population study. **(Med Decis Making 1997;17:1–9**

The cost–effectiveness and medical-technology-assessment literatures are increasingly using changes in quality-adjusted life years (QALYs) and quality-adjusted life expectancy (QALE) as the denominations of health outcomes.[1] Even a casual glance through this literature reveals many modeling studies that make secondary use of previously published data about qualities of life in various health states to compute QALYs and QALE. (For example, Wong et al.[2] develop a computational model for QALE citing data from Pliskin et al.[3])

But not all published data about health-related quality of life (HRQL) are collected using measures suitable for QALY and QALE analyses. Broadly speaking, HRQL measures can be fit into a three-way classification.[4] They may be classified as generic, measuring all important aspects of health and applicable across all health conditions, or specific, applying only to patients with a specific disease or condition. Generic instruments can be further classified as health profiles or utility measures. Health profiles

Received June 22, 1995, from the Departments of Preventive Medicine (DGF, PAM), Medicine (WFL), and Ophthalmology (RK, BEKK), the University of Wisconsin–Madison. Revision accepted for publication March 4, 1996. Supported by grant HS-06491 from the Agency for Health Care Policy and Research. An earlier version of this paper was presented at the annual scientific meeting of the Society for Medical Decision Making, October 1992.

Address correspondence and reprint requests to Dr. Fryback: Department of Preventive Medicine, 109 Bradley Memorial Hospital, 1300 University Avenue, Madison, WI 53706. e-mail: ⟨dfryback@facstaff.wisc.edu⟩.

Cost-Effectiveness in Health and Medicine

Edited by

MARTHE R. GOLD
U.S. Public Health Service

JOANNA E. SIEGEL
U.S. Public Health Service

LOUISE B. RUSSELL
Rutgers University

MILTON C. WEINSTEIN
Harvard University

New York Oxford
OXFORD UNIVERSITY PRESS
1996

1

Cost-Effectiveness Analysis as a Guide to Resource Allocation in Health: Roles and Limitations

L.B. RUSSELL, J.E. SIEGEL, N. DANIELS,
M.R. GOLD, B.R. LUCE and J.S. MANDELBLATT

Cost-effectiveness analysis (CEA) is a method used to evaluate the outcomes and costs of interventions designed to improve health. It has been used to compare costs and years of life gained for such interventions as screening for breast cancer (Eddy, 1989), bypass surgery for coronary artery disease (Weinstein and Stason, 1982), and vaccination against pneumococcal pneumonia (Willems et al., 1980). The results of an analysis are usually summarized in a series of cost-effectiveness ratios that show the cost of achieving one unit of health outcome—for example, the cost per year of life gained—for different kinds of patients and variations of the intervention (Table 1.1).

By providing estimates of outcomes and costs, CEA shows the tradeoffs involved in choosing among interventions or variants of an intervention. Put another way, it helps define and illuminate the "opportunity cost" of each choice: the health benefits lost because the next-best alternative was not selected. It thus gives decision makers in diverse settings—physicians' offices, health maintenance organizations (HMOs), or state or federal programs—important data for making informed judgments about interventions.

When the same measure of health outcome, such as years of life gained or cases of a particular disease prevented, is used for all interventions, they can be ranked on the basis of their cost-effectiveness ratios. Those with the lowest cost per year or per case are the most efficient ways of improving health; the ratios show which interventions produce the most years of life, or prevent the most cases of disease, for a given expen-

A utility maximization model for eval
7:118–33.
R. Barr. 1992. *Multi-attribute preference*
fication system. Working Paper No. 92
entre for Health Economics and Policy
ess of antepartum prevention of Rh im-
Weinstein. 1990. Cost-effectiveness of
eoporisis: Bone-densitometry and hor-
594–603.
games and economic behavior. Prince-
m short-form health survey. *Med Care*
. Weinstein. 1994. The Q-tility Index:
f life and utilties in clinical trials and
ciety of Clinical Oncology 13:436 (ab-
—or is it? *J Health Economics* 7:289–
iveness of hormone replacement. *Ann*
efits, risks, and costs of immunization
lth 75:739–44.
health: A chronicle. Discussion Paper
mics, University of York.
QALY calculations. Discussion Paper
mics, University of York.
ever too old. *N Engl J Med* 328:971–

5

Assessing the Effectiveness of Health Interventions

J.S. MANDELBLATT, D.G. FRYBACK,
M.C. WEINSTEIN, L.B. RUSSELL, M.R. GOLD, and
D.C. HADORN

Cost-effectiveness analysis (CEA) requires a numerical estimate of the magnitude of the effects of an intervention on health outcomes. The denominator of a cost-effectiveness (C/E) ratio is the difference in effectiveness between an intervention and the alternative to which it is being compared (the net effect), just as the numerator is the difference in cost between the two (the net cost). To estimate the net effect of an intervention, the analyst needs to know the health states that may occur as a consequence of the intervention and the alternative, the probability that each state will occur, when each is likely to occur, and how long each will last. These health states turn on the sequence of events and consequent decisions that take place during or following the intervention and the condition the intervention is intended to treat (or prevent). For example, screening may detect a condition, and treatment may alter it. If the treatment is successful it will alter the condition for the better, but it may also bring undesirable side effects. Screening, treatment, and their immediate and delayed direct effects and side effects comprise a connected chain of events that must be taken into account to assess the overall net effect in this example.

A complete and careful description of the cascade of events emanating from the decision to intervene (or to engage in prevention activities) is fundamental to cost-effectiveness analysis. Appropriate calculation of effectiveness—as well as costs—depends on it. Thus, it is critical that the analysis consider all events that change the health of the patient or that generate costs. Since CEA is a comparative analysis, similar care must be taken to describe the events and health consequences deriving from the alternative to which the intervention or program is being compared.

J Clin Epidemiol Vol. 49, No. 11, pp. 1239–1245, 1996
Copyright © 1996 Elsevier Science Inc.

ELSEVIER

0895-4356/96/$15.00
PII S0895-4356(96)00220-X

Health Status and Hypertension: A Population-Based Study

William F. Lawrence, Dennis G. Fryback, Patricia A. Martin, Ronald Klein, and Barbara E.K. Klein

DEPARTMENTS OF MEDICINE, PREVENTIVE MEDICINE, AND OPHTHALMOLOGY, UNIVERSITY OF WISCONSIN, MADISON, WISCONSIN

ABSTRACT. We describe the relation between self-reported hypertension and measures of health-related quality of life (HRQOL) in a community-dwelling population. In a cross-sectional study, 1430 randomly selected adults, aged 45 to 89 years, were interviewed to obtain a medical history and health status measures, including the SF-36 questionnaire, the Quality of Well Being (QWB) index, and time trade-off (TTO) assessments. A total of 519 participants reported being affected by hypertension (HTN group). The HTN group, compared to the No HTN group, had significantly lower age-adjusted health status scores measured by the General Health (GH) scale of the SF-36 and by TTO, with differences between groups for each measure comprising approximately 5% of the total scale. HTNs also had a significant decline in general health status measures associated with increasing numbers of antihypertensive medications but not with specific classes of medications. We conclude that hypertension and hypertension drug therapy are associated with clinically meaningful decreases in reported health status. J CLIN EPIDEMIOL 49;11:1239–1245, 1996.

KEY WORDS. Health status, quality of life (health-related), hypertension, antihypertensive agents, population study, cross-sectional study

INTRODUCTION

It is difficult to make the asymptomatic patient feel better.
Hoerr's Law [1]

Clinicians often have to deal with trade-offs between quality of life and quantity of life when making decisions in diagnosis and therapy. Hypertension, especially in mild to moderate stages, is usually considered an asymptomatic condition. Treatment of hypertension, particularly with pharmacologic therapy, may be associated with adverse effects that potentially make an asymptomatic person symptomatic. Detection of hypertension may subject people to a labeling effect; people who are otherwise "healthy" now have an "illness." Several studies have shown that the diagnosis of hypertension was associated with increased absenteeism from work due to illness [2], and with increased number of visits to physicians [3]. Avoiding adverse effects in treating an asymptomatic condition can be difficult, as S. O. Hoerr has noted. Thus diagnosis and treatment of hypertension potentially involve balancing a decreased future risk of cardiovascular morbidity and mortality with a decreased current health-related quality of life. As many as 50 million people in the United States either have an elevated blood pressure or are taking antihypertensive medications [4]; given the frequency of this condition, it is important that clinicians and researchers understand that the impacts of hypertension and hypertension therapy are on quality of life.

Address reprint requests to: William Lawrence, Section of General Internal Medicine, Department of Medicine, J5/210 CSC, University of Wisconsin Hospitals and Clinics, 600 Highland Ave., Madison, Wisconsin 53792.

This paper was presented in part at the Sixteenth Annual Meeting of the Society of General Internal Medicine, Arlington, Virginia, April 1993, and at the Fifteenth Annual Meeting of the Society for Medical Decision Making, Research Triangle Park, North Carolina, October 1993.

Accepted for publication on 30 April 1996.

While the long-term benefits of treating hypertension have been extensively studied, the effects of hypertension diagnosis and treatment are not as well known. Several randomized clinical trials of antihypertensive medications have examined health and functional status measures [5–13]. While these studies have been helpful in comparing health status effects of specific antihypertensive medications, most tend to be relatively short-term studies, and may not reflect clinical practice well due to the necessities of study design. The Medical Outcomes Study examined the cross-sectional changes in health status associated with hypertension [14], showing a lower general health perception score in hypertensives compared to those with no chronic conditions. Since the Medical Outcomes Study was based on patients visiting physicians' offices, it may have been subject to selection bias.

The Beaver Dam Health Outcomes Study (BDHOS) represents a unique opportunity to understand further the effects of diagnosis and treatment of hypertension on health-related quality of life (HRQOL). The BDHOS is a population-based epidemiologic study that evaluates the health status of randomly selected adults over age 45 years in Beaver Dam, Wisconsin [15]. Health status is measured using two widely used health questionnaires, as well as a preference-based assessment technique to measure overall HRQOL. We observed the relationship between hypertension diagnosis and therapy on HRQOL within this community, where adults with hypertension are likely to have had this condition on a relatively long-term basis, allowing them time to adjust and accommodate to their hypertension and to their antihypertensive medications. We hypothesized that the diagnosis and treatment of hypertension in this cohort would be associated with lower health status.

METHODS

Participant Selection

The protocol for the BDHOS is described in detail elsewhere [15]. Briefly, the BDHOS draws from the cohort of participants in the

Public Health Benefit of Prescription vs Over-the-Counter Nicotine Transdermal Patch Therapy for Smoking Cessation

William F. Lawrence[1,2,3], Stevens S. Smith[1,4], Timothy B. Baker[1,4], and Michael C. Fiore[1,2]

[1]Center for Tobacco Research and Intervention, University of Wisconsin Medical School

[2]Division of General Internal Medicine, Department of Medicine, University of Wisconsin Medical School

[3]Currently at: Cancer Clinical and Economic Outcomes Core, Lombardi Cancer Center, Georgetown University Medical Center

[4]Department of Psychology, University of Wisconsin-Madison

Address Correspondence and Reprint Requests to:

Michael C. Fiore, M.D., M.P.H.
Center for Tobacco Research and Intervention
University of Wisconsin Medical School
7275 Medical Sciences Center
1300 University Avenue
Madison, WI 53706
608-262-8673 / FAX 265-3102

Abstract = 174 words; Text = 1900 words; 4 Tables; 2 Figures

Funding: This study was funded by a grant from SmithKline Beecham. Dr. Lawrence is supported in part by Contract DAMD 17-96-C-6069, "Breast Cancer Support Contract," from the Department of the Army.

Abstract

Purpose: To determine the public health benefits of making nicotine transdermal patches available without prescription.

Methods: A decision-analytic model was created to compare over-the-counter (OTC) vs. prescription (Rx) availability of nicotine patches. Outcomes for the U.S. adult smoking population were: long-term (6 month) quit rates, life expectancy, and smoking attributable mortality (SAM) rates.

Results: OTC availability of nicotine patches would result in 115,229 additional successful quitters over a 6 month period, and a cumulative total of approximately 1.5 million additional quitters over 19 years. All cause SAM would decrease by 442 deaths/year and 3,627 deaths/year at 6 months and 5 years, respectively. Relative to Rx patch availability, OTC availability would result in an average gain in life expectancy across the entire adult smoking population of 0.144 years per smoker. In sensitivity analyses, the benefits of OTC availability were evident across a wide range of changes in baseline parameters.

Conclusions: Compared to Rx availability of nicotine patches, OTC availability would result in more successful quitters, fewer smoking-attributable deaths, and increased life expectancy for current smokers.

Keywords: Smoking cessation, public health, nicotine replacement therapy, decision analysis

The Costs and Effects of Cervical and Breast Cancer Screening in a Public Hospital Emergency Room

Jeanne Mandelblatt, MD, MPH, Harold Freeman, MD, Deidre Winczewski, MA, Kate Cagney, MA, Sterling Williams, MD, Reynold Trowers, MD, Jian Tang, MA, Karen Gold, PhD, Ting Hsiang Lin, PhD, and Jon Kerner, PhD, with the Cancer Control Center of Harlem

Objectives. This study assessed the cost-effectiveness of cervix and breast cancer screening in a public hospital emergency room.

Methods. Age-eligible women with nonurgent conditions and without recent screening were offered screening by a nurse. A decision analysis compared the costs and outcomes of emergency room screening and standard hospital screening efforts.

Results. The undiscounted cost-effectiveness results for establishing new programs were $4050 (cervical cancer), $403 203 (breast cancer), and $4375 (joint cervix and breast cancer) per year of life saved. If screening is added to an existing program, results are more favorable ($429, $21 324, and $479 per year of life saved for cervix, breast, and joint screening, respectively). Results were most sensitive to volume and probability of receiving treatment after an abnormal screen.

Conclusions. Emergency room screening was cost-effective for cervical cancer; breast cancer screening was relatively expensive given the low number of women reached. More intensive recruitment and follow-up strategies are needed to maximize the cost-effectiveness of such programs. (*Am J Public Health.* 1997;87:1182–1189)

Introduction

Minority women and women of low socioeconomic status are often not reached by traditional cancer screening programs[1,2]; many of these women lack regular access to health care providers and tend to rely on emergency rooms for their primary care.[3–9] As a result, the emergency department has recently served as a site for a variety of prevention activities targeted to high-risk groups.[10–16] Thus far, the costs and yields of such demonstration programs have not been evaluated. We report the results of implementing cervical and breast cancer screening in an urban public hospital emergency room serving a low-income minority population.

Methods

The costs and effects of opportunistic emergency room screening for cervical and/or breast cancer during visits for nonurgent conditions were compared with those seen in routine hospital screening efforts. A major objective was to evaluate the feasibility and costs of implementing similar emergency room programs in other public hospitals. Thus, the analyses considered the costs and outcomes from the perspective of the city health budget.[17]

Decision trees[18,19] were used to evaluate five possible decisions involved in emergency room screening: providing cervical cancer screening alone, adding cervical cancer screening services to an already established emergency room cancer screening program (i.e., excluding the costs of establishing the screening program in the emergency room), providing breast cancer screening alone, adding breast cancer screening to an existing program, and providing joint breast and cervix cancer screening. The results were discounted to reflect the different time frames of the expenditures relative to the benefits of lifesaving.

Screening Program

This project, funded by the National Cancer Institute and approved by the Institutional Review Board, offered screening from September 1, 1990, to July 31, 1992. Age eligibility followed the guidelines of the American Cancer Society during the study period (Pap smears: 18 years or older; mammography and clinical

At the time this study was conducted, Jeanne Mandelblatt and Jon Kerner were with the Department of Epidemiology and Biostatistics, Memorial-Sloan-Kettering Cancer Center, New York City. They are now with the Lombardi Cancer Center and the Institute for Health Care Policy and Research, Georgetown University School of Medicine, Washington, DC. Harold Freeman is with the Department of Surgery, Harlem Hospital Center, New York City. Deidre Winczewski, Kate Cagney, and Jian Tang are with the Department of Epidemiology and Biostatistics, Memorial-Sloan-Kettering Cancer Center. At the time this study was conducted, Sterling Williams was with the Department of Obstetrics and Gynecology, Harlem Hospital Center. He is now with the College of Physicians and Surgeons, Columbia University, New York City. Reynold Trowers is with the Division of Emergency Services, Department of Surgery, Harlem Hospital Center. Karen Gold and Ting Hsiang Lin are with the Department of Medicine, Georgetown University School of Medicine. The staff of the Cancer Control Center of Harlem is listed in the Acknowledgments.

Requests for reprints should be sent to Jeanne Mandelblatt, MD, MPH, Georgetown University Medical Center, Lombardi Cancer Center, 2233 Wisconsin Ave, Suite 535, Washington, DC 20007.

This paper was accepted January 10, 1997.

Reprint

FROM RESEARCH TO PRACTICE

Assessing the Effectiveness of Health Interventions for Cost-Effectiveness Analysis

Jeanne S. Mandelblatt, MD, MPH, Dennis G. Fryback, PhD, Milton C. Weinstein, PhD, Louise B. Russell, PhD, Marthe R. Gold, MD, MPH, and members of the Panel on Cost-Effectiveness in Health and Medicine

Cost-effectiveness analysis (CEA) is an analytic tool in which the costs and effects of an intervention designed to prevent, diagnose, or treat disease are calculated and compared with an alternative strategy to achieve the same goals. The results of a CEA are presented as a ratio of costs to effects, where the effects are health outcomes such as cases of disease prevented, years of life gained, or quality-adjusted life years gained, rather than monetary measures, as in cost-benefit analysis. Conducting a CEA requires a framework for portraying the cascade of events that occur as a consequence of the decision to intervene, for describing the probability that each event will occur, for accounting how long each event will last, and describing how much each event costs and is valued by the population or individuals targeted by the intervention. Mathematical models are well suited to these purposes.

The purpose of this article is to provide an overview of modeling to estimate *net* effectiveness in a CEA (the difference in effectiveness between an intervention and the alternative to which it is being compared). Many of the principles described for estimating effectiveness apply equally to determining costs in a CEA. The main difference is that health events are weighted by costs in the numerator of the cost-effectiveness ratio, while they are often weighted by preference values in the denominator. Preference values, or utilities, reflect the fact that individuals or populations with similar ability (or disability) to function may regard that level of functioning differently. When preferences are incorporated into CEAs, the results are generally expressed as costs per quality-adjusted life years.[1,2] A discussion of measurement of costs and valuing outcomes is beyond the scope of this article; for further information on these, and other components of a CEA, the reader is referred elsewhere.[3-5] Following some definitions of terms, this article is organized into two sections describing the process of estimating effectiveness in a CEA: the first presents a review of the sources of event probabilities, and the second describes the use of modeling to estimate effectiveness.

DEFINITIONS

Effectiveness, which reflects the impact of an intervention of health in real practice settings, should be distin-

From Research to Practice, *a Journal series, presents articles to heighten the clinician's awareness of research and methodology issues that have direct relevance to practice. If you wish to submit a manuscript for consideration for this series, please contact Cynthia D. Mulrow, MD, MSc, Associate Editor, at mulrow@uthscsa.edu, or contact the* Journal of General Internal Medicine *at (215) 823-4471 to receive the appropriate guidelines.*

Received from the Department of Medicine, Lombardi Cancer Center (Cancer Clinical and Economic Outcomes Core) and the Institute for Health Care Policy and Research, Georgetown University School of Medicine, Washington, DC (JSM); Departments of Preventive Medicine and Industrial Engineering, University of Wisconsin–Madison (DGF); Department of Health Policy and Management, Harvard School of Public Health, and Department of Medicine, Harvard Medical School, Boston, Mass. (MCW); Institute for Health, Health Care Policy, and Aging Research, and Department of Economics, Rutgers University, New Brunswick, NJ (LBR); and Community Health and Social Medicine, City University of New York Medical School, NY (MRG).

The Panel on Cost-Effectiveness in Health and Medicine was convened by the Office of Disease Prevention and Health Promotion. The work presented in this paper is the responsibility of the authors, and does not reflect the views of the U.S. Public Health Service.

Dr. Mandelblatt's work was supported, in part, by grant RO1 HS08395, "Care, Costs, and Outcomes of Breast Cancer in the Elderly," from the Agency for Health Care Policy and Research, and Contract DAMD17-96-C-6069, "Breast Cancer Center Support Contract," from the Department of the Army (the "Cancer Clinical and Economic Outcomes Core" is one of the projects funded by this contract).

Dr. Gold's work was conducted while she served as a Senior Policy Advisor in the Office of Disease Prevention and Health Promotion in the U.S. Public Health Service, Department of Health and Human Services, Washington, DC.

Address correspondence and reprint requests to Dr. Mandelblatt: Georgetown University School of Medicine, Lombardi Cancer Center, Cancer Clinical and Economic Outcomes Core, 2233 Wisconsin Ave., Suite 430, Washington, DC 20007.

Implementation of a Breast and Cervical Cancer Screening Program in a Public Hospital Emergency Department

Jeanne Mandelblatt, MD, MPH*
Harold Freeman, MD‡
Deidre Winczewski, MA*
Kate Cagney, MA*
Sterling Williams, MD§
Reynold Trowers, MD||
Jian Tang, MA*
Jon Kerner, PhD*
and the Cancer Control Center of Harlem

From the Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center; and the Department of Surgery‡, Department of Obstetrics and Gynecology§, and Division of Emergency Services, Department of Surgery||, Harlem Hospital Center, New York, New York.*

The Staff of the Cancer Control Center of Harlem included Mary Baird, RN; Stacey Bennett; Diana Godfrey, MA; Diane Kelly, RN; Leka Murdock; Elizabeth Nelson; Annette Nixon; David Smith; and Socorro Rios.

Received for publication March 4, 1996. Revision received June 28, 1996. Accepted for publication July 5, 1996.

Supported by National Cancer Institute grant RO1 CA 50520.

Copyright © by the American College of Emergency Physicians.

Study objective: To assess the feasibility and yields of screening for breast and cervical cancer in an urban public hospital emergency department.

Methods: Women who presented to the ED of a large, urban public hospital during the study period with nonurgent conditions were eligible for a Papanicolaou test (Pap smear) and a clinical breast examination (CBE) if they were 18 years of age or older, and for a mammogram if they were 40 years of age or older, provided they had not had the screening examination within the past year. The Pap smear and CBE were performed by a nurse, and mammography was scheduled for a later date. Women with gynecologic complaints were excluded.

Results: On the basis of screening history, medical status, and age, 1,850 (32%) of the 5,830 women seen in the ER during the 23-month study period were eligible for both mammography and CBE, and 2,361 (41%) were eligible for Pap smears. Of these women, 116 (6%) completed mammography and CBE, and 644 (27%) received Pap smears. Among screened women, 10 (9%) and 20 (3%), respectively, had results that were suspicious or positive for breast or cervical cancer. Follow-up rates were low: 20% for breast screening and 50% for Pap smears. Among those receiving follow-up, 1 woman was found to have breast cancer and 8 were found to have cervical neoplasia.

Conclusion: ED cancer screening was feasible and yielded a high rate of cancer detection. Program efficiency was hampered by low volume and high numbers of patients lost to follow-up after abnormal screening results. Greater integration into the acute care setting and more intensive recruitment and follow-up strategies are needed to maximize the potential yield and cost-effectiveness of such programs.

[Mandelblatt J, Freeman H, Winczewski D, Cagney K, Williams S, Trowers R, Tang J, Kerner J, and the Cancer Control Center of Harlem: Implementation of a breast and cervical cancer screen-

reprint

The Late-Stage Diagnosis of Colorectal Cancer: Demographic and Socioeconomic Factors

Jeanne Mandelblatt, MD, MPH, Howard Andrews, PhD, Richard Kao, MS, Rodrick Wallace, PhD, and Jon Kerner, PhD

ABSTRACT

Objectives. This study described factors related to colorectal cancer stage at diagnosis.

Methods. Logistic regression analyses were used on data from the New York State Tumor Registry and US Census area-level social class indicators.

Results. After the effects of other predictors were controlled for, the odds of late-stage cancer increased as age decreased; women and African Americans were significantly more likely to have late stage than men and Whites; and individuals living in areas of low socioeconomic status (SES) were significantly more likely to be diagnosed at late stage than those living in higher SES areas. Stratified analyses showed that living in a low SES area was the most important determinant of stage for all age, race, gender, and source-of-care groups.

Conclusions. While all populations would benefit from the systematic use of screening, socioeconomically disadvantaged groups may also benefit from targeted screening. (*Am J Public Health.* 1996;86:1794–1797)

Introduction

For several cancer sites, age,[1–3] race,[3,4–9] socioeconomic status (SES),[5,9–13] and insurance status[14] have been noted to be related to stage at diagnosis. Stage data are often readily available and correlate with survival. To date, few studies have examined predictors of colorectal cancer stage.[10,15] This paper presents findings on the effects of age, gender, race, ethnicity, type of health care setting, and area socioeconomic status on colorectal cancer stage. We attempt to delineate the pathways leading to having late-stage disease among persons diagnosed with colorectal cancer.

Methods

The sample consisted of 28 872 cases of colorectal cancer among New York City residents reported to the New York State Department of Health Registry between 1980 and 1985 (reporting was 95% complete). The percentage of late-stage disease was calculated through the use of cases with known stage as the denominator; stage was categorized as *early* (in situ or localized) and *late* (regional or distant). Data on Hispanic ethnicity were missing for almost one half of the cases. Since ethnicity and birthplace were highly correlated for cases with nonmissing data, missing cases were recoded as Hispanic on the basis of country of birth. Data on race and ethnicity were then combined; Asians were included with Whites (similar distributions of all variables). Hospitals were classed as "public" for municipal hospitals and "nonpublic" for the remaining hospitals. All public hospitals were teaching hospitals, providing primary care and specialty services, largely to low-income populations. No individual measures of SES were available.

Data from the 1970 and 1980 US Census were used to define ecological measures of SES, on the basis of a ranking of the health area of residence at the time of diagnosis. Health areas are geographically contiguous areas composed of two to six census tracts; there are 365 areas, each with a mean population of 20 000 residents. Area ranks were based on a composite index of the percentage of families below the poverty level and the percentage of unemployment as has been previously described.[16] By subtracting SES rank in 1970 from SES rank in 1980, we also developed an index of SES change.

SAS programs were used to assess bivariate relationships; logistic regression models were developed to predict late- versus early-stage disease; and categorical stratified analyses were used to explore interactions between significant variables.[17,18] Independent predictors included the following characteristics of individuals: age, race/ethnicity, gender, and hospital. Area variables included SES and change in SES.

Results

Characteristics of the sample and associations of individual predictor variables and stage are summarized in Table 1. There was a significant difference in the mean age of diagnosis by ethnic group (73.7, 68.4, and 65.9 for Whites, Blacks,

At the time of the study, Jeanne Mandelblatt, Jon Kerner, and Richard Kao were at the Memorial Sloan-Kettering Cancer Center, Department of Epidemiology and Biostatistics, New York, NY. Dr Mandelblatt and Dr Kerner are now with the Lombardi Cancer Center and Institute of Health Care Research and Policy, Georgetown University Medical Center, Washington, DC, and Mr Kao is now with the Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY. Howard Andrews and Rodrick Wallace are with the New York State Psychiatric Institute, Epidemiology of Mental Disorders Research Department, New York, NY.

Requests for reprints should be sent to Jeanne Mandelblatt, MD, MPH, Georgetown University Medical Center, Lombardi Cancer Center, Cancer Prevention and Control, 2233 Wisconsin Ave, NW, Suite 535, Washington, DC 20007.

This paper was accepted April 4, 1996.

reprint

The Late-Stage Diagnosis of Colorectal Cancer: Demographic and Socioeconomic Factors

Jeanne Mandelblatt, MD, MPH, Howard Andrews, PhD, Richard Kao, MS, Rodrick Wallace, PhD, and Jon Kerner, PhD

ABSTRACT

Objectives. This study described factors related to colorectal cancer stage at diagnosis.

Methods. Logistic regression analyses were used on data from the New York State Tumor Registry and US Census area–level social class indicators.

Results. After the effects of other predictors were controlled for, the odds of late-stage cancer increased as age decreased; women and African Americans were significantly more likely to have late stage than men and Whites; and individuals living in areas of low socioeconomic status (SES) were significantly more likely to be diagnosed at late stage than those living in higher SES areas. Stratified analyses showed that living in a low SES area was the most important determinant of stage for all age, race, gender, and source-of-care groups.

Conclusions. While all populations would benefit from the systematic use of screening, socioeconomically disadvantaged groups may also benefit from targeted screening. (*Am J Public Health.* 1996;86:1794–1797)

Introduction

For several cancer sites, age,[1–3] race,[3,4–9] socioeconomic status (SES),[5,9–13] and insurance status[14] have been noted to be related to stage at diagnosis. Stage data are often readily available and correlate with survival. To date, few studies have examined predictors of colorectal cancer stage.[10,15] This paper presents findings on the effects of age, gender, race, ethnicity, type of health care setting, and area socioeconomic status on colorectal cancer stage. We attempt to delineate the pathways leading to having late-stage disease among persons diagnosed with colorectal cancer.

Methods

The sample consisted of 28 872 cases of colorectal cancer among New York City residents reported to the New York State Department of Health Registry between 1980 and 1985 (reporting was 95% complete). The percentage of late-stage disease was calculated through the use of cases with known stage as the denominator; stage was categorized as *early* (in situ or localized) and *late* (regional or distant). Data on Hispanic ethnicity were missing for almost one half of the cases. Since ethnicity and birthplace were highly correlated for cases with nonmissing data, missing cases were recoded as Hispanic on the basis of country of birth. Data on race and ethnicity were then combined; Asians were included with Whites (similar distributions of all variables). Hospitals were classed as "public" for municipal hospitals and "nonpublic" for the remaining hospitals. All public hospitals were teaching hospitals, providing primary care and specialty services, largely to low-income populations. No individual measures of SES were available.

Data from the 1970 and 1980 US Census were used to define ecological measures of SES, on the basis of a ranking of the health area of residence at the time of diagnosis. Health areas are geographically contiguous areas composed of two to six census tracts; there are 365 areas, each with a mean population of 20 000 residents. Area ranks were based on a composite index of the percentage of families below the poverty level and the percentage of unemployment as has been previously described.[16] By subtracting SES rank in 1970 from SES rank in 1980, we also developed an index of SES change.

SAS programs were used to assess bivariate relationships; logistic regression models were developed to predict late- versus early-stage disease; and categorical stratified analyses were used to explore interactions between significant variables.[17,18] Independent predictors included the following characteristics of individuals: age, race/ethnicity, gender, and hospital. Area variables included SES and change in SES.

Results

Characteristics of the sample and associations of individual predictor variables and stage are summarized in Table 1. There was a significant difference in the mean age of diagnosis by ethnic group (73.7, 68.4, and 65.9 for Whites, Blacks,

At the time of the study, Jeanne Mandelblatt, Jon Kerner, and Richard Kao were at the Memorial Sloan-Kettering Cancer Center, Department of Epidemiology and Biostatistics, New York, NY. Dr Mandelblatt and Dr Kerner are now with the Lombardi Cancer Center and Institute of Health Care Research and Policy, Georgetown University Medical Center, Washington, DC, and Mr Kao is now with the Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY. Howard Andrews and Rodrick Wallace are with the New York State Psychiatric Institute, Epidemiology of Mental Disorders Research Department, New York, NY.

Requests for reprints should be sent to Jeanne Mandelblatt, MD, MPH, Georgetown University Medical Center, Lombardi Cancer Center, Cancer Prevention and Control, 2233 Wisconsin Ave, NW, Suite 535, Washington, DC 20007.

This paper was accepted April 4, 1996.

IN: Behavioral Medicine and Women: A Comprehensive Handbook,
edited by Elaine A. Blechman and Kelly D Brownell,
New York: Guilford Publications, Inc., In press, 1997.

96

Breast Cancer: Psychosocial Aspects

Julia H. Rowland

With one in every eight women in the United States expected to develop breast cancer in her lifetime, this disease has become a national health concern. Indeed, probably no other type of malignant disease has been more thoroughly researched with respect to its psychosocial impact. This is attributable only in part to breast cancer's prevalence and the attendant threat it poses to an organ intimately associated with self-esteem, sexuality, and femininity. The fact that studies of breast cancer serve as a paradigm for understanding a wide range of social, emotional, and behavioral issues associated with life-threatening illness and care is equally important. All the major treatment modalities (surgery, radiotherapy, chemotherapy, hormonal therapy) are used in treating and controlling the disease. The broad age range at time of diagnosis means that patients and their families cover the developmental spectrum. Finally, increasing numbers of women are living longer with the disease cured or controlled.

In the past decade, the two most important changes in the breast cancer area have been the growing emphasis on choices in treatment, and the broadening array of psychosocial interventions available to women and those caring for them. Research has begun to show that psychological and social variables may influence not only risk for developing and detecting breast cancer, but also adaptation to and survival from this illness. A number of factors go into a woman's adaptation to breast cancer (see Table 96.1). These are covered in more general detail in Chapters 97 and 98 of this volume. In this chapter, research addressing specific aspects of women's responses to the diagnosis, treatment, and outcome of breast cancer will be reviewed.

DIAGNOSIS

Increasing numbers of women with breast cancer are diagnosed at an early stage, where the chance for cure is 70% or better. The broader availability of mammography, and

SENT BY: XEROX 3006; 9-23-97 11:45AM; 2026870694 => #9/9

E20 OUTCOMES MEASUREMENT

CHAIR

Kevin A. Schulman, MD
Georgetown University Medical Center
Washington, DC

SPEAKERS

Julia H. Rowland, PhD
Georgetown University School of Medicine
Washington, DC

Dennis A. Revicki, PhD
MEDTAP International
Bethedsa, MD

Jane Weeks, MD
Dana Farber Cancer Institute
Boston, MA

Outcomes Assessment: Cancer-Specific Quality-of-Life Measures—Beyond the Research Setting

By Julia H. Rowland, PhD, Session Speaker

ONE OF THE MORE DRAMATIC shifts in cancer medicine in the past decade has been the increasing attention given to psychosocial issues in patient care.[1] While the reasons for this change are several (Table 1), taken as a whole they can be viewed as a direct consequence of both the success and failure of the clinical research enterprise. The latter half of this century has seen marked progress in the development of therapies that have proven successful in curing or slowing the growth of many cancers. One outcome of this success is that there are now growing numbers of cancer survivors. Most patients diagnosed today with cancer can expect to be cured of, or to live long periods of time with, their disease. At the same time, the newer treatments have become more complex, often involving intensive, frequently toxic, multimodality care. This in turn has placed greater demands on patients' resources and the patient-medical team relationship. Effective as many have been, these newer therapies have also made us realize that we have not yet won the war on cancer. Indeed, cancer for many will become a chronic disease. With more of their patients living longer and continuing to be treated or followed (sometimes, as in the case of breast cancer survivors, for life), oncology staff are being required to monitor and address the adverse sequelae on patient's psychologic and social, as well as physical, performance of cancer illness and treatment. Finally, these changes have all occurred in the context of greater demand by patients for involvement in their own care, consumer activism, attention to ethical and informed consent issues, and, most recently, emphasis on cost efficacy in care. The result is that significant differences exist in the way oncology is currently practiced and will likely be practiced as we head into the next century.

Address reprint requests to Julia H. Rowland, PhD, Department of Psychiatry, Georgetown University School of Medicine, 3800 Reservoir Rd, 311 Kober Cogan, Washington, DC 20007; Email rowland@gunet.georgetown.edu.

© 1997 by American Society of Clinical Oncology.

1022-9418/97/6383.00

Support for the inclusion of cancer-specific quality-of-life (QOL) assessment in the research setting has occurred at many levels.[2] A critical impetus for such evaluations was the 1985 statement by the Food and Drug Administration (FDA) that quality of life could be considered one of two requirements for approval of new anticancer agents, the first being improved survival.[3] In 1990 and again in 1995, the National Institutes of Health and National Cancer Institute held working meetings to discuss issues and the progress relating to the integration of QOL end points in cancer clinical trials.[4,5] Further, clinical trials groups in the United States, Canada, and Europe adopted policy statements that encouraged the use of quality-of-life evaluation in research protocols.[6-12] In the wake of these changes, there has been a veritable explosion of studies using, as well as instruments to assess, QOL outcomes.[9,13-15] More recently, attention has focused on taking these assessments beyond the research setting and applying them to clinical practice.[16,17] Interest in doing so has been fueled by multiple sources, not least among them patients themselves. Added validity to their request for greater response on the part of the medical community to health-related QOL issues is lent by findings from the few, but provocative, studies suggesting that QOL may affect survival.[18-20] Thus, the challenge has become how best to make the transition from studying QOL in the research setting to incorporating health-related QOL assessment across the course of care.

DEFINING AND MEASURING CANCER-SPECIFIC QOL

The World Health Organization defines QOL as "The perception by individuals or groups that their needs are being satisfied and that they are not being denied opportunities to achieve happiness and fulfillment."[21] While this definition appears appropriate and all encompassing, it provides little help in suggesting how this might be operationalized to permit measurement of such a state. Cella and Cherin have developed a definition that establishes at least the groundwork for measurement: "Quality of life refers to patients'

MR and Conventional Angiography:

Work in Progress toward Assessing Utility in Radiology[1]

J. Shannon Swan, MD, Dennis G. Fryback, PhD, William F. Lawrence, MD[2]
David A. Katz, MD, Dennis M. Heisey, PhD, Mary Ellen Hagenauer, BS
Peter M. Selzer, MD, Bruce K. Jacobson, MD

Rationale and Objectives. The authors assessed health-related quality of life changes associated with peripheral x-ray angiography and magnetic resonance (MR) angiography.

Materials and Methods. Utility (the desirability or preference that individuals exhibit for a particular health state) was assessed in 30 patients with peripheral vascular disease referred for angiography by using a rating scale, additional categoric scaling questions to separate preference from experience, a willingness-to-pay technique, functional and cognitive status questions, and a time trade-off technique. All patients underwent both MR angiography and x-ray angiography.

Results. Patients reported significantly ($P < .05$) less anxiety after the test, less pain after the test, fewer new physical limitations, and less effect on performance of daily activities with MR angiography. Findings from the overall rating scale and categoric scaling questions also significantly ($P < .05$) favored MR angiography. Patients were willing to pay a mean of 2.12% of annual income to avoid MR angiography and a mean of 7.41% to avoid x-ray angiography. The median quality-adjusted life gain required by patients to undergo the procedures was 52.5–60 days for x-ray angiography and 10.5 days for MR angiography, without discounting.

Conclusion. X-ray angiography has more profound short-term adverse effects on quality of life than does MR angiography. Preference-based measures can be adapted to elicit patient values for short-term health states as seen in radiology.

Key Words. Angiography, comparative studies; cost-effectiveness; quality of life.

Cost-effectiveness analysis is the principal method used to assess the relative value of medical interventions (1). The motivation for such evaluation is particularly strong in the face of the considerable expenses of some types of care. Radiology is unlikely to escape such scrutiny, even though the problems of measuring the ultimate effects of diagnostic procedures in terms of length and quality of life are difficult (2,3).

The importance of quality of life and patient preference has only recently been recognized in the radiology literature. The difficulty of applying such methods, however, has not yet been addressed (4,5). A particular problem encountered by evaluators of therapeutic and diagnostic interventions is measurement of short-term morbidities associated with those procedures (6). For instance, a potential benefit of magnetic resonance (MR) angiography is that it produces less acute morbidity than x-ray angiography yet provides high diagnostic accuracy (7–9). The purpose of this study was to see whether several known methods of utility assessment might be used to measure these short-term morbidities on scales that are compatible with cost-effectiveness analysis.

In a cost-effectiveness analysis in which quality of life is considered, each life year or fraction of a year lived is

Acad Radiol 1997; 4:475–482

[1] From the Departments of Radiology (J.S.S., M.E.H.), Preventive Medicine (D.G.F., D.A.K.), Industrial Engineering (D.G.F.), Internal Medicine (W.F.L., D.A.K.), and Surgery (D.M.H.), University of Wisconsin-Madison, Clinical Science Center, 600 Highland Ave, Madison, WI 53792; and the Departments of Radiology (P.M.S.) and Surgery (B.J.), Meriter Hospital, Madison, Wis. Received January 6, 1997; accepted after revision March 7. Supported by National Institutes of Health grant 1 RO1 HL51370. J.S.S. is a GE-AUR Fellow. **Address reprint requests to** J.S.S.

[2] Current address: Georgetown University Medical Center Cancer Prevention and Control, Washington, DC.

© AUR, 1997

Running head: POMS FOR CANCER PATIENTS

Toward Brief Forms of the Profile of Mood States for Cancer Patients

Kevin P. Weinfurt, M.A.

Department of Psychiatry and Department of Psychology

Georgetown University

Julia H. Rowland, Ph.D.

Department of Psychiatry

Georgetown University Medical Center

Address correspondence to Kevin P. Weinfurt, M.A., Department of Psychiatry, Georgetown University Medical Center, 3750 Reservoir Road, NW, Washington, D.C. 20007.

This research was supported in part by funds provided by the Michele Susan Kogod Memorial Foundation to the Psycho-oncology Program at Georgetown University. The authors thank Hyse Spertus and Pamela Witcher, Ph.D. for their assistance with data collection.

12/12/96
VERSION

SENT BY: XEROX 3006; 9-23-97 11:45AM; 2026870694 => #4/6

American Society of Clinical Oncology Educational Book

33rd Annual Meeting Spring 1997

EDITOR

Michael C. Perry, MD, *Columbia, MO*

Managing Editor

Deborah Whippen, *Chestnut Hill, MA*

© 1997 American Society of Clinical Oncology

Alexandria, VA

AA

OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

Grant Application

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

LEAVE BLANK-FOR PHS USE ONLY		
Type	Activity	Number
Review Group	Formerly	
Council/Board *(Month/Year)*		Date Received

1. TITLE OF PROJECT *(DO not exceed 56 characters, including spaces and punctuation.)*
Regular Mammogram Use in Elderly African Americans: An RCT

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT [ ] NO [X] YES *(If "Yes" state number and title*
PA-96-034; Aging Women and Breast Cancer

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME *(Last, first, middle)*
Burnett, Caroline Burnett

3b. DEGREE(S)
R.N., Sc.D.

3c. SOCIAL SECURITY NO.

3d. POSITION TITLE
Clinical Associate Professor

3e. MAILING ADDRESS *(Street, city, state, zip code)*
Lombardi Cancer Center
The Research Building
Georgetown University Medical Center
3970 Reservoir Road, NW
Washington, DC 20007-2197

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Lombardi Cancer Center

3g. MAJOR SUBDIVISION
School of Nursing

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: (202) 687-0801
FAX: (202) 687-0651

E-MAIL ADDRESS

4. HUMAN SUBJECTS
[ ] No
[X] Yes

4a. If "Yes", Exemption no. or
IRB approval date Pending
[ ] Full IRB or [X] Expedite Review

4b. Assurance of Compliance
M-1255

5. VERTEBRATE ANIMALS
[X] No or
[ ] Yes

5a. If "Yes," IACUC approval date

5b. Animal welfare assurance no.

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year--MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
01/01/98	12/31/02	405,824	599,040	2,036,675	2,776,356

9. APPLICANT ORGANIZATION
Name: Lombardi Cancer Center
Address: The Research Building
3970 Reservoir Road, NW
Washington, DC 20007-2197

10. TYPE OF ORGANIZATION
Public: → [ ] Federal [ ] State [ ] Local
Private: → [X] Private Nonprofit
Forprofit: → [ ] General [ ] Small Business

11. ORGANIZATIONAL COMPONENT CODE 01

12. ENTITY IDENTIFICATION NUMBER
1-530196603-A1

Congressional District
DC

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IS AWARD IS MADE
Name: Monique Anderson
Title: Grants Administrator
Address: Division of Research Grants and Contracts
2115 Wisconsin Avenue, NW
Washington, DC 20007
Telephone: (202) 687-1366
FAX: (202) 687- 3182
E-Mail Address: Andersonm@odrge.odr.georgetown.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: James F. Burris, M.D.
Title: Associate Dean for Research Operations
Address: 2115 Wisconsin Avenue, NW
Washington, DC 20007
Phone: (202) 687-7007
FAX: (202) 687-2585
E-Mail Address: burrisj@odrge.odr.georgetown.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)*
Caroline B Burnett

DATE
1/12/97

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the Best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may be subject to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per signature not acceptable).*
James F Burris MD

DATE
1/30/97

DESCRIPTION. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. DO NOT EXCEED THE SPACE PROVIDED.

In the last two decades, the death rate from breast cancer has fallen by about seven percent in women under 65. However, elderly African-American women have yet to realize any mortality reductions. In fact, in this period, elderly African-American women have experienced a 26% increase in mortality, despite having a lower incidence of disease than their white counterparts. The lack of mortality reduction in elderly African-American women may be explained, in part, by the fact that mortality reductions assume regular, on-going screening. However, for all women, **rates of regular, on-going screening mammograms** remain below recommended levels. There are little data on methods to enhance regular, on-going breast cancer screening, and fewer data still on how to increase utilization of regular screening in **elderly African-American women.** To address this important gap in knowledge, The Georgetown University's Cancer and Aging Research group, Lombardi Cancer Center, is leading an **inter-institutional consortium of DC institutions** (DC General Hospital, Georgetown University, George Washington Hospital, Providence Hospital, Washington Hospital Center, and the DC Department of Health) that provide the majority of care to elderly African-American women in DC. The **goal** of this multi-disciplinary, inter-institutional consortium is to **conduct and evaluate a nurse-based 2 x 2 factorially designed randomized clinical trial (RCT) to increase return screening rates.** We will use the **Behavioral Model for Health Services Use** as a theoretical framework to guide the design and guide and analyses. A sample of 2,193 elderly African-American women, with a history of at least one previous mammogram, and who attend radiology will be randomized to one of four arms: nurse counseling with standard reminders, tailored reminders, a combination of counseling and tailored reminder letters, and standard reminders (control). The project has three primary aims: 1) To test the hypothesis that women who receive the combination of the tailored reminder and nurse counseling will return mammography screening at significantly higher rates than those who receive either approach alone, or the control; 2) To test the hypothesis that the Behavioral Model for Health Services Use, which describes predisposing, enabling, and need factors, predicts repeat screening; and 3) To use cost-effectiveness analyses to test the hypothesis that the combination of a tailored reminder and nurse-based counseling will have the lowest incremental costs per additional return mammogram than either intervention alone, or than the control. These data are critical to our success in reducing the disproportionately high breast cancer mortality and morbidity experienced by elderly African-American women.

PERFORMANCE SITE(S) *(organization, city, state)*

Lombardi Cancer Center
Georgetown University School of Nursing
2233 Wisconsin Avenue, NW, #400
Washington, DC 20007

D.C General Hospital
George Washington Hospital
Providence Hospital
Washington Hospital Center

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Caroline B. Burnett, R.N., Sc.D	Lombardi Cancer Center and Georgetown University School of Nursing	Principal Investigator
Jeanne Mandelblatt, M.D., M.P.H.	Lombardi Cancer Center	Co-Principal Investigator
Patricia Cloonan, Ph.D.	School of Nursing	Co-Investigator
Kathryn Taylor, Ph.D.	Lombardi Cancer Center	Co-Investigator
Caryn Lerman, Ph.D.	Lombardi Cancer Center	Co-Investigator
Karen Gold, Ph.D.	Lombardi Cancer Center	Co-Investigator

AA

Form Approved Through 7/31/97
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

Grant Application

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

LEAVE BLANK-FOR PHS USE ONLY		
Type	Activity	Number
Review Group	Formerly	
Council/Board(*Month/Year*)		Date Received

1. TITLE OF PROJECT (*DO not exceed 56 characters, including spaces and punctuation.*)
Cancer Screening Guideline Adherence: Underserved Elderly Women

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT [ ] NO [X] YES (*If "Yes" state number and title*
K01 - Mentored Research Scientist Development Award - Nursing (MRSDA-N)

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME (*Last, first, middle*)
Burnett, Caroline B.

3b. DEGREE(S)
R.N., Sc.D.

3c. SOCIAL SECURITY NO.

3d. POSITION TITLE
Clinical Associate Professor

3e. MAILING ADDRESS (*Street, city, state, zip code*)
Lombardi Cancer Center
The Research Building
Georgetown University Medical Center
3970 Reservoir Road, NW
Washington, DC 20007-2197

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Lombardi Cancer Center

3g. MAJOR SUBDIVISION
Department of Nursing

3h. TELEPHONE AND FAX (*Area code, number and extension*)
TEL: (202) 687-0801
FAX: (202) 687-0651

E-MAIL ADDRESS

4. HUMAN SUBJECTS
[ ] No
[X] Yes

4a. If "Yes", Exemption no. or
IRB approval date 05/16/96 [ ] Full IRB or [X] Expedite Review

4b. Assurance of Compliance
M-1255

5. VERTEBRATE ANIMALS
[X] No or
[ ] Yes

5a. If "Yes," IACUC approval date

5b. Animal welfare assurance no.

6. DATES OF PROPOSED PERIOD OF SUPPORT (*month, day, year--MM/DD/YY*)
From 12/01/97 Through 11/30/00

7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD
7a. Direct Costs ($) $82,000
7b. Total Costs ($) $88,376

8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT
8a. Direct Costs ($) $246,001
8b. Total Costs ($) $265,497

9. APPLICANT ORGANIZATION
Name Georgetown University
Address 37th & O Streets, NW
Washington, DC 20057

10. TYPE OF ORGANIZATION
Public: → [ ] Federal [ ] State [ ] Local
Private: → [X] Private Nonprofit
Forprofit: → [ ] General [ ] Small Business

11. ORGANIZATIONAL COMPONENT CODE 01

12. ENTITY IDENTIFICATION NUMBER
1-530196603-A1

Congressional District
DC

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IS AWARD IS MADE
Name Monique Anderson
Title Grants Administrator
Address Division of Research Grants and Contracts
2115 Wisconsin Avenue, NW
Washington, DC 20007
Telephone (202) 687-1366
FAX (202) 687-23182
E-Mail Address Andersonm@odrge.odr.georgetown.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name James F. Burris, M.D.
Title Associate Dean for Research Operations
Address 2115 Wisconsin Avenue, NW
Washington, DC 20007
Phone (202) 687-7007
FAX (202) 687-2585
E-Mail Address burrisj@odrge.odr.georgetown.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. (*In ink. "Per" signature not acceptable.*)
Caroline B Burnett

DATE
2/17/97

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the Best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may be subject to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. (*In ink. "Per signature not acceptable).*
James F Burris MD

DATE
2/24/97

AA

DESCRIPTION. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The candidate's long-term career goal is to develop the skills to become an independent nurse-researcher in cancer prevention and control, with a primary **focus on elderly, minority, and medically under-served populations.** Related career development objectives include to: 1) Develop a **research agenda** that targets key issues for **nurse-based cancer control** targeted to high-risk women, such as non-adherence to **cancer screening** guidelines, and **cost implications** of innovative approaches to screening; 2) Develop strong **theoretical knowledge base** in cancer prevention and control and related sciences, e.g., epidemiology, behavioral science, and health services research; and, 3) Explore **ethical issues** surrounding provision of cancer screening to vulnerable and at risk populations. **This proposal is consistent with the candidates immediate and long-term career goals.** We will **conduct and evaluate a randomized controlled trial (RCT) designed to increase return mammography screening rates among elderly African-American women. The RCT will compare nurse counseling plus standard reminder to standard reminders alone in two health care settings - a mobile mammography van and a stationary radiology facility.** The Anderson and Aday Behavioral Model for Health Services Use, which includes predisposing, enabling, and need factors, will be used as a theoretical framework to guide the design and analyses. A sample of 1300 African-American women ages 65 or more years, with a history of at least one previous mammogram, will be recruited for the RCT. The specific aims are to: 1) test the hypothesis that women who receive nurse counseling plus a standard reminder, will return for screening at significantly higher rates than those receiving the standard reminder alone (control); 2) test the hypothesis that components of the Behavioral Model for Health Services predict return screening; and, 3) use cost-effectiveness analyses to test the hypothesis that nurse counseling will have lower incremental costs per additional return mammogram than standard reminder control. This research will fill important gaps in our knowledge on how to using nursing practice to improve the poor breast cancer outcomes experienced by elderly, African-American women.

PERFORMANCE SITE(S) *(organization, city, state)*

Lombardi Cancer Center
Georgetown University School of Nursing
2233 Wisconsin Avenue, NW, #400
Washington, DC 20007

George Washington University Medical Center
2150 Pennsylvania Avenue, NW
Washington, DC 20037

Providence Hospital
1150 Varnum Street, NE
Washington, DC 20017

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Caroline B. Burnett, RN, Sc.D	Lombardi Cancer Center and Georgetown University School of Nursing	Candidate
Jeanne Mandelblatt, MD, MPH	Lombardi Cancer Center	Co-Mentor
Jon F. Kerner, Ph.D.	Lombardi Cancer Center	Co-Mentor
Marilyn Frank-Stromborg, RN, Ed.D, FAAN	Northern Illinois University School of Nursing	Consultant
Karen Gold, Ph.D.	Lombardi Cancer Center	Biostatistician
Daniel P. Sulmasy, MD, Ph.D.	Center for Clinical Bioethics	Advisor
Bruce J. Trock, Ph.D.	Lombardi Cancer Center	Advisor

AA

Form Approved Through 9/30/97
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

Grant Application

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

LEAVE BLANK—FOR PHS USE ONLY.		
Type	Activity	Number
Review Group	Formerly	
Council/Board *(Month, Year)*		Date Received

1. TITLE OF PROJECT *(Do not exceed 56 characters, including spaces and punctuation.)*
CEA of Breast Cancer Control for African Americans

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT [ ] NO [X] YES *(If "Yes," state number and title)*
Number: PA 94-011 Title: Economic Studies in Cancer Prevention

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME *(Last, first, middle)*
Fahs, Marianne C.

3b. DEGREE(S)
PhD, MPH

3c. SOCIAL SECURITY NO.
386-48-7900

3d. POSITION TITLE
Director

3e. MAILING ADDRESS *(Street, city, state, zip code)*
66 Fifth Avenue
9th floor
New York, NY 10011

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Health Services Management

3g. MAJOR SUBDIVISION
Health Policy Research Center

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 212-229-5678
FAX: 212-229-5335

E-MAIL ADDRESS: Fahsm@newschool.edu

4. HUMAN SUBJECTS
[ ] No
[X] Yes

4a. If "Yes," Exemption no. or IRB approval date: Pending
[ ] Full IRB or [X] Expedited Review

4b. Assurance of compliance no.

5. VERTEBRATE ANIMALS
[X] No
[ ] Yes

5a. If "Yes," IACUC approval date

5b. Animal welfare assurance no.

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*
From: 01/01/98 Through: 12/31/00

7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD
7a. Direct Costs ($): $504,403
7b. Total Costs ($): $566,805

8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT
8a. Direct Costs ($): $1,417,007
8b. Total Costs ($): $1,605,495

9. APPLICANT ORGANIZATION
Name: New School for Social Research
Address: 66 Fifth Avenue
New York, NY 10011

10. TYPE OF ORGANIZATION
Public: → [ ] Federal [ ] State [ ] Local
Private: → [X] Private Nonprofit
Forprofit: → [ ] General [ ] Small Business

11. ORGANIZATIONAL COMPONENT CODE 20

12. ENTITY IDENTIFICATION NUMBER 13-3297197

Congressional District 8

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: Joseph F. Porrino
Title: Executive Vice President
Address: 66 West 12th Street, 8th floor
New York, NY 10011
Telephone: 212-229-2650
FAX: 212-229-5330
E-Mail Address: Porrinoj@newschool.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: Joseph F. Porrino
Title: Executive Vice President
Address: 66 West 12th Street, 8th floor
New York, NY 10011
Phone: 212-229-5650
FAX: 212-229-5330
E-Mail Address: Porrinoj@newschool.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI / PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)* Marianne Fahs
DATE 2/26/97

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per" signature not acceptable.)* Joseph F. Porrino
DATE 2/26/97

DESCRIPTION. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

In the last two decades, the death rate from breast cancer has fallen by about seven percent in younger white women. However, in this period African-American women, particularly older African-American women, have experienced a 26% increase in mortality, despite having a lower incidence of disease than their white counterparts. For all races of women, mammography screening can potentially reduce mortality by up to 30%. Prior cost-effectiveness analyses of breast cancer screening among general populations have demonstrated that reductions in mortality can be achieved at a reasonable cost per life year saved. However, there are no data on whether additional expenditures to enhance the cancer control process for African-American women, particularly older African-American women, might affect the overall cost-effectiveness of screening. To address this important gap in our knowledge, we have assembled an experienced multi-disciplinary team of health economists, geriatricians, mathematical modelers, oncologists, health service researchers, decision analysts, and epidemiologists. We will extend prior cost-effectiveness analyses by 1) using existing race-specific data to develop a simulation model of the natural history of disease specific to African-American women ages 50 to 74 years; 2) obtaining primary data on the utilities for breast cancer outcomes among African-Americans to generate quality-adjusted life-years (QALYs) as the outcome of analysis; 3) including non-medical direct (e.g., patient transportation costs, patient time costs); and 4) developing and estimating sub-models which evaluate the incremental costs and effects of programs specifically designed to improve the value of screening in this high-risk population (e.g., programs designed to enhance breast cancer screening use, prompt diagnosis after abnormal screening, and adherence to recommended treatment). We hypothesize that the added costs of targeted cancer control programs for vulnerable African-American women will be offset by the gains in quality-adjusted life years saved as a result of down-staging disease and improving treatment. The results of such analysis will be useful to inform the optimal design of health services delivery programs, and to highlight priority research and service areas to ensure that we reach targeted levels of breast cancer mortality reduction among all women in the US.

PERFORMANCE SITE(S) *(organization, city, state)*

New School for Social Research	New York	NY
Mount Sinai-NYU Medical Center	New York	NY
Georgetown University Medical Center	Washington	DC

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Marianne C. Fahs, PhD, MPH	New School for Social Research	Principal Investigator
Nina J. Kontos, PhD	New School for Social Research	Project Coordinator
Clyde B. Schechter, MD	Mount Sinai-NYU Medical Center	Principal Investigator-Subcontract
Albert L. Siu, MD	Mount Sinai-NYU Medical Center	Investigator
Nina A. Bickell, MD	Mount Sinai-NYU Medical Center	Investigator
Donna R. Shelley, MD	Mount Sinai-NYU Medical Center	Investigator
Henry S. Sacks, MD, PhD	Mount Sinai-NYU Medical Center	Investigator
Jeanne S. Mandelblatt, MD	Georgetown University Medical Center	Principal Investigator-Subcontract
William Lawrence, MD	Georgetown University Medical Center	Investigator
Jon Kerner, PhD	Georgetown University Medical Center	Investigator
Caroline Burnett, RN, ScD	Georgetown University Medical Center	Investigator
Lenora Johnson, CHES	Georgetown University Medical Center	Sr. Health Educator

BREAST CANCER: PREPARING FOR SURVIVORSHIP

A. SPECIFIC AIMS

In our current research program with breast cancer survivors (BCS), we have explored in great detail the issues of sexuality and intimacy in women beyond the acute phase of treatment. We have found that sexual dysfunction in this population is common, age-related, and influenced by the receipt of chemotherapy and induction of premature menopause; however, sexual functioning was similar to age-matched healthy postmenopausal women without a breast cancer diagnosis (Ganz, et al; Meyerowitz, et al.). In spite of experiencing increased symptoms as a result of breast cancer treatment (e.g., menopausal symptoms, changes in body image), many women reported high levels of well-being, as well as the transforming and positive aspects of the breast cancer experience, [Ganz et al., see manuscript in Appendix XX]. However, we also learned from these women that there had been challenges in their recovery, and that focused preparation for survivorship might have made some tasks easier. In our preliminary work, we have identified cognitive, emotional, physical/behavioral, and interpersonal well-being as the quality of life domains that are particularly salient for examining the transition from patient to survivor.

This competing continuation application focuses on the development and evaluation of a cost-effective intervention to facilitate the transition from the patient to survivor. Using a theory-driven conceptual model, that is guided by the clinical and research experience of the investigative team, we will examine a little studied aspect of the breast cancer patient's experience---the period of recovery from the physical and psychological effects of primary breast cancer treatment. This transitional period requires new energy and personal resources to reclaim aspects of life that have been put on hold, as well as a time to finding new meaning from the cancer experience. The <u>specific aims</u> of this application are:

1. To register 1680 newly-diagnosed breast cancer patients one month after surgery, and prospectively recruit them for participation in a randomized controlled intervention trial that will be initiated at the time primary/adjuvant therapy is completed.

2. To randomize 500 participating patients to one of three treatment conditions:
   a) Control/standard written information (NCI publication "Facing Forward")
   b) a + videotape which discusses the issues of transition from patient to survivor
   c) b + brief counseling (1 in person session with follow-up telephone call)

3. To measure the impact of the three treatments on subsequent cognitive, emotional, physical/behavioral and interpersonal functioning 2 months and 6 months after randomization.

4. To measure the cost-effectiveness of the three treatment approaches, as well as their feasibility for use in the health care setting

<u>Research Questions</u>

1. Do models of coping and preparatory/educational interventions have relevance for breast cancer patients preparing for long term survivorship?

2. What is the pattern of recovery after each of the treatment conditions, and is one more effective than the other?

SENT BY: XEROX 3006; 9-23-97 11:44AM; 2026870694 => #3/6

Office of the President:
Interdisciplinary Initiative Proposal 11/1/96
Karen F. Gold, Ph.D. Assistant Professor
Department of Biomathematics and Biostatistics
Georgetown University Medical Center

Statistical Computing Program

In order to better integrate academic and research components in the area of statistical computing at Georgetown University, the Department of Biomathematics and Biostatistics (School of Medicine),and the Departments of Computer Science and of Mathematics (College of Arts and Sciences) propose the development of an interdisciplinary program in statistical computing. The purpose of this program is three-fold: 1) provide formal course work in standard and advanced statistical programming languages for academically prepared seniors and first year master's students, 2) provide academically prepared seniors and first year master's students opportunities for mentored research work experience and 3) provide Georgetown researchers a resource for their statistical computing needs. The proposed course will include a research requirement that can be fulfilled by participating in the mentored apprenticeship. In addition, a monthly seminar offered in conjunction with the apprenticeship will provide students a venue to present and discuss their research problems.

Interdisciplinary Course in Statistical Computing

This one-semester course will be team taught, providing hands-on computer experience in a survey of statistical software and languages. Language exposure will include a structured query language (SQL) example for databases and geographical information systems (GIS); high level statistical analysis programming languages including SAS, HLM and LISREL; matrix programming languages such as SAS IMSL and GAUSS; graphical presentation software such as BMDP DIAMOND and Statistica as well as languages that are suited for data simulations. Each class will be divided into two parts: 1) a theoretic introduction to the methods implemented by the language/package and 2) an introduction to the use of the language/package. In addition to providing students an introduction to the methodological basis for statistical software, the survey nature of the course will provide an overview of the currently available statistical computing resources. This will allow students to select tools most appropriate for the problems that they will encounter in applied research environments. With the rapid advent in technology, making software obsolete in the course of a short period of time, this course will focus on learning how to learn new methods, software and languages. In addition, it will provide an academic anchor to the statistical apprenticeship. Course and materials will be developed by Professor Gold in collaboration with Professors Engler and Benke. The class will be offered as a statistical computing course in the Department of Biomathematics and cross-listed by both the Department of Mathematics and the Department of Computer Science.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 1996	Annual (1 Aug 95 - 31 Jul 96)

4. TITLE AND SUBTITLE
Cost Effectiveness of Alternative Treatments for Local Breast Cancer in the Elderly

5. FUNDING NUMBERS
DAMD17-94-J-4212

6. AUTHOR(S)
Jack Hadley, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Georgetown University
Washington, DC 20057

8. PERFORMING ORGANIZATION REPORT NUMBER
IR96-01 (RX341800)

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*

The purpose of this project is to conduct cost-effectiveness analyses (CEA) of three treatment alternatives (modified radical mastectomy, breast conserving surgery with radiation therapy, and breast conserving surgery without radiation therapy) for elderly women (67 and older) with early stage breast cancer. Data for the CEA will be obtained from surveys of breast cancer patients at three, four, and five years post-treatment, their surgeons, and Medicare's National Claims History File. (Data for women up to two years post-treatment will be obtained from a complementary resarch project.) Analyses of preliminary data from the physicians and patients in the related project were begun for the purpose of constructingthe final survey instruments. The samples of physicians and patients for the national surveys have been drawn from Medicare data for 1992-1994.

14. SUBJECT TERMS
breast cancer in elderly women; cost-effectiveness analysis; patient and physician survey instruments

15. NUMBER OF PAGES

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

OMB No. 0925-0001

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

GRANT APPLICATION

Follow instructions carefully. Type in the unshaded areas only. Type density must be 10 c.p.i.

LEAVE BLANK FOR PHS USE ONLY		
Type	Activity	Number
Review Group		Formerly
Council/Board (Month, Year)		Date Received

1. TITLE OF PROJECT (Do not exceed 56 typewriter spaces.)
Care, Costs and Outcomes of Local Breast Cancer

2a. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES (If "YES," state number and title)
Number: HS-94-002 Title: Medical Treatment Effectiveness Program - PORT-II

2b. TYPE OF GRANT PROGRAM: R01

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME (Last, first, middle): Hadley, Jack

3b. DEGREE(S): Ph.D.

3c. SOCIAL SECURITY NO.: 029-34-6585

3d. POSITION TITLE: Associate Professor

3e. MAILING ADDRESS (Street, city, state, zip code):
Georgetown Univ. Medical Center
5 PHC
3800 Reservoir Road, N.W.
Washington, D.C. 20007

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT: Department of Medicine

3g. MAJOR SUBDIVISION: General Internal Medicine

3h. TELEPHONE AND FAX (Area code, number and extension)
TEL: (202) 342-0107
FAX: (202) 625-6685

BITNET/INTERNET ADDRESS:

4. HUMAN SUBJECTS

4a. NO	X YES	If "Yes," exemption no. or IRB approval date	4b. Assurance of compliance no.
		PENDING	M-1255

5. VERTEBRATE ANIMALS

5a. NO	X YES	If "Yes," IACUC approval date	5b. Animal welfare assurance no.
X			

6. DATES OF ENTIRE PROPOSED PROJECT PERIOD
From (MMDDYY): 070194 Through (MMDDYY): 063099

7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD
7a. Direct Costs ($): 970,481
7b. Total Costs ($): 1,405,951

8. COSTS REQUESTED FOR ENTIRE PROPOSED PROJECT PERIOD
8a. Direct Costs ($): 4,950,053
8b. Total Costs ($): $6,789,890

9. PERFORMANCE SITES (Organizations and addresses)
Georgetown Univ. Medical Center
3800 Reservoir Road, N.W.
Washington, D.C. 20007
Lombardi Cancer Center
3800 Reservoir Road, N.W.
Washington, D.C. 20007

10. INVENTIONS AND PATENTS (Competing continuation application only)
X NO ☐ YES If "YES" ☐ Previously reported ☐ Not previously reported

11. NAME OF APPLICANT ORGANIZATION
Georgetown University
ADDRESS: 37th & O Streets, N.W.
Washington, D.C. 20057

12. TYPE OF ORGANIZATION
☐ Public: Specify ☐ Federal ☐ State ☐ Local
X Private Nonprofit
☐ Forprofit (General) ☐ Forprofit (Small Business)

13. ENTITY IDENTIFICATION NUMBER: 1530196603-A1
Congressional District: DC

14. BIOMEDICAL RESEARCH SUPPORT GRANT CREDIT
Code: 01 Identification: School of Medicine

15. NAME OF ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Doris Lyons
TELEPHONE: (202) 687-3928
FAX: (202) 687-1963
TITLE: Asst. V.P. for Fiscal Affairs
ADDRESS: 37th & O Streets, N.W.
Washington, D.C. 20057
BITNET/INTERNET ADDRESS:

16. NAME OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Manuel Corday
TELEPHONE: (202) 687-1958
FAX: (202) 687-1963
TITLE: Grants and Contracts Administrator
ADDRESS: 37th and O. Streets, N.W.,
Washington, D.C. 20057
BITNET/INTERNET ADDRESS:

17. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79).

SIGNATURE OF PERSON NAMED IN 3a. (In ink. "Per" signature not acceptable.): Jack Hadley
DATE: 11-15-93

18. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79).

SIGNATURE OF PERSON NAMED IN 16. (In ink. "Per" signature not acceptable.): Manuel Corday
DATE: 11-15-93

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. **DO NOT EXCEED THE SPACE PROVIDED.**

This project will identify the determinants of and calculate cost-effectiveness ratios for 3 alternative treatments for local breast cancer in the elderly: modified radical mastectomy (MRM), breast conserving surgery (BCS) with radiotherapy (RT), and BCS without RT. Treatment choice and short- and intermediate-term outcomes will be analyzed using data from a prospective convenience cohort of approximately 800 newly-diagnosed elderly (65+) breast cancer patients who will be interviewed post-treatment and followed for up to 2 years. Their surgeons will be surveyed by mail with telephone follow-up. We will also conduct surveys of nationally representative, retrospective, random samples of breast cancer surgeons (n=1,000) and their Medicare patients (1,575 decedents and 3,000 survivors) who were treated in 1992 in order to (a) validate and extend the treatment choice model to a national sample and (b) measure 5-year outcomes. Cost-effectiveness ratios for each treatment will be calculated for all older women and for substrata defined by age, race, geography, and initial health status, based on 5-year outcomes and short- and intermediate-term outcomes imputed from the convenience sample. Medical care costs will be measured using Medicare claims data.

The proposed analyses are multidisciplinary, drawing on theoretical models and prior research in economics, behavioral science, and cost-effectiveness analysis, as well as the relevant clinical literature. Recognizing the observational nature of the data, estimation of the treatment choice and treatment-outcome models uses the instrumental variable approach, a common econometric method, to adjust for the joint selection of providers and treatment choices by patients and for the effects of unobservable differences in patients' initial health and preferences. The project will develop clear recommendations regarding the appropriateness of observed patterns of treating local breast cancer in the elderly, taking account of circumstances that may differ with age, initial health, and access to different types of providers.

PERSONNEL ENGAGED ON PROJECT, INCLUDING CONSULTANTS/COLLABORATORS. *Use continuation pages as needed* to provide the required information in the format shown below on *all* individuals participating in the project.

Name Jack Hadley	Degree(s) Ph.D.	Social Security No. 029-34-6585
Position Title Co-Director/Assoc. Professor	Date of Birth (MM/DD/YY) 12/26/46	Role on Project Co-P.I.
Organization Georgetown University Medical Center		Department Health Policy Stud.
Name Jeanne S. Mandelblatt	Degree(s) M.D., M.P.H.	Social Security No. 058-44-8916
Position Title Associate Professor	Date of Birth (MM/DD/YY) 09/10/51	Role on Project Co-P.I.
Organization Georgetown University Medical Center		Department Lombardi Cancer Ctr.
Name Jon Kerner	Degree(s) Ph.D.	Social Security No.
Position Title Assoc. Director	Date of Birth (MM/DD/YY)	Role on Project Investigator
Organization Georgetown University Medical Center		Department Lombardi Cancer Ctr.
Name Caryn E. Lerman	Degree(s) Ph.D.	Social Security No.
Position Title Associate Professor	Date of Birth (MM/DD/YY)	Role on Project Investigator
Organization Georgetown University Medical Center		Department Lombardi Cancer Ctr.
Name Julia Rowland	Degree(s) Ph.D.	Social Security No.
Position Title Asst. Professor in Psychiatry	Date of Birth (MM/DD/YY)	Role on Project Investigator
Organization Georgetown University Medical Center		Department Lombardi Cancer Ctr.
Name Caroline B. Burnett	Degree(s) Sc.D.	Social Security No.
Position Title Assistant Professor	Date of Birth (MM/DD/YY)	Role on Project Investigator
Organization Georgetown University		Department School of Nursing
Name Bruce J. Trock, Ph.D.	Degree(s) Ph.D.	Social Security No.
Position Title Associate Professor	Date of Birth (MM/DD/YY)	Role on Project Investigator
Organization Georgetown University Medical Center		Department Lombardi Cancer Ctr.

AA

Form Approved Through 9/30/97
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

Grant Application

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

LEAVE BLANK—FOR PHS USE ONLY.		
Type	Activity	Number
Review Group	Formerly	
Council/Board *(Month, Year)*		Date Received

1. TITLE OF PROJECT *(Do not exceed 56 characters, including spaces and punctuation.)*
Care, Costs and Outcomes of Breast Cancer: Elderly African Americans

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT [ ] NO [X] YES *(If "Yes," state number and title)*
Number: Title: FCCBC Administrative Supplements

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME *(Last, first, middle)*
Hadley, Jack

3b. DEGREE(S)
Ph.D.

3c. SOCIAL SECURITY NO.

3d. POSITION TITLE
Research Professor

3e. MAILING ADDRESS *(Street, city, state, zip code)*
Institute for Health Care Research and Policy
2233 Wisconsin Avenue, N.W.
Suite 525
Washington, DC 20007
E-MAIL ADDRESS: hadleyj@GUNET.georgetown.edu

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Medicine

3g. MAJOR SUBDIVISION
Institute for Health Care Research

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: (202) 687-0880
FAX: (202) 687-3110

4. HUMAN SUBJECTS
[ ] No
[X] Yes

4a. If "Yes," Exemption no. or
IRB approval date: Pending
[ ] Full IRB or [X] Expedited Review

4b. Assurance of compliance no.
M-1255

5. VERTEBRATE ANIMALS
[X] No
[ ] Yes

5a. If "Yes," IACUC approval date

5b. Animal welfare assurance no.

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*
From: 10/01/97
Through: 09/30/98

7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD
7a. Direct Costs ($): 141,337
7b. Total Costs ($): 158,305

8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT
8a. Direct Costs ($): 141,337
8b. Total Costs ($): 158,305

9. APPLICANT ORGANIZATION
Name: Georgetown University
Address: 37th & O Streets, N.W.
Washington, DC 20057

10. TYPE OF ORGANIZATION
Public: → [ ] Federal [ ] State [ ] Local
Private: → [X] Private Nonprofit
Forprofit: → [ ] General [ ] Small Business

11. ORGANIZATIONAL COMPONENT CODE 01

12. ENTITY IDENTIFICATION NUMBER
1530196603A1

Congressional District
D.C.

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: W. Walker Pheil
Title: Grants and Contracts Admin.
Address: Div. of Research Grants
2115 Wisconsin Ave., N.W., #108
Washington, DC 20007
Telephone: (202) 687-1207
FAX: (202) 687-3182
E-Mail Address: pheilw@odrge.odr.georgetown.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: James F. Burris, M.D.
Title: Assoc. Dean for Research Oper.
Address: Georgetown University Medical Center
Washington, DC 20007
Phone: (202) 687-7007
FAX: (202) 687-2585
E-Mail Address: burrisj@macpost.odr.georgetown.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI / PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)*
Jack Hadley

DATE
8-19-97

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per" signature not acceptable.)*
James F. Burris MD

DATE
8/19/97

I. ABSTRACT

The elderly have the highest incidence of breast cancer, and account for the largest prevalence of breast cancer survivors, yet little is known about the treatment patterns, costs and sequelae of disease in this underserved population. Further, there are virtually no data on minority populations historically at risk for under-treatment and poor breast cancer outcomes, particularly **African-American elderly women**. At all ages, despite somewhat lower incidence rates, when African-American women do develop breast cancer they are two to three times more likely to die of their disease than Whites; even within each disease stage, African-American women fair less well than Whites. The **excess morbidity and morality** experienced by elderly and other African-American women may be related to the interaction of several complex phenomenon: age, socioeconomic status (SES), adequacy of early detection and treatment services, tumor biology, and comorbid medical conditions. While prior studies have demonstrated significant underservice among select groups of Medicare beneficiaries, none have had sufficient data to explore the pathways whereby sociodemographics, clinical characteristics, regional patterns of care, and other variables exert their influence on observed racial variations in breast cancer care, costs, and outcomes. The one cost-effectiveness analysis that included a sub-group analysis for African-American elderly women demonstrated that screening for cervical cancer actually saved Medicare dollars, as well as years of life, compared to an overall population result of about $4,500 per year of life saved, and substantially higher costs for White women with good prior access to care. Thus, the cost-effectiveness of breast cancer treatment may also differ for racial subgroups.

In this supplement to the Breast Cancer PORT II (Patient Outcome Research Team), Georgetown University is leading a multi-disciplinary team from a national consortium of cancer research centers, universities, and consumer and professional organizations to address these important gaps in knowledge. We are proposing to draw a **nationally representative** over-sample of **African-American Medicare beneficiaries** with **local stage breast cancer** who were treated in 1994. The sample will be drawn to yield 400 completed interviews with African-American women surviving 3-4 years post-treatment. The data from this African-American supplemental sample will complement data currently being collected in the PORT for approximately 450 White and 50 African-American surviving Medicare beneficiaries treated in 1994. We will use data from the combined PORT and supplemental samples (n= 450 women in each race group) to: 1) evaluate patient, physician, and medical care environmental factors associated with **treatment patterns in African-American elderly women**; 2) evaluate the **factors contributing to quality of life and functional status outcomes** of these **African-American elderly women** 3 to 4 years post-surgery; and 3) **compare** the **treatment patterns** and **outcomes** of treatment for **African-American** and **White elderly** women. The data collected in this supplement will also be used to examine the **treatment-related costs per quality-adjusted life year saved** for African-American elderly women.

The supplement builds on the existing structure and expertise of the Breast Cancer PORT. While the PORT sample will be adequate to detect large differences in treatment patterns by race, it will not include sufficient numbers of African-American women to test detailed hypotheses explaining any observed racial variations. Thus, this supplement presents a unique opportunity to address important new research questions to fill important gaps in our knowledge about treatment patterns, costs, and 3-4 year sequelae of breast cancer in elderly African-American women at marginal costs.

With few exceptions, elderly African-Americans are not likely to be the major focus of future randomized controlled trials (RCTs) of breast cancer treatments. Observational studies such as this are an important source of key data needed for the complex clinical and policy decision making involved in caring for racially diverse, heterogeneous groups of elderly women. The proposed supplement will be the first large cross-sectional, nationally representative sample of elderly African-American breast cancer patients studied to date. A major contribution of this study is the addition of tumor stage, which is not presently collected by HCFA. The comprehensive data and analyses from this supplement will be critical to developing patient education interventions, clinical practice recommendations, and to providing guidance to decision makers and consumer groups who are concerned with the health of this vulnerable, underserved group.

SUBMITTED IN RESPONSE TO RFA: Health Policy and Outcomes- Prostate

Please read carefully the "TARGETED Research Project Grants Policies & Instructions" and the instructions on all pages of this form before completing the application.

TO: **American Cancer Society, Inc.**
Extramural Grants Department
1599 Clifton Road, N.E.
Atlanta, GA 30329-4251

Application* is hereby made for a TARGETED Research Project Grant

Total amount requested: $ 732,944

DATE: 3/19/97

Period: 1/1/98 through 12/31/00

TITLE OF PROJECT: Racial, Age, and Payor Differences in the Treatment of Prostate Cancer

X NEW _RENEWAL of ACS Grant # _____ _RESUBMISSION OF APPLICATION # _____

PRINCIPAL INVESTIGATOR	OFFICIAL AUTHORIZED TO SIGN FOR INSTITUTION
Last name, first name, initial, degree Lawrence, William F., MD, MS	Last name, first name James F. Burris, MD
Title Assistant Professor of Medicine	Name of institution Georgetown University
Social Security number 234-02-0203	Number and street 37th & O Street, NW
Name of Institution Georgetown University	City, state, zip code Washington, DC 20057
Department and/or Division Lombardi Cancer Center Division of Cancer Prevention and Control	Telephone (area code, number, extension) 202-687-7007
Number and street 2233 Wisconsin Ave, NW, Suite 535	Title of official authorized to sign for applicant's institution Associate Dean for Research Operations
City, state, zip code Washington, DC 20007	Signature of Official James F Burris MD
Telephone, fax, e-mail Phone: (202) 687-0817 Fax: (202) 687-0820 E-mail: lawrence@gunet.georgetown.edu	**Eligibility Assurance:** Committed, independent research space: 1805 sq. ft. **Verification by Department Chair:**
Signature of Principal Investigator William F. Lawrence, MD, MS	Name: Marc E. Lippman, MD Signature:

*It is understood that each applicant, by the act of applying for a grant, agrees, if the grant is made, to abide by the Society's TARGETED RESEARCH PROJECT GRANT POLICIES.

Checks to be made payable to: Georgetown University

Attention of (office): Sponsored Program Accounting

Street and number, room no., bldg: 37th & O St., NW, 2 Ryan Bldg.

City, state, zip code: Washington, DC, 20057

Abstract

Name of Applicant
William F. Lawrence, MD, MS

Title
Assistant Professor of Medicine

Department
Department of Medicine, Lombardi Cancer Center, Georgetown University

Institution

Title
Racial, Age, and Payor Differences in the Treatment of Prostate Cancer

Use this space to summarize **concisely** your proposed research, outlining objectives, methods, and relevance to the cancer problem.

Prostate cancer is a major cause of morbidity and mortality in US men. Incidence and mortality rates increase with age and are higher in African-Americans than Whites. Hispanic men have lower disease incidence than Whites, but comparable mortality; it is not known whether this represents increased screening in Whites or disproportionate mortality in Hispanics. African-American and Hispanic men are less likely to undergo prostatectomy or radiation therapy than Whites; elderly men of all races/ethnicities are also less likely to receive these therapies than younger men. These variations in treatment choices are largely unexplored, particularly for Hispanics, the fasting growing minority group in the US. Treatment variation also exists in the context of uncertainty regarding treatment efficacy. There are no studies that we are aware of that comprehensively examine treatment choices in prostate cancer patients. To address this important gap, the Cancer Clinical and Economics Outcomes Core of Georgetown University's Lombardi Cancer Center will conduct a population-based cross-sectional study of a cohort of 830 African-American, Hispanic, and White men. We will use the SEER rapid case ascertainment system in Northern California to identify men newly diagnosed with prostate cancer, and their physicians. This geographic region has a large African-American and Hispanic population, and a high managed care market. We will use the Anderson and Aday Model of Health Services Use to determine the relationships between predisposing, enabling, and need factors in treatment choices. We also extend the model to include an economic assessment of treatment choices. The specific aims of the study are to: 1) Determine if payor type (managed care vs FFS; an enabling factor) explains a significant amount of the variation in treatment choice; 2) Determine the pathways through which key predisposing (age, race/ethnicity), enabling factors (socioeconomic status [SES] and payor type), and need factors (stage, comorbidity, and MD treatment propensity) influence treatment choice; 3) Evaluate the role of patient preferences and attitudes towards cancer [predisposing factors] in treatment choice; and 4) Conduct an economic evaluation of different stage-specific treatment strategies. We will evaluate costs per patient satisfaction as an intermediate outcome; we will also develop a mathematical model to evaluate costs per quality-adjusted life year. This will be the first study to apply a comprehensive model of health services use in a population-based, racially/ethnically diverse cohort to explain prostate cancer treatment choices. The economic evaluation will extend prior work by including non-direct medical costs, quality-adjustment, and subgroup analyses (e.g., by payor type). These data are a first step in targeting future interventions for patients, providers, and health care payors to optimize the outcomes of prostate cancer for all US men.

FOR USE BY THE AMERICAN CANCER SOCIETY

Form Approved Through 9/30/97
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

Grant Application

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

LEAVE BLANK-FOR PHS USE ONLY		
Type	Activity	Number
Review Group	Formerly	
Council/Board (Month/Year)		Date Received

1. TITLE OF PROJECT (*DO not exceed 56 characters, including spaces and punctuation.*)
Decisions & Outcomes of BRCA1/2 Test for Breast Patients

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☐ YES (*If "Yes" state number and title*

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME (*Last, first, middle*)
Lerman, Caryn,

3b. DEGREE(S)
Ph.D.

3c. SOCIAL SECURITY NO.
177-52-3308

3d. POSITION TITLE
Associate Professor of Medicine

3e. MAILING ADDRESS (*Street, city, state, zip code*)
Lombardi Cancer Center
The Research Building
Georgetown University Medical Center
3970 Reservoir Road NW
Washington, DC 20007-2197

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Lombardi Cancer Center

3g. MAJOR SUBDIVISION
Georgetown University Medical Center

3h. TELEPHONE AND FAX (*Area code, number and extension*)
TEL: (202) 687-0806
FAX: (202) 687-0820

E-MAIL ADDRESS
lermanc@gunet.georgetown.edu

4. HUMAN SUBJECTS
☐ No
☒ Yes

4a. If "Yes", Exemption no. or
IRB approval date 2/15/96 ☒ Full IRB Review ☐ Expedite Review

4b. Assurance of Compliance or

5. VERTEBRATE ANIMALS
☒ No
☐ Yes

5a. If "Yes," IACUC approval date or

5b. Animal welfare assurance no.

6. DATES OF PROPOSED PERIOD OF SUPPORT (*month, day, year--MM/DD/YY*)
From 07/01/97 Through 01/31/02

7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD
7a. Direct Costs ($) 376,271
7b. Total Costs ($) 602,136

8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT
8a. Direct Costs ($) 1,921,385
8b. Total Costs ($) 3,089,770

9. APPLICANT ORGANIZATION
Name Georgetown University
Address 37th and O Streets, NW
Washington, DC 20057

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☐ State ☐ Local
Private: → ☒ Private Nonprofit
Forprofit: → ☐ General ☐ Small Business

11. ORGANIZATIONAL COMPONENT CODE 01

12. ENTITY IDENTIFICATION NUMBER 1-530196603-A1

Congressional District DC

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IS AWARD IS MADE
Name Monique Anderson
Title Grants and Contracts Officer
Address Division of Research Grants and Contracts
2115 Wisconsin Avenue NW
Washington, DC 20007
Telephone (202) 687-1366
FAX (202) 687-3182
E-Mail Address Andersom@odrge.odr.georgetown.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name James F. Burris, M.D.
Title Associate Dean for Research Operations
Address Division of Research Grants and Contracts
2115 Wisconsin Avenue NW
Washington, DC 20007
Phone (202) 687-7007
FAX (202) 687-2585
E-Mail Address

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. (*In ink. "Per" signature not acceptable.*)
Caryn Lerman
DATE 9/12/96

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:
I certify that the statements herein are true, complete and accurate to the Best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may be subject to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. (*In ink. "Per signature not acceptable).*
James F Burris MD
DATE 9/27/96

DESCRIPTION. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

As a result of the recent isolation of the BRCA1 and BRCA2 breast cancer susceptibility genes, genetic testing is currently being integrated into the medical management of high risk individuals and families (ASCO, 1996). Women newly diagnosed with breast cancer represent a group for whom BRCA1/2 testing may have important clinical implications. Those who have BRCA1/2 mutations may have elevated risks of second primary breast cancers; as such, breast-conserving surgery may not be a preferred option for these women. We propose a prospective, longitudinal study to examine decision-making about pre-surgery BRCA1/2 testing and the medical, psychosocial, and economic outcomes of testing among newly-diagnosed breast cancer patients who are at high risk for having a BRCA1/2 mutation. The theoretical framework for this investigation is derived from Expected Utility Theory. The specific aims are: (1) to establish rates of uptake of BRCA1/2 testing prior to surgical treatment for breast cancer, and to identify the determinants of the decision to be tested; (2) to evaluate the impact of BRCA1/2 testing on patients' surgical treatment choices; (3) to evaluate the impact of pre-surgery BRCA1 testing on psychosocial well-being; and (4) to develop a model to estimate the costs of BRCA1/2 testing for newly-diagnosed breast cancer patients per quality-adjusted life years saved. The subjects in this prospective longitudinal study are 400 newly-diagnosed breast cancer patients who have $\geq$ 25% prior probability of having a BRCA1/2 mutation. A baseline assessment will be conducted prior to the offer of testing to collect data on background/controlling variables (sociodemographics, medical, physician and family factors), predictor/moderator variables (preferences for health outcomes, coping style, anxiety, social support), and baseline levels of outcome variables (psychosocial well-being, prevention/surveillance practices). Following pre-test education and informed consent, patients will have an opportunity to have BRCA1/2 testing and receive their result during an individual session with a genetic counselor. Follow-up interviews will be conducted at 1-, 6-, 12-, and 18-months post-surgery to collect outcome data. The primary group comparisons in multiple regression models will be between BRCA1/2 carriers, noncarriers, and pre-surgery test decliners. The proposed cost-effectiveness analysis will incorporate prospective data on patient preferences and outcomes, together with secondary data from the literature, into a decision-analytic model.

PERFORMANCE SITE(S) *(organization, city, state)*

Lombardi Cancer Center (LCC), Georgetown University Medical Center (GUMC), Washington, D.C.

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Caryn Lerman, Ph.D.	GUMC	Principal Investigator (PI)
Claudine Isaacs, M.D.	GUMC	Co-PI
Jeanne Mandelblatt, M.D.	GUMC	Co-PI
Marc Schwartz, Ph.D.	GUMC	Co-PI
William Lawrence, M.D.	GUMC	Co-investigator
Beth Peshkin, M.S.	GUMC	Genetic counselor / Co-investigator
Gary Chase, Ph.D.	GUMC	Biostatistician / Co-investigator
Marie Pennanen, M.D.	GUMC	Surgeon / Co-investigator
Christine Berg, M.D.	GUMC	Radiation Oncologist / Co-investigator
Mark Hughes, M.D., Ph.D.	GUMC	Genetics / Co-investigator
Karen Rothenberg, J.D., M.P.A.	GUMC	Consultant / Ethics
Colette Magnant, M.D.	GUMC	Consultant / Surgery
Peter Petrucci, M.D.	GUMC	Consultant / Surgery

AA

Form Approved Through 9/30/97
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

Grant Application

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

LEAVE BLANK-FOR PHS USE ONLY		
Type	Activity	Number
Review Group	Formerly	
Council/Board *(Month/Year)*		Date Received

1. TITLE OF PROJECT (*DO not exceed 56 characters, including spaces and punctuation.*)
Comparing Models of Counseling for BRCA1/2 Testing

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT [X] NO [ ] YES (*If "Yes" state number and title*
Competitive Renewal MH/HG 54435

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME (*Last, first, middle*)
Lerman, Caryn E.

3b. DEGREE(S)
Ph.D.

3c. SOCIAL SECURITY NO.

3d. POSITION TITLE
Associate Professor

3e. MAILING ADDRESS (*Street, city, state, zip code*)
Lombardi Cancer Center
The Research Building
Georgetown University Medical Center
3970 Reservoir Road NW
Washington, DC 20007-2197

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Lombardi Cancer Center

3g. MAJOR SUBDIVISION
Georgetown University Medical Center

3h. TELEPHONE AND FAX (*Area code, number and extension*)
TEL: (202) 687-0801
FAX: (202) 687-0820

E-MAIL ADDRESS

4. HUMAN SUBJECTS
[ ] No
[X] Yes

4a. If "Yes", Exemption no. or
IRB approval date 2/20/97
[X] Full IRB [ ] Expedite Review

4b. Assurance of Compliance or
M-1255

5. VERTEBRATE ANIMALS
[X] No
[ ] Yes

5a. If "Yes," IACUC approval date

5b. Animal welfare assurance no.

2.27.97

6. DATES OF PROPOSED PERIOD OF SUPPORT (*month, day, year--MM/DD/YY*)		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
12/01/97	11/30/01	$440,071	$605,813	$1,844,172	$2,437,320

9. APPLICANT ORGANIZATION
Name Georgetown University
Address 37th and O Streets, NW
Washington, DC 20057

10. TYPE OF ORGANIZATION
Public: → [ ] Federal [ ] State [ ] Local
Private: → [X] Private Nonprofit
Forprofit: → [ ] General [ ] Small Business

~~11. ORGANIZATIONAL COMPONENT CODE~~ 01
~~12. ENTITY IDENTIFICATION NUMBER~~ 1-530196603-A1
~~Congressional District~~ DC

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IS AWARD IS MADE
Name Monique Anderson
Title Grants and Contracts Officer
Address Division of Research Grants and Contracts
2115 Wisconsin Avenue NW
Washington, DC 20007
Telephone (202) 687-1366
FAX (202) 687-3182
E-Mail Address Andersom@odrge.odr.georgetown.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name James F. Burris, M.D.
Title Associate Dean for Research Operations
Address Division of Research Grants and Contracts
2115 Wisconsin Avenue NW
Washington, DC 20007
Phone (202) 687-7007
FAX (202) 687-2585
E-Mail Address

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. (*In ink. "Per" signature not acceptable.*)
Caryn Lerman

DATE
2-20-97

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:
I certify that the statements herein are true, complete and accurate to the Best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may be subject to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. (*In ink. "Per signature not acceptable).*
James F Burris MD

DATE
2/27/97

DESCRIPTION. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. DO NOT EXCEED THE SPACE PROVIDED.

As a result of the isolation of the BRCA1 and BRCA2 genes, genetic testing for breast-ovarian cancer susceptibility is now commercially available. Our ongoing research has documented the need for adjunctive psychosocial counseling approaches to improve the outcomes of genetic counseling and testing among identified carriers of BRCA1/2 mutations. The evaluation of such interventions has been highlighted as a research priority in two recent cancer research workshops. Thus, in this competitive renewal application, we propose a multi-institutional randomized trial to evaluate whether the outcomes of BRCA1/2 testing among female mutation carriers are improved by providing a psychosocial telephone counseling (PTC) intervention *in addition to* standard genetic counseling (SGC). The specific aims are: (1) to evaluate the efficacy of PTC delivered in conjunction with SGC, compared to SGC only; (2) to explore the mechanisms by which the PTC impacts on psychosocial and behavioral outcomes; (3) to identify carriers who are most and least likely to benefit from PTC; and (4) to conduct an economic evaluation of the two counseling strategies. The participants in this randomized trial are 290 female carriers of BRCA1/2 mutations and 290 female noncarriers. A baseline assessment will be conducted prior to the offer of testing to collect data on background variables (sociodemographics, medical and family history), moderator variables (personality style, social support), and baseline levels of outcome variables. Following *in-person* pre-test genetic counseling and informed consent, participants will have an opportunity to have BRCA1/2 testing. After providing additional written consent, they will receive their result during an individual *in-person* session with a genetic counselor. Following disclosure of mutation status, carriers of BRCA1/2 mutations will be assigned randomly to receive either SGC follow-up only or SGC plus PTC. The PTC protocol, adapted from the previous research of the study investigators, will be delivered in 6 sessions over a 3-month period after disclosure. Sessions will include supportive counseling and provide training in coping skills to enhance the outcomes of genetic testing. Follow-up interviews will be conducted at 1-, 4-, 6-, and 12-months post-disclosure to collect data on the following outcomes: comprehension, distress, family communication and functioning, adoption of recommended cancer screening practices, and satisfaction with decisions about prophylactic surgery. If beneficial and cost-effective, the proposed PTC intervention can be disseminated to varied research and clinical settings in which BRCA1/2 testing is offered.

PERFORMANCE SITE(S) *(organization, city, state)*

Lombardi Cancer Center (LCC), Georgetown University Medical Center (GUMC), Washington, D.C.
AMC Cancer Center/University of Colorado Health Sciences Center, Denver, Colorado
Rush Cancer Institute (RCI), Chicago, Illinois
Duke Comprehensive Cancer Center (DCCC), Durham, North Carolina

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Caryn Lerman, Ph.D.	GUMC	Principal Investigator (PI)
Alfred Marcus, Ph.D.	AMC	Co-PI, Site PI
David Cella, Ph.D.	RCI	Co-PI, Site PI
Eric Winer, M.D.	DCCC	Co-PI, Site PI
Marc Schwartz, Ph.D.	GUMC	Co-PI
Lari Wenzel, Ph.D.	AMC	Co-investigator
Judith Benkendorf, M.S.	GUMC	Co-investigator
Jeanne Mandelblatt, M.D.	GUMC	Co-investigator
William Lawrence, M.D.	GUMC	Co-investigator
John Hanfelt, Ph.D.	GUMC	Co-investigator/Biostatistics
Mohammad Abbaszadegan, Ph.D.	GUMC	Co-investigator
Barbara Rimer, Dr., P.H.	DCCC	Co-investigator
Amy Peterman, Ph.D.	RCI	Co-investigator
Beth Peshkin, M.S.	GUMC	Co-investigator
Madison Powers, J.D., D.Phil.	GUMC	Consultant/Bioethics

AA

Form Approved Through 9/30/97
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

Grant Application

Follow instructions carefully.
Do not exceed character length restrictions indicated on sample.

LEAVE BLANK-FOR PHS USE ONLY		
Type	Activity	Number
Review Group	Formerly	
Council/Board(*Month/Year*)		Date Received

1. TITLE OF PROJECT (*DO not exceed 56 characters, including spaces and punctuation.*)
Cost-Effectiveness of HPV Screening for Cervix Cancer

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES (*If "Yes" state number and title*
PA-94-011 Economic Studies in Cancer Prevention, Screening, and Care

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME (*Last, first, middle*)
Mandelblatt, Jeanne S.

3b. DEGREE(S)
M.D.

3c. SOCIAL SECURITY NO.
058-44-8916

3d. POSITION TITLE
Associate Professor of Medicine

3e. MAILING ADDRESS (*Street, city, state, zip code*)
Lombardi Cancer Center
The Research Building
Georgetown University Medical Center
3970 Reservoir Road, NW
Washington, DC 20007-2197

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Lombardi Cancer Center

3g. MAJOR SUBDIVISION
Department of Medicine

3h. TELEPHONE AND FAX (*Area code, number and extension*)
TEL: (202) 687-0801
FAX: (202) 687-0651

E-MAIL ADDRESS

4. HUMAN SUBJECTS
☐ No
☒ Yes

4a. If "Yes", Exemption no. or
IRB approval date Pending ☐ Full IRB or ☐ Expedite Review

4b. Assurance of Compliance
M-1255

5. VERTEBRATE ANIMALS
☒ No or
☐ Yes

5a. If "Yes," IACUC approval date

5b. Animal welfare assurance no.

6. DATES OF PROPOSED PERIOD OF SUPPORT (*month, day, year--MM/DD/YY*)
From 01/01/97 Through 12/31/99

7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD
7a. Direct Costs ($) $260,285
7b. Total Costs ($) $393,924

8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT
8a. Direct Costs ($) $766,392
8b. Total Costs ($) $1,095,592

9. APPLICANT ORGANIZATION
Name Lombardi Cancer Center
Address The Research Building
3970 Reservoir Road, NW
Washington, DC 20007-2197

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☐ State ☐ Local
Private: → ☒ Private Nonprofit
Forprofit: → ☐ General ☐ Small Business

11. ORGANIZATIONAL COMPONENT CODE 01

12. ENTITY IDENTIFICATION NUMBER 1-530196603-A1
Congressional District DC

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IS AWARD IS MADE
Name Monique Anderson
Title Grants Administrator
Address Division of Research Grants and Contracts
2115 Wisconsin Avenue, NW
Washington, DC 20007
Telephone (202) 687-1366
FAX (202) 687-23182
E-Mail Address

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name James F. Burris, M.D.
Title Associate Dean for Research Operations
Address 2115 Wisconsin Avenue, NW
Washington, DC 20007
Phone (202) 687-7007
FAX (202) 687-2585
E-Mail Address

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. (*In ink. "Per" signature not acceptable.*)
J Mandelblatt
DATE 5-16-96

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the Best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may be subject to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. (*In ink. "Per signature not acceptable).*
James F Burris MD
DATE 5/29/96

A.

PHS 398 (Rev. 5/95)

DESCRIPTION. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

Although the incidence and mortality from cervical cancer has declined substantially over the last four decades, worldwide, cervical cancer continues to be a leading cancer cause of death in women, second only to breast cancer in incidence and mortality. At present, the Pap smear is the only accepted technique for screening for cervical neoplasia. In the US, an estimated 27 million smears are performed annually. However, despite recent implementation of widespread quality assurance standards, Pap smear test characteristics remain less than optimal, with up to 25% of smears reported as falsely negative and 5% reported as falsely positive. Since cervical cancer is strongly related to human papilloma virus (HPV), it has been proposed that the addition of HPV DNA testing to routine cytology screening could improve the detection of cervical neoplasia.

We propose to form an inter-institutional consortium of investigators, including virologists, gynecology oncologists, nurse oncologists, epidemiologists, and health economists to estimate the cost-effectiveness of human papilloma virus (HPV) testing as an adjunct to Pap smear screening for cervical neoplasia in older women (defined as women aged 45 or more years of age). We will develop a population-based transition-state model of the natural history of cervical cancer to estimate the incremental cost-effectiveness of triennial screening for cervical cancer using HPV and Pap smears combined, and HPV alone, compared to traditional Pap testing. Secondary research questions include: 1) Does the cost effectiveness (CE) of different screening strategies vary by age (ie, under and over 65) or race; and 2) Does the presence of HPV infection alter the natural history of disease (ie, decrease the sojourn time from low grade to higher grade SIL). The data from this proposal will provide a framework for the development of clinical management guidelines and policy decisions that maximize the health of a population for an acceptable cost.

PERFORMANCE SITE(S) *(organization, city, state)*

Georgetown University Medical Center, Washington, D.C.
Johns Hopkins School of Public Health, Baltimore, M.D.
George Washington University, Washington, D.C.

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Jeanne Mandelblatt	Georgetown University School of Medicine	Principal Investigator
Bruce Trock	Georgetown University School of Medicine	Co-Investigator
William Lawrence	Georgetown University School of Medicine	Co-Investigator
Jack Hadley	Institute for Health Care Research and Policy	Co-Investigator
Karen Gold	Georgetown University School of Medicine	Co-Investigator
Caroline Burnett	Georgetown University School of Medicine	Co-Investigator
Keeerti Shah	Johns Hopkins University	Consultant
Annette Bicher	George Washington University	Consultant
Laura Koutsky	University of Washington	Consultant
Paul Levine	George Washington University	Consultant
Michelle Manos	Kaiser Permanente - Oakland, CA	Consultant
Ralph Richart	Columbia Univ-College of Physicians & Surgeons	Consultant
Clyde Schechter	Mt. Sinai School of Medicine	Consultant
Mark Schiffman	National Cancer Institute	Consultant
Nicole Urban	Fred Hutchinson Cancer Research Center	Consultant
Thomas Wright	Columbia Univ-College of Physicians & Surgeons	Consultant

A PROSPECTIVE ANALYSIS OF LIFE EXPERIENCES AND MEANING SYSTEMS AS THEY RELATE TO QUALITY OF LIFE AND EXTENDED SURVIVAL AMONG WOMEN WITH METASTATIC BREAST CANCER

Principal Investigator: Marilyn J. Schlitz, Ph.D.
Keywords: psychosocial, spiritual, narratives, meaning, coherence

ABSTRACT

When a diagnosis of breast cancer is made, the probable length of survival or recovery can be predicted based on tumor type, nodal involvement, and metastatic status.[1] Yet some women survive an exceptionally long time compared to that predicted by their stage of disease at diagnosis.[2-3] Very scant scholarly attention has been paid to the extended survival of these women.[4-11]

Important progress has been made in identifying biological factors influencing survival rates for women with metastatic breast cancer.[12-13] Still, biology alone is not an adequate predictor when estimating survival time for any individual woman. The question remains, are there other, non-biological factors that may help us to understand how some women survive longer than others and that may inform us about issues related to quality of life? Based on the biographies of cancer survivors, and a growing body of scientific literature on social, psychological, and spiritual factors in survival, it is of special relevance to ask: do extended survivors have different life experiences and personal meaning systems that might distinguish them from non-survivors?

To address these questions, it is necessary to focus on the patient herself as a starting place for analyzing relevant categories of life experience and personal meaning associated with the breast cancer experience.[14] To do so, the proposed work involves a naturalistic population-based study of extended survivors from breast cancer metastatic at the time of diagnosis in comparison to an internally emerging control group of non-survivors. While known biological variables are responsible for a significant portion of any differences found between survivors and nonsurvivors, we predict that these alone will not be sufficient to predict survival.

The objectives of the study will be addressed within a prospective/longitudinal design in which we will follow for up to 34 months a group of approximately 148 women in Regions 1 and 8 of the Greater Bay Area Cancer Registry (GBACR) who have received an initial diagnosis of metastatic breast cancer. All women will be interviewed within approximately two months from the time of diagnosis. The goal is to identify those factors that the women themselves see as important to their disease experience and to their quality of life. Based on survival outcomes at approximately 20.6 months (the 50% survival point for women with metastatic breast cancer) we will compare two principal subgroups: survivors and non-survivors. Data will take the form of personal narratives, psychometric assessments, and medical records.

Extensive scholarly documentation exists to show that explanations for illness usually are given in narrative form.[15] As Brody[16] and others have documented, the telling of a story is a way to give meaning to the experience of ill-health. The proposed research builds upon the leads of previous work, specifically looking at how patients conceptualize the diagnosis within the larger context of how they view their life story and how they articulate their own personal meaning system relative to the disease. Based on issues identified within the literature, the interviews will focus on social support, meaning of life, meaning of the illness, coherence in the face of stress, religious and spiritual beliefs, and life events. The interview schedule is being tested and refined during an on-going pilot study using life history narratives to explore the meaning systems of 20 year survivors from metastatic cancer. A small battery of psychometric assessments will be used to corroborate the validity and reliability of the qualitative data. Administration and analysis of all measurements, data entry, and interview procedures will all be performed blind as to the individual's ultimate outcome.

This exploratory program represents a promising new direction for breast cancer research. The focus on extended survivors enables us to ask new questions about each individual's interpretations, coping styles, personal meaning systems, and social and spiritual/religious support and orientation that may influence quality of life and length of survival of women with metastatic breast cancer. The use of a controlled prospective study design that makes use of life history narratives, combined with selected psychometric, demographic, and socioeconomic data is highly innovative and may generate a deeper understanding of the experience of metastatic breast cancer. In addition, the proposed study may lead to new research and treatment directions for women with metastatic breast cancer.

SENT BY: XEROX 3006; 9-23-97 11:43AM; 2026870694 => ; #2/6