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PRINCIPAL INVESTIGATOR: Mary B. Daly, M.D., Ph.D.

CONTRACTING ORGANIZATION: Fox Chase Cancer Center
Philadelphia, Pennsylvania 19111

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The wealth of research regarding the complex interaction of the genetic, biologic and environmental factors associated with breast carcinogenesis offers promise towards better understanding of breast cancer. The progress in molecular genetics provides us with opportunities to expand our knowledge about modifiable causes of breast cancer. The development of the Fox Chase Cancer Center Breast Cancer Risk Registry was proposed to facilitate research in the epidemiologic and genetic predictors of disease and permitted evaluation of the effectiveness of new risk counseling, surveillance and prevention strategies. Staff training, sharing resources and administrative support were critical components to assist the community hospital to develop a high-risk program. Formal and on-going inservice training in cancer genetics, breast cancer risk and genetic educational resources, telephone consultation, DNA blood collection procedures, and continuous monitoring were necessary for implementation and coordination of a community-based risk registry. The establishment of an Advisory Panel helped address additional issues of informed consent, reimbursement, and community-based counseling strategies. This project demonstrates that with appropriate resources and support, it is feasible to establish a registry for individuals at high risk for breast cancer and further our understanding of the genetic and epidemiologic basis of the disease.

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Mary P. Daly 10/13/95

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Final Report

Introduction

A. Subject

As our understanding of the process of carcinogenesis advances, there is a growing appreciation of the role of prevention in the control of cancer. Although the multifactorial nature of cancer makes it unlikely that the alteration of any one risk factor will prevent the disease, recent advances in understanding the genetic basis of carcinogenesis are providing extraordinary opportunities to identify and apply novel tools for estimating cancer risk and initiating preventive strategies. The National Human Genome Research Institute (NHGRI) is an international effort jointly funded by the National Institutes of Health (NIH) and the Department of Energy (DOE) to map the entire human genome and a series of model organisms. By the year 2005 the project has the potential to describe the 4000 genes thought to be responsible for human genetic disease **(1).** Already, the technology to identify mutations in cancer susceptibility genes for familial adenomatous polyposis (*APC*), hereditary breast and ovarian cancer (*BRCA1/2*), hereditary nonpolyposis colon cancer syndrome (*hMLH1, hMSH2*), multiple endocrine neoplasia 2a and 2b (*RET*), the Li-Fraumeni Syndrome (*TP53*) and hereditary melanoma syndrome (CDKN2, CDK4) is clinically available. In 1996, the American Society of Clinical Oncology (ASCO) issued practice guidelines for the incorporation of genetic risk assessment and counseling into standard oncologic care **(2).** Additionally, in 1998, the National Cancer Institute published a compilation of family cancer syndromes to assist clinicians in recognizing thirty-five known syndromes. **(3).** Breast cancer was associated with ten familial syndromes. These findings will have major public health implications in terms of patient and provider education, counseling strategies, and genetic screening and health care policies. However, before this rapidly accumulating genetic information can be transferred to the clinical setting in an effective and responsible way, a great deal of collaborative basic, clinical, epidemiological, behavioral and bioethical research needs to be done.

B. Purpose

The ability to systematically study the diverse aspects of breast cancer susceptibility in high risk populations within a structure of an established high risk registry, to stimulate progress in our basic understanding of the genetic events which accompany the carcinogenic process, and to transfer this information to the public health realm was the intent of this project. The purpose was to establish a registry which included both genetic and environmental risk information from a racially and ethnically diverse set of patients with familial breast cancer and from women at increased risk due to a positive family history. Furthermore, the project evaluated the feasibility of creating this infrastructure for the Registry within a network of community-based hospitals. The registry information would allow investigators from a wide range of disciplines to address questions of gene-environment interactions, of the relative role of reproductive events in women with a genetic risk for breast cancer, and of the underlying reasons for the differences in morbidity and mortality from breast cancer in different age and racial groups. It also proposed to help further the understanding of the genetic basis of breast cancer by identifying families appropriate for genetic studies. Moreover, preparing community providers to identify and

counsel women at high risk for breast cancer was proposed to serve as a model for transferring genetic information into the public health realm. Therefore, the specific aims of this project were:

1. To establish a protocol for identifying and recruiting women with one or more first degree relatives with breast cancer into a regional FCCC Network-wide registry of high risk individuals.

2. To establish a computerized data base system of comprehensive information including family history, personal medical history, lifestyle and environmental factors, health practices and beliefs, and psychological status which will serve as a resource for a spectrum of research activities.

3. To develop protocols for the selection of individuals and families for closer genetic investigation and genetic counseling.

4. To expand the FCCC/Network Breast Cancer Tissue Registry to include specimens of benign breast lesions as well as serum and DNA from women in the high risk registry.

5. To develop educational tools for primary care physicians at the community level to prepare them to take a leading role in the identification of women with a family history of breast cancer, in the interpretation of genetic test data, and in its relevance and application to clinical medicine.

6. To develop workshops for training nurses at the community level to provide breast cancer risk information, risk assessment, tailored preventive recommendations, and psychosocial support to high-risk women and their families.

7. To develop and test behavioral interventions which are sensitive to cultural, ethnic and racial differences which will promote positive outcomes to breast cancer risk information, including the results of genetic testing.

8. To form a Breast Cancer Risk Advisory Panel to provide guidance and counsel regarding the social, legal and ethical aspects of genetic testing for breast cancer.

C. Scope of Research

1. Epidemiology of Cancer

Coincident with the steady rise in cancer death rates observed over the past 25 years has come epidemiologic evidence of preventable causes for most of the common cancers, including breast, lung, and colorectal. Intervention strategies to modify health promoting behaviors have been developed and are being widely tested in an effort to significantly reduce the burden of cancer **(4)**. Along with widespread application of cancer control technologies, attempts to target special high risk populations for more cost effective use of interventions have gained acceptance **(5)**, particularly in view of the crisis facing the health care system today and the growing realization of the importance of preventive health strategies to reduce morbidity and mortality from cancer and other major diseases **(6)**. A redirection of research efforts towards a

better understanding of the multistage process of carcinogenesis to identify additional points of prevention is one of the most significant events to accompany the current revolution in genetics.

2. Genetic Model of Cancer

Family studies have long documented an increased risk among first and second degree relatives for several forms of cancer, including breast, ovarian, and colorectal. Hereditary patterns of cancer are often characterized by early age at onset, high penetrance, bilaterality of paired organs, vertical transmission through either parent, and an association with other types of tumors **(7, 8).** Recent advances in molecular genetic technology have led to the identification of genes associated with many human cancers. The *BRCA1* gene, on chromosome 17q12-q21, was isolated in 1994 and is thought to account for the majority of families in whom both early onset breast and ovarian cancer occur, and for approximately 45% of families with site-specific breast cancer **(9)**. Susceptibility is dominantly inherited with a 50% risk of inheritance for each child of a gene carrier. In these families, the cumulative risk for breast cancer in women with an altered *BRCA1* gene is estimated to be between 56 and 87% by age 70 yr, with approximately half of the cancers occurring before the age of 50 yr.**(10, 11).** A second breast cancer gene, *BRCA2*, has been identified on chromosome 13q12-q13, and appears to confer a high risk of site-specific breast cancer for both males and females **(12, 13, 14).** Three particular mutations, 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2* have been observed in 2.3% of a sample of Ashkenazi Jewish individuals, suggesting an especially high risk for developing breast and/or ovarian cancer in this population **(11).** Over 100 different mutations have been observed in *BRCA1* and *BRCA2*, and work is ongoing to characterize the penetrance and expressivity of each.

These and other advances in the isolation of genes associated with hereditary cancer will help to elucidate the basic mechanisms of carcinogenesis as well as the nature of the complex gene-environment interactions which characterize most sporadic cancers. The characterization of specific mutations within ethnic groups will permit more precise and targeted risk estimations. This work will also provide precise biomarkers of cancer susceptibility for clinical use in assessing an individual's risk for cancer. The incorporation of genetic information into clinical cancer risk assessment paradigms is being proposed as a way to target preventive strategies to the most appropriate individuals and to maximize their effectiveness.

3. Research and Educational Needs

Despite the incredible progress made in cancer genetics in the past decade, the ability to apply this knowledge to better understand human disease is in its infancy. The new molecular genetic tools will be the keys to open doors of knowledge for every aspect of cancer genetics including basic science, clinical implications, genetic epidemiology, psychosocial dimensions, and ethical issues. In addition to continuing to search for new cancer-related genes, we must establish the incidence, prevalence, penetrance and expressivity of known cancer susceptibility genes in different segments of the population. The natural history and clinical course of hereditary cancers must be defined. A whole host of related clinical questions, such as the safety of exogenous hormones among women with *BRCA1/2*-related cancers, remains to be addressed. On a population level, the exploration of gene/environment interactions may provide crucial clues about the etiology of sporadic as well as hereditary cancers. By identifying populations with a defined genetic risk we can also begin to explore the legal and ethical issues surrounding cancer genetic testing, and to lay the groundwork for finding new primary and secondary prevention approaches. Effective strategies for the communication of genetic risk

information and for the psychosocial support of individuals who receive this information can be explored and established.

4. Potential Public Health Impact

The potential for widespread use of genetic testing for cancer susceptibility genes will have major public health implications in terms of screening policies, patient and physician education, counseling strategies, the clinical management of inherited cancers, and health care policy. Already we are witnessing quantum leaps in the public awareness of cancer risk, the significance of family history, and in the search for preventive practices that will address these risks. Medical care is also changing rapidly, with the shift from the disease-oriented model of care to one which places a strong emphasis on preventive care and patient education. Preliminary guidelines for the management of individuals within BRCA1, BRCA2 and HNPCC families have been proposed for use in the clinical setting **(15, 16).** Furthermore, the American Society of Clinical Oncology (ASCO) has published a position paper on genetic testing for cancer susceptibility affirming the responsibility of clinical oncologists to identify and counsel individuals for whom genetic testing may aid in the choice of prevention and early detection options **(2)**.

The ability to systematically study the diverse aspects of breast cancer susceptibility in high risk populations within a structure of an established high risk registry was proposed to stimulate continual progress in the understanding of the genetic events which accompany the carcinogenesis process and allow transfer of this information to the public and professional communities.

D. Background of Previous Work

The Family Risk Assessment Program (FRAP) was established at FCCC in 1991 by Dr. Mary Daly to meet several needs: 1) to offer to cancer patients and their family members education and information about cancer risk, screening, diagnosis, and treatment; 2) to serve as a research base for ongoing evaluation of the epidemiologic, biologic, genetic, and environmental lifestyle factors which influence disease risk; 3) to develop predictive models which will incorporate pedigree data, mutation analysis and epidemiologic risk factors to more precisely estimate cancer risk, and 4) to develop models for communication of cancer risk information. FRAP is a collaborative effort of multiple disciplines including oncologists, gynecologists, gastroenterologists, urologists, pathologists, nurses, health educators, genetic counselors, epidemiologists, behavioral scientists, nutritionists and basic scientists. The program has established a series of goals for cancer risk counseling, including the communication of accurate information on the genetic, biologic, and environmental factors related to individual risk, the formulation of options and recommendations for prevention and screening, and the provision of psychological support to facilitate adjustment to the information received **(17)**.

To date, we have accrued a cohort of over 1500 families with a history of breast and/or ovarian cancer. More recently, with the collaboration of Harold Frucht, M.D., head of Gastrointestinal Medicine at FCCC, and Gerald Hanks, M.D., Chair of the Department of Radiation Oncology, the program has expanded to include individuals with a clinical and/or familial risk for colorectal and prostate cancer. Over 250 individuals fitting these criteria have been accrued into the program.

The Genetics Research Laboratory, under the direction of Dr. Andrew Godwin, has created an extensive specimen bank, including over 1200 research participant samples from 350 high risk families participating in the FRAP. Clinical genetic testing is available in a CLIA-

approved lab for appropriate individuals and families through a collaboration between Dr. Godwin and A. Patchefsky, M.D., Chairman of the Department of Pathology.

The FRAP program also provides a source of accrual for multiple chemoprevention studies, including a leadership role in accrual to the national cooperative group chemoprevention trials, as well as several Phase I chemoprevention studies in breast, colorectal, lung and oropharyngeal cancers. One of our greatest strengths is our research exploring cancer-related health attitudes and behavior, screening and prevention strategies, quality of life concerns, and the psychosocial dynamics generated by a cancer susceptibility diagnosis. In collaboration with Dr. Caryn Lerman of Georgetown Medical Center and Dr. Barbara Rimer of Duke University we have conducted a randomized trial to evaluate the psychological and behavioral impact of individualized breast cancer risk counseling and breast self exam (BSE) training among women with a family history of breast cancer. Of interest was the finding at baseline that adherence to mammography among this population was not related to the presence of standard risk factors, including family history **(18).** Three months after the breast cancer risk counseling and BSE skills training intervention, adherence to correct BSE frequency was significantly improved **(19).** Furthermore, the counseling intervention had small but significant positive effects on comprehension of personal risk of breast cancer and on decreased breast cancer-specific distress. However, in both groups a significant proportion of women continue to overestimate their lifetime risk for breast cancer after the counseling session, indicating the need for additional strategies to optimize risk comprehension **(20).**

To pursue other variables modifying risk comprehension, we are working with Suzanne Miller, Ph.D., Director of Behavioral Research at FCCC, and her staff to examine how psychological factors moderate outcomes in the risk counseling setting, to explore the impact of a structured psychological support intervention on the outcome of education and counseling for genetic risk for breast/ovarian cancer **(21),** to evaluate the effect of genetic susceptibility status on spouses and other family members, to identify types of cognitive and affective profiles that influence the decision to enter a chemoprevention trial, and to determine the effect of cancer-specific psychologic distress on cancer-protective behaviors **(22).**

One of the first needs to emerge from our work with cancer-prone families was the need to educate patients and their families about their cancer risk profile and about appropriate primary and secondary prevention options. We have developed a series of educational materials to meet this need.

Breast (Ovarian/Colon/Prostate) Cancer Risk Education: An Educational Kit for Professionals, a series of booklets, color slides and flip chart prints which describe the normal anatomy and physiology of the breast, ovary, colon and prostate glands, cancer risk factors, the genetic origin of cancer, and early detection and prevention. These materials have been used with over 1400 family members, in both group and individual settings, to provide information regarding personal cancer risk and to invite participation in current prevention and research studies.

- *Genetic Risk Education*, an interactive multimedia program on breast and ovarian cancer genetics and cancer risk education. The program uses interactive CD-i technology and offers a variety of media, including text, narration, still graphics, animation and full motion video. It provides multiple self-guided pathways of learning to enable users to process information at their own pace and to take an active role in their learning process. The CD-i is programmed to test a user's knowledge regarding the genetics of breast and ovarian cancer before and after viewing, and to record time spent and the number of content pieces chosen by the user.

- *Focus on Prevention*, a guide to Diet and Nutrition, which provides the rationale for a low-fat high-fiber diet and offers helpful tips on food preparation and exercise regimens.

- The FRAP newsletter which keeps participants aware of research and scientific findings.

- *Familial Cancer Risk Counseling: A Training Program for Nurses*, a three day nurses training program to provide nurses with the skills to identify individuals with potential hereditary cancer profiles, assess genetic cancer risk, and guide individuals to counseling and testing services. This course has been successfully offered to almost 100 nurses from all over the US, with documented improvements in knowledge and skills **(23).** We are now in the process of developing an advanced course for nurses and genetic counselors to offer more intensive and skills-based training in cancer risk assessment and communication, and more in-depth experience with the genetic testing situation.

- *Training Family Practice Residents in Cancer Risk Counseling*, a four-part physician training program to provide primary care practitioners a background in cancer genetics, and the skills to incorporate genetic risk counseling into their practices. The residents who participated in the pilot presentation of this course will be followed prospectively to measure actual skills practice as they move through their careers. The course is being integrated into family practice residency training programs and serves as a model for putting state-of-the-art information into the hands of primary care providers **(24)**.

- *Train the Counselor*, an ongoing training program for CIS staff to keep them updated on new developments in cancer genetics and new research opportunities in the tri-state region.

- Access to the multiple resources and materials from the NCI, the ACS and the CIS.

- The FRAP home page (www.fccc.edu/clinical research/family riskassessment/frap.htm) which provides information about the risk assessment programs available at FCCC and its Network affiliates, and which directs users to appropriate referral sources.

Providing an overarching community framework to all of these outreach efforts is the Fox Chase Network, a unique cooperative effort between FCCC and 14 Network Institutes and health systems representing 20 community hospitals in Pennsylvania and New Jersey. The Network was established in 1986 with a mission to enhance the quality of cancer care in the community. The extension of the FRAP program to the Fox Chase Network is one of many examples of our commitment to bring state-of-the-art cancer services to the community. In addition, the FCCC Community and Physician Awareness Program targets primary care practitioners and members of the community to make them aware of the FCCC-affiliated cancer programs in their communities and the range of cancer services available to them. Through the Physicians Services Program, physicians in the tri-state area are visited by a physicians' services coordinator who, using an academic detailing approach, provides information about current protocols and clinical programs, including cancer prevention and control initiatives available at the Center.

Body

A. Methods/Assumptions/Procedures

The methods of accomplishing the proposed goals were set out in the grant proposal in eight specific aims (see Figure 1.)

Figure 1. Specific Aims of the Breast Cancer Risk Registry

1. To establish a protocol for identifying and recruiting women with one or more first degree relatives with breast cancer into a regional FCCC Network-wide registry of high risk individuals.

2. To establish a computerized data base system of comprehensive information including family history, personal medical history, lifestyle and environmental factors, health practices and beliefs, and psychological status which will serve as a resource for a spectrum of research activities.

3. To develop protocols for the selection of individuals and families for closer genetic investigation and genetic counseling.

4. To expand the FCCC/Network Breast Cancer Tissue Registry to include specimens of benign breast lesions as well as serum and DNA from women in the high risk registry.

5. To develop educational tools for primary care physicians at the community level to prepare them to take a leading role in the identification of women with a family history of breast cancer, in the interpretation of genetic test data, and in its relevance and application to clinical medicine.

6. To develop workshops for training nurses at the community level to provide breast cancer risk information, risk assessment, tailored preventive recommendations, and psychosocial support to high risk women and their families.

7. To develop and test behavioral interventions which are sensitive to cultural, ethnic and racial differences, which will promote positive outcomes to breast cancer risk information, including the results of genetic testing.

8. To form a Breast Cancer Risk Advisory Panel to provide guidance and counsel regarding the social, legal and ethical aspects of genetic testing for breast cancer.

Specific Aim 1: Establish a Protocol for the High Risk Registry.

The protocol for recruitment was part of a broader implementation plan. Program implementation began with collaborative meetings with the Medical Director of each Network Oncology Program. This approach first assessed interest in participation in the program as well as determined training, education and administrative needs. Those institutions interested in participation were guided through a process that included: 1) the development of an administrative and implementation plan; 2) training and preparation of nursing staff to coordinate and conduct the program; 3) training in all protocols and procedures, and 4) on-going mentoring and monitoring in cancer risk assessment and counseling. The protocols developed for recruitment have included community outreach and education or physician referral. Community outreach included education programs regarding breast cancer risk offered to the community at large. Education regarding risk included personal, biologic and genetic risk for developing breast cancer as well as information about participation in the Registry Program. Physician referral was

aimed at breast cancer patients concerned with cancer risk for their family or with known family history of cancer. These women were referred to the program coordinator for attendance in the education program. Recruitment followed the education program since informed consent in both setting required knowledge of cancer risk and research requirements. Women who were interested in participation completed the set of questionnaires **(Submitted in Appendix D in 1995 Report)**. These questionnaires included the following categories of data:

a. Demographic data; date of birth, race, ethnicity, religion, sex, marital status, education, and income.

b. Family history; cancer diagnoses, age at onset, cancer deaths, age at death, and place of treatment and/or death was recorded for all first and second-degree relatives of Network participants. Using our current format, this data can readily be translated into a family pedigree for counseling and teaching purposes. Our success in confirming diagnoses with medical records and/or death certificates in the Family Risk Assessment Program supports the reliability of self-report of family history observed by other investigators **(7).**

c. Medical History; relevant medical conditions, (e.g. colonic polyps, benign breast disease) medication use, and weight history was recorded. For females, a thorough review of reproductive events, including menstrual history, pregnancy history, lactation experience, history of spontaneous and induced abortions, and exogenous hormone use, including fertility drugs, was collected.

d. Epidemiologic Risk Factors; radiation and occupational exposures, smoking history, dietary history, alcohol use, and exercise history.

e. Clinical history (for affected individuals); tumor stage, grade, histologic type, prognostic factors (e.g. hormone receptor status for breast cancer), treatment (type of surgery, radiation, and systemic therapy), and disease outcome, as measured by disease-free and overall survival.

f. Health Attitudes and Behavior Survey; Our research among high risk individuals has begun to identify the importance of sociocultural and psychological determinants of perceived risk of cancer and related health behaviors **(25).** A series of measures was used to assess self-perceived risk for cancer, previous screening behaviors, and attitudes towards genetic testing for individuals and their families.

g. Annual Follow-up; a computer-generated annual follow-up questionnaire will provide an update on new cancer diagnoses among participants and their relatives, interval surveillance results, changes in risk status, and disease course in affected individuals.

Specific Aim 2. Establishment of a Network-wide Data Base System

The data management system for the Breast Cancer Risk Registry built upon the methods and operations of the FCCC Family Risk Assessment Program system. The Data Management Core (DMC) staff was responsible for all data management aspects of the High Risk Registry at FCCC. The nursing coordinator at each of the network institutions was responsible for data collection. They worked in close contact with the DMC to assure efficient data transfer, precise documentation and quality control of the data collected.

Data entry, storage, and retrieval were achieved through the relational database management system (RDBMS) ORACLE. The program used a relational structure that permits substantial flexibility in ad hoc query formulation. Relatively straightforward procedures, such as SQL*FORMS, were used to generate forms which provide a visually attractive user interface for data entry. In addition, these forms were used for editing and simple database queries. For more demanding data management, ORACLE provided a complete implementation of the structured query language (SQL).

The existing database consisted of a series of 18 tables linked by a common unique identifier(s): (1) Health History Data, (2) Family History Data, (3) Clinical Data (i.e. tumor stage, grade, type, treatment type, hormonal evaluation where appropriate, etc.), (4) Epidemiologic Data (i.e. smoking history, weight history, radiation exposure, etc.), (5) Socio-Demographic Data (i.e. age, sex, race, etc.), (6) Diet Data, (7) Follow-up Data (i.e. survival, disease free survival, etc.), (8) Psycho-social data, (9) Blood sample data (i.e. date received, amount of blood received, number of whole blood and plasma aliquots, number of guthrie cards, etc.), (10) Lymphoblastoid Line Data, (11) Tissue Data (i.e. type of tissue, amount of tissue, etc.), (12) DNA Data (i.e. date DNA made, amount of DNA isolated, etc.), (13) RNA Data (i.e. source of RNA, amount of tissue used, date RNA made, amount of RNA isolated, etc.), (14) Blood Aliquot Dispatch Data, (15) Tissue Dispatch Data ,(16) DNA Dispatch Data, (17) RNA Dispatch Data, and (18) Destination Data.

The software system ran on a UNIX-based distributed computing system consisting of multiple DecStation 5000 and Digital Alpha RISC processors managed and operated by the Research Computer Services group at FCCC. These multi-user systems were fully integrated into the FCCC computer network. This network supported a variety of software products including ORACLE, SAS, BMDP and IMSL and provided access to the global Internet. Daily backups were conducted to protect against accidental corruption or deletion of essential data. The software system was capable of generating multigenerational pedigrees. The data which fed pedigree generation was easily updated to include deaths or new cancers reported for previously listed family members, as well as new births. The software was also capable of creating the union of family histories provided by two or more distinct study subjects in the same family in order to create an "extended" pedigree.

During data entry, a series of edit checks validated accuracy and logistical consistency of the data. After data entry was completed, the user requests an output of all input from the session. This verification log documented accomplishments and served as the basis for verifying the entered data against the original observations. Any aberrant values identified were corrected by reselecting the appropriate form, querying the data for the record, and updating the incorrect information

Specific Aim 3. Development of Protocols for Genetic Testing

Upon completion of data entry, a pedigree was generated and reviewed by a multidisciplinary team for assignment of family risk. The selection criteria is based on accepted definitions of hereditary cancer syndromes (See Table 1). However, clinical and molecular definitions were subject to change as new findings allowed more precise definitions of hereditary cancer syndromes or as new cancer susceptibility genes were identified and cloned. The Pedigree Review Committee additionally assigned a pattern of cancer for both the maternal and paternal lines. Patterns were defined as negative, sporadic, familial, or putative hereditary to assist classification for research **(See attached Appendix A Pedigree Review Categories).** Each network institution then received documentation of the assigned pattern of cancer and eligibility status for genetic studies. With this information, the nurse counselor met individually with high-

risk individuals to ascertain clinical history and provide cancer risk information, discuss participation in the Breast Cancer Risk Registry and eligibility for genetic studies.

Table 1: Clinical Definitions of Hereditary Cancer Syndromes[1]
a) Hereditary Breast/Ovarian Syndrome. No personal history, positive family history of breast/ovarian cancer: 1) at least 2 relatives with ovarian cancer at any age; 2) at least 1 relative with breast and 1 relative with ovarian cancer at any age; 3) at least 2 relatives with breast cancer <50 yr, if 1 is a first degree relative; 4) at least 3 relatives with breast cancer at any age in 2 or more generations. Personal history of breast/ovarian cancer and family history in a first- or second-degree relative: 1) personal history of breast cancer <50 yrs and at least 1 relative with breast cancer at <50 yr or 1 relative with ovarian cancer at any age; 2) personal history of breast cancer at age >50 yr and at least 2 relatives with breast cancer at any age or 1 relative with ovarian cancer at any age; 3) personal history of ovarian cancer and at least 1 relative with breast or ovarian cancer at any age. Personal history of breast/ovarian cancer without a family history: 1) personal history of breast or ovarian cancer at <35 yr; 2) personal history of breast cancer at age <45 yr in an Ashkenazi Jewish woman; 3) personal history of ovarian cancer in an Ashkenazi Jewish woman; 4) personal history of multiple primary breast or breast and ovarian cancer.
b. Hereditary non-polyposis Colon Cancer (HNPCC)[2] 1) biliary tract, ovary, and transitional cell cancers of the genitourinary tract; one member of the kindred must be a first degree relative. 2) affected members in at least two generations; 3) at least one affected member must be <50 yr.
c. Li Fraumeni Syndrome 1) familial cluster of cancers including sarcoma, breast, leukemia, lymphoma, brain, lung and adrenocortical; 2) sarcoma occurring <45 yr; 3) at least 1 first degree relative with cancer <45 yr; 4) at least 1 first or second degree relative with a sarcoma at any age.
d. Hereditary Prostate Cancer 1) 3 or more affected first or second degree relatives; 2) affected individuals in two or more successive generations; 3) a cluster of 2 or more relatives each affected <55 yr.

Specific Aim 4. Biospecimen Collection and Storage

Biological samples were collected at all participating sites and forwarded to FCCC for processing and storage. Blood for B-cell transformation and DNA was drawn into tubes containing Acid Citrate Dextrose (ACD) and kept at room temperature during transfer to FCCC via Federal Express. Two to four tubes of approximately 10 mls each were collected from each participant: one used for the preparation of plasma and blood spots, a second to be used to prepare DNA. The additional tubes were designated by eligibility for research studies.

(1). Preparation and Storage of DNA

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[1] As clinical definitions of hereditary cancer syndromes are subject to interpretation, it is reasonable to expect that the Steering Committee may chose to set standardized eligibility criteria for adoption by all participating centers, which may require revision of the standards outlined above.

[2] Amsterdam criteria

DNA was prepared by a modification of the salting out procedure of Miller et al **(26)**. Each tube of blood was estimated to yield approximately 75-250 micrograms of DNA. Isolated DNA was be stored at -70°C in 20 mg aliquots. All DNA was characterized for the following: (a) OD_{260}/OD_{280}, (b) protein concentration using the BioRad Protein Bioassay Kit, and (c) agarose gel electrophoresis to confirm integrity and digestibility with EcoR1 and HindIII. Additionally, to confirm the identity of the DNA sample, DNA isolated from whole blood will be analyzed by PCR using four highly polymorphic microsatellite primer pairs, GATA44, F13B, EGF, and HPRT, and the pattern following polyacrylamide gel electrophoresis of the products of PCR amplification will be compared to that obtained with DNA isolated from blood spots.

(2). Preparation and storage of plasma

Blood collected for plasma storage was centrifuged at low speed to pellet the red cells and buffy coat. The supernatant was removed, dispensed into 1ml aliquots, and frozen at -70°C. This plasma bank will comprise an extraordinary resource for future studies exploring the roles of endogenous hormones, dietary components, and their potential interactions in cancer development.

(3). Tissue preparation

For participants who have undergone surgery and for whom archived material is available, paraffin blocks, as well as stained and unstained slides were requested from living affected patients or from next of kin. The available material was assigned a specimen number. When appropriate amounts of tissue were available, specimens were cut, catalogued and stored. All access to files was by specimen number and neither the specimen librarian nor the laboratory technicians had access to information on any individual.

Specific Aim 5. Education of Primary Care Providers

The methods for physician training included regional updates through the physicians services program, grand rounds, one formal symposium, presentations at Network physician groups, and a pilot training in cancer risk assessment. Dr. Daly, in conjunction with the faculty of the Hunterdon Medical Center Family Practice Residency Program, developed an educational program in Familial Cancer Risk Counseling designed to prepare community-based primary care physicians to take an active role, along with the nursing staff, in the identification and assessment of familial cancer syndromes. The curriculum was adapted from the Nurses' Training, and was based on the Medical School Core Curriculum in Genetics **(25)**. The curriculum was organized into four three-hour modules plus a clinical practicum. The modules were a mix of didactic and interactive teaching covering the following topics: fundamentals of cancer genetics; cancer inheritance patterns; risk assessment and notification; genetic testing and counseling; and cancer prevention and control options.

Specific Aim 6. Training Community Nurses

Essential to the success of the Registry has been the development of programs to train nurses at each Network hospital for their expanded role in cancer risk identification and counseling. The education methods for nurses have included focus groups to assess training needs. Based on these interviews a formal three-day training and one-day practicum was developed. The major components of the training included: 1) background on breast cancer and cancer genetics, 2) obtaining a medical and cancer family history, 3) assessment of cancer risk, 4) communication of cancer risk information, 5) tailoring recommendations and support to promote adherence to screening and cancer control practices, 6) legal, social and ethical implications of genetic information, and 7) referral for further medical and genetic investigation

when appropriate **(Submitted in Appendix E in 1995 Report)**. Videotaped and case demonstrations of counseling sessions were developed to provide nurses with opportunities for observation and role modeling. Along with the training materials, evaluations were conducted to determine the effectiveness of the training **(Submitted in Appendix B, C, and D in 1996 Report).**

To assess the impact of the Nurses' Training, the following methods were used: (1) pretest/posttest measure of knowledge; (2) subjective evaluation of course objectives for each session and total program; (3) baseline and six-month follow-up survey items were included in the pre/posttest to assess self-reported practice and confidence as well as facilitators and barriers to implementing Cancer Risk Counseling (CRC) in community practice.

In the evaluation phase, descriptive analysis was used to measure the subjective responses to program objectives. Univariate analysis was conducted to compare pre- to posttest measure of knowledge using a t-test. Univariate analysis was used to measure change over time from baseline to six months post-training on taking cancer family histories, practicing cancer risk counseling and confidence in skills in cancer risk counseling in genetic risk assessment and counseling.

In order to assist the Network nurses in skill development, an ongoing mentoring process was developed. This process has included observation and supervision by FCCC staff of the breast cancer risk education session and the individual cancer risk counseling session. All Network nurses had the opportunity to observe in the FRAP program. Their observations included attending pedigree review and the individual pedigree evaluation session. Feedback on pedigrees was given prior to each individual session. For the initial individual counseling session at the Network hospital, the nursing coordinator observed FCCC staff conduct an individual risk assessment session. Afterwards, FCCC staff supervised the nurse coordinator conduct two sessions. A monthly mailing of current literature has continued in Year Four to address the advances in genetic information and issues related to the counseling and testing process. A quarterly inservice training has also continued. These four-hour trainings consist of peer updates regarding individual Network hospital progress in the Risk Registry, review of administrative concerns or issues, and two hours of educational inservice. Additional monitoring of the program was provided by telephone conferencing and site visit.

Specific Aim 7. Development and Evaluation of Cancer Risk Counseling Interventions

A genetic counseling protocol was developed that included the following components of the cancer risk assessment and counseling process **(Submitted in Appendix C in 1995 report),** and counseling interventions for receipt of genetic test results including predisclosure, disclosure and follow-up interventions **(Submitted in Appendix C in 1997 report)**. The cancer risk assessment protocol included: 1) obtaining and interpreting the cancer family history, 2) providing risk information based on the family history, 3) determining eligibility for genetic testing, and 4) informed consent to participate in genetic research. The predisclosure intervention utilized presentation of information, counseling and role-play to help prepare individuals for genetic test results. A multi-disciplinary team conducts the disclosure session designed to provide genetic test results, to address adjustment to the information and to develop a plan for medical management and follow-up. Follow-up is conducted via phone at one and 12 months post-disclosure to evaluate the impact of genetic test results and provide information for resources or referrals if necessary.

Specific Aim 8. Establish Breast Cancer Risk Advisory Panel

The Breast Cancer Risk Advisory Panel has brought together health care professionals, both at FCCC and the Fox Chase Network, community representatives, as well as lay consumers **(Submitted in Appendix E in 1996 report).** During the first year of the project, a steering committee identified panel members with expertise in the area of genetics, cancer control, genetic counseling, nursing, medicine, ethics, psychology, public relations, and genetic testing. This group was convened and met on an annual basis. The panel has identified and addressed pertinent issues related to the Registry and established smaller working groups to address on-going project issues. These groups met on an ad hoc basis.

B. Results and Discussion

This project overall has demonstrated that it was feasible to create an infrastructure to identify breast cancer patients and women at risk in view of their family history of breast cancer. With appropriate training, educational resources and supervisory support, the transfer of genetic knowledge into community-based practice was also accomplished. The FCCC Network Breast Cancer Risk Registry has provided the opportunity to further epidemiologic and molecular research related to breast cancer risk and to develop and evaluate educational and psychological strategies to optimize breast cancer risk counseling in the community setting. The major results of the project, which represent the statement of work outlined in the proposal, and discussion points are presented in the following sections: 1) implementation, 2) recruitment and accrual, 3) training of health professionals, 4) research endeavors, and 5) work of the breast cancer registry advisory panel.

1. Implementation of the Breast Cancer High-Risk Registry

This project demonstrated that community hospitals could implement a Breast Cancer Risk Registry program when strategic planning and resources were provided **(See methods section)**. Administrative planning with Medical Directors, staff physicians, administrators and outreach to community primary care providers was foundational to the implementation process. These initial meetings laid out the program requirements and timeframe for implementation. Each hospital identified a nurse coordinator and physician team leader. Each nurse coordinator was trained in the cancer risk assessment and counseling process and supervised at all points of program implementation. Educational resources designed to provide genetic cancer risk information regarding breast cancer were supplied to each institution **(Submitted in Appendix G in 1995 Report)**. Uses of these resources were accompanied by a training, supervision, and feedback process. All institutions were also supplied with a procedures manual and training for data entry, and collection of biologic specimens **(Submitted in Appendices C, D, & H in 1995 Report; and Appendix A in 1996 Report)**. In view of the planning and training time necessary for implementation, on average, three hospitals per year operationalized the program with six to eight months needed for start up.

Program implementation was established in all but three of the Fox Chase Network institutions. Administrative planning with Cancer Center medical directors and staff physicians was conducted in thirteen Network facilities. Nursing staff has been trained in those thirteen facilities; of these, eleven have had a nursing program coordinator assigned. Education and program resources have been provided to those eleven hospitals with a nurse coordinator. Ten sites have conducted the breast cancer risk education through community education and have

been accruing participants for the Risk Registry with the remaining institution expected to begin education and accrual in October 1998. Table 2 outlines the status of the individual Network facilities and their participation status. Two of the hospital systems, St. Luke's and Montgomery left the Fox Chase Network during the course of the project due to joining larger university networks which required affiliation of all specialty services with one network. Eight network hospitals will maintain the program and continue to recruit women for on-going cancer genetic research studies.

Table 2. Network Participation in the Risk Registry Program

	Contact-Med. Dir	Nurse trained	Nurse coord.	Education resources	Education initiated	Accrual begun
Bonsecours	-	-	-	-	-	-
St. Luke's*	X	X	X	X	X	X
Reading	X	X	X	X	-	-
Pinnacle	X	X	X	X	X	X
Burlington (Mem.)	X	X	X	X	X	X
St. Francis	X	X	X	X	X	X
Montgomery*	X	X	X	X	X	X
North Penn	-	-	-	-	-	-
St. Mary's	-	X	-	-	-	-
Paoli	X	X	X	X	X	X
Riverview	X	X	X	X	X	X
Hunterdon	X	X	X	X	X	X
Delaware County	X	X	X	X	X	X
South Jersey	X	X	-	-	-	-
Community Med.	X	X	X	X	X	X

* In-active

Discussion

The original program time-line estimated that all interested Network institutions would have implemented the program within the first two years of the project. On average three hospitals per year operationalized the program with implementation of new sites continuing into the fourth year of the project. The operational plan required intensive support prior to implementation as well as having trained staff to conduct risk assessment and recruitment. In several settings, appointed and trained staff had job changes; this caused significant delays in program implementation and on-going recruitment. Furthermore, programmatic materials such as brochures, letters and informed consents had to be adapted to the specific hospital's conditions. Each hospital had to meet requirements of their respective Institutional Review Boards (IRB) with some settings having a two to three month process before IRB approval. Some of the major IRB issues were confidentiality of genetic information and the concern that research results potentially would not benefit the patient.

Mergers and realignment of health care systems affected the implementation process. Two hospitals left the Fox Chase Network to affiliate with other hospital or university based systems. One hospital merged with two other institutions and program accrual was delayed for

over one year. Economic concerns were also barriers for several Network Institutions. The current health care environment influenced several administrators to weigh the economic advantages and disadvantages of this research project. Unlike other research protocols, there was no financial incentive for accrual. Institutions who perceived a marketing advantage to the genetic research studies were more willing to participate with the expectation that this project would prepare them to implement cancer genetic services when they become commercially available. We recommend that future infrastructure projects address the economic concerns of participating community-based hospitals and build in some financial incentive for implementation and case recruitment.

2. Recruitment and Accrual to the Breast Cancer Risk Registry

Women were recruited to the Risk Registry in two ways: 1) physician referral of breast cancer patients and 2) community education programs on breast cancer risk. In the former, the medical oncologist alerted breast cancer patients about the program. The patients in turn contacted their relatives. To date, there were a total of 52 education sessions with 512 women attending. Fifty-two per cent (N=296) of those attending the education sessions expressed interest in the Risk Registry and took Health History Questionnaires. Of those who took the questionnaires 55% (N= 164) from 106 families, returned them and were accrued to the Registry. These women all have had their family history information reviewed by the Pedigree Review Committee at FCCC. The purpose of the review is to assign a preliminary diagnosis of the cancer family pattern, and identify appropriate individuals for further genetic evaluation and collection of blood or tissue samples. Each family received a diagnosis for both the maternal and paternal side of the family by cancer type and by pattern **(See attached Appendix B, Genetic Diagnosis).** The patterns included sporadic or negative, familial or putative hereditary. Family cancer patterns for the 106 families in the Risk Registry have shown maternal patterns to include 34% sporadic or negative, 39% familial and 32% putative hereditary. Ninety-six percent (96%) of the maternal patterns included breast and or ovarian cancer as the part of the cancer pattern diagnosis. Only 19% (N= 31) of the paternal case patterns included breast cancer with other varieties of cancer types represented including prostate, colon, thyroid, kidney, esophageal and hematopoeitic cancers. Of those 31 paternal cases with breast cancer, patterns included 19% sporadic, 36% familial and 45% putative hereditary.

All 164 participants received individual education and counseling regarding their breast cancer risk and more detailed information regarding the Breast Cancer High Risk Registry. Of the 106 families recruited into the registry 52 families had a putative hereditary pattern of breast cancer. Ninety percent (90%) of those families have provided biologic samples for the registry. Some samples were utilized in the research study for the Ashkenazi Jewish population. Six families have received genetic test results from this study. None of these samples were positive for the 185delAG and 5382insC in *BRCA1* or 6174delT in *BRCA2*, which have been observed in Ashkenazi Jewish individuals. However, one sample tested positive for a novel mutation in a splicing region in an intron in *BRCA1*. This family is cooperating with recruiting extended family members to determine whether this alteration represents a polymorphism or deleterious mutation. Other epidemiologic, molecular and psychosocial studies have incorporated data from the Breast Cancer High Risk Registry. **(See Research Endeavors)**

Discussion

It has been established that 5% to 10% of breast cancers are attributed to hereditary cancer syndromes, 70% attributed as sporadic and the remaining 20% falling into a familial

category **(27).** Since hereditary cancer is expected to account for 5 to 10% of breast cancers, the proportion of putative hereditary and familial patterns found in participants suggests that the Risk Registry program appropriately recruited individuals that carry a higher degree of risk for breast cancer than the general population.

This study determined that the majority of participants had a breast cancer pattern in the maternal line. Ninety-five percent (95%) of maternal cases had a breast or breast/ovarian cancer pattern compared to 19% of the paternal patterns. This research suggests that a common misperception persists about the transmission of breast cancer solely through the maternal line. It is recommended that future work in community health education continue to address modes of transmission for predisposition to breast cancer.

Although the framework of the Breast Cancer Risk Registry remains in place to continue recruitment, the program did not achieve its projected accrual of 1200 participants. As discussed in the implementation section, several factors, i.e. administrative planning, staff training, and IRB approval slowed program implementation and therefore accrual. Public attitude toward genetic research also effected accrual. Potential participants reported that media attention to genetic issues raised their concerns. Issues related to participation in genetic research included stigmatization, employment and insurance discrimination, misinterpretation of test results, use of genetic information beyond the scope of the research, and lack of legislation to prevent genetic discrimination. Fear of medical insurance discrimination was cited as the major barrier to participation. Clinical trials research indicates that primary reasons for research participation are a perceived benefit to health outcomes, control over the medical course of the disease, and a desire to help future generations. **(28, 29).** A proportion of the women indicated concern that participation in genetic research would not benefit them. Even with assurances of the privacy measures employed in the study, a subset of women were concerned that genetic information would become known and potentially harmful to them. Lastly, education about genetic research, the needed involvement of family members and the impact of genetic information on the family have been noted to decrease interest in genetic testing **(30).** Some of these factors may explain the large proportion of women (75%) who attended community education sessions who did not pursue entry to the Registry Program.

Almost half of the women who expressed interest in the program and took Health History Questionnaires never returned them. A sample of these women reported barriers to program participation which included lack of time to complete the family history questionnaire and need to involve other family members. For those women who consented to participate, it is imperative to note that the recruitment and the informed consent process are lengthy. Under ideal circumstances the recruitment phase entailed a minimum of 3 hours of the participant's time. This includes questionnaire completion, group education and individual risk counseling with each component taking at least one hour. This translates into equivalent staff support for each person recruited. These factors indicate that recruitment was more complex and time intensive than estimated.

In order to accumulate appropriate data for genetic studies, family members need to be included in the planning and recruitment strategies. The staff support necessary to accomplish this was beyond the scope of this project. We recommend that future genetic research include sufficient staff support to provide the ability to collect appropriate family members. Additional lessons learned from this study indicate that external factors in community based hospitals are often beyond the control of the research design. Close contact with administration and program staff along with creative problem solving can maintain the integrity of the research. Furthermore,

awareness of the population's perception of research and sensitivity to their issues can enhance participation in genetic research. Needs assessment strategies prior to recruitment and an informed consent process which thoughtfully and directly addresses these concerns are essential to future programmatic design.

3.Training Health Professionals

The Risk Registry program has helped prepare community-based providers with the knowledge and the skills to make familial cancer risk counseling available. In total, 23 Network nurses and 2 Network social workers have attended the three-day training. A total of 164 nurses nationwide have participated in the training, and of those, 62 attended the optional one-day practicum.

Eighty-two participants have completed evaluation measures, i.e. pretest/posttest measures of knowledge, and baseline and six-month follow-up of self-reported practice and confidence in Cancer Risk Counseling (CRC) skills. Of the 82, 43 (52%) attended the three-day training, and 39 (48%) attended both the training and the one-day practicum. There was a statistically significant improvement in knowledge scores from pre- to posttest, with a mean of 18 correct items out of 28 at pretest compared to 23 at posttest ($p<0.01$, Wilcoxon signed rank test). There were no significant knowledge differences between the practicum and training only groups at both baseline and follow-up.

In order to evaluate the impact of the practicum on attainment of confidence in skills, bivariate analysis was conducted on self-report of confidence from the 60 participants who had practiced CRC at least once since the training. Those who had attended the practicum were more active in counseling than those who attended the training only (mean of 5 vs 3 individuals counseled/month respectively). Statistically significant differences were found at six months between groups in levels of confidence in all of the cancer risk assessment skills (Fisher's Exact Test). The practicum group reported more confidence in all skills, with the greatest improvement in taking and assessing family history. Overall, the lowest levels of confidence were reported for the more complex skills of communicating risk information and making recommendations for follow-up. Qualitative six month data showed that those practicing CRC worked as a team with a medical oncologist; and the most important facilitators to practicing skills were having a genetic resource person, access to on-going genetic information, and clear performance guidelines for nursing **(23).**

The process of training and preparing nurses to assume the role of providing cancer risk information has underscored the need to bring physicians into the loop of a genetic based approach of cancer prevention. Physicians in the Network hospitals were offered ongoing updates regarding the advances in genetics via the Network's Physician Services. This service organized regional inservice updates and grand rounds. Cancer risk assessment and genetic updates were presented at two regional meetings and four grand rounds at Network institutions. Dr. Mary Daly, in cooperation with the FCCC Continuing Medical Education Department, provided an offering for physicians in the genetic advances in cancer control. This one-day symposium addressed breast cancer genetics and prevention.

As part of FCCC's effort to educate physicians, the needs of practicing physicians regarding the identification of genetic risk for disease and the options available for high risk

families became more apparent. Following from the work of the Risk Registry grant, FCCC was awarded funds from the National Cancer Institute to pilot an education program for family practice residents. This program called: "Training Family Practice Residents in Familial Cancer Risk Counseling," was designed with the faculty of one of the participating Risk Registry institutions. The design was unique in that the faculty of the Hunterdon Medical Center Family Practice Residency Program participated in both the development and teaching sessions on familial cancer risk assessment and counseling. The sixteen hour course included lectures, case studies, and a practicum at which residents took a cancer family history, created a pedigree and performed risk analysis during a supervised patient visit. Pre to posttest results showed a significant increase in cancer genetics knowledge ($p=.00009$) with a change from 57% to 77% correct responses on average. Confidence in cancer risk counseling skills increased from 1.9 to 2.7 ($p = 0.034$) on a confidence scale where 1 = "not at all confident" to 4 = "very confident". All residents rated the practicum as the most helpful component for building confidence and skill attainment, and the best way to incorporate cancer risk assessment into their practice. Based on the success of this project a mini-course was conducted with a second group of family practice residents. Also in attendance at this course were practicing physicians and faculty from the Hunterdon Family Practice Program. This four hour course focused on identification, counseling and referral of high risk women as well as medical management and surveillance in high-risk populations.

Further physician training needs were identified after the genetic disclosure counseling protocols were developed **(Submitted in Appendix C in 1997 Report)**. With the recommendations of the Advisory Panel, physician involvement in the disclosure process was essential. An advisory panel working group determined that practicing oncologists had constraints on the amount of time that could be given to additional training. A survey conducted with the community-based oncologist supported the panel's assumptions. When asked "how much time is realistic for you to attend a continuing education seminar", 75% responded that 2 hours was realistic with a range from 1 hour to 6 hours. The content areas rated most often as "very much needed" to assist in providing cancer genetic test results were: a) interpretation of genetic test results, b) identification of eligibility for genetic testing via use of probability tables, c) risk estimates associated with being a carrier of a genetic mutation, and d) prevention options for high risk populations. Content area most often cited as "somewhat needed" was types of laboratory procedures for genetic testing. When asked about "which educational methods for keeping up to date with genetic information were most feasible and effective", continuing education seminars and receiving selected educational journals were most often cited. Approximately 20% of the physicians indicated that they did not have resources to facilitate long distance learning via Internet or video-conferencing.

Discussion

The results of this work in training nurses suggest that knowledge alone does not predict skill performance and on-going skill development needs to be addressed. After the three-day training, the total group showed improvement in knowledge scores, but the majority reported needing more observation and practice time. The majority of the network nurses related their need for more practice to the newness of cancer genetic information and the lack of genetic resources and staff expertise within their own institutions. Therefore, an on-going mentoring process was developed which incorporated observation, supervision and feedback related to the

nurses' cancer risk counseling skills. A quarterly inservice program was also established to provide updates on cancer genetic information. Based on these above findings FCCC has sought and received further funding to provide nurses with advanced skills in genetic cancer risk counseling (**"Advanced Cancer Risk Counseling Training for Nurses" 2 R25 CA66061-04**).

The work of the FCCC Network Breast Cancer Risk Registry has provided the opportunity to develop and evaluate educational strategies to optimize breast cancer risk counseling in the community setting. It is also providing important information on relevant issues to transferring genetic knowledge into community-based practice. These findings suggest that the role of risk assessment and identification of appropriate candidates for genetic testing services is within the scope of community primary care if appropriate training is provided. To ensure that physicians and other health professionals are prepared to provide cancer genetic risk information, it is recommended that further genetics education and training projects become a priority.

4. Research Endeavors

The Registry has added to the larger FRAP research base for many ongoing studies spanning the dimensions of basic science, clinical genetics, epidemiology, and psychological and educational interventions. The resources of the Genetics Research Lab continue to provide material for the identification of novel genes, mutations, and cancer family syndromes, including the identification of two candidate tumor suppressor genes associated with hereditary ovarian cancer **(31).** Dr. Godwin has provided evidence of two distinct lines of transmission for the 185del AG mutation, only one of which has its origins in the Jewish Ashkenai population **(32).** In collaboration with the Breast Cancer Genetics Consortium we have contributed to the understanding of the APCI1307K allele and breast cancer risk **(33).** Currently, Drs. Daly and Godwin are collaborating with Dr. Steven Narod of the Centre for Research in Women's Health in Toronto to identify significant gene-environment interactions within these families. In collaboration with Drs. Barbara Weber and Tim Rebbeck at the University of Pennsylvania, we are prospectively following women who undergo bilateral mastectomy for prophylaxis to determine the beneficial and adverse sequelae of the procedure.

To pursue other variables modifying risk comprehension, we are working with Suzanne Miller, Ph.D., Director of Behavioral Research at FCCC, and her staff to examine how psychological factors moderate outcomes in the risk counseling setting, to explore the impact of a structured psychological support intervention on the outcome of education and counseling for genetic risk for breast/ovarian cancer **(21),** to evaluate the effect of genetic susceptibility status on spouses and other family members, to identify types of cognitive and affective profiles that influence the decision to enter a chemoprevention trial, and to determine the effect of cancer-specific psychologic distress on cancer-protective behaviors **(22).**

The availability of mutation analysis for *BRCA1* and *BRCA2* at FCCC has provided the opportunity to extend our research to the setting of genetic testing. We have begun to explore the patterns of communication and emotional support which emerge within families after receipt of genetic test information **(34, 35)**, and are piloting a support group intervention as a means of providing long-term support for individuals undergoing genetic counseling and testing. Emerging from these studies is a model of cancer risk genetic counseling that optimizes medical and psychological outcomes, and has direct relevance to the clinical care setting.

On the basis of the scope and experience of the Genetics Program at Fox Chase, and the success of the Breast Cancer Risk Registry, the Center has been chosen to be one of six

international sites for the Cooperative Family Registry for Breast Cancer Studies (CFRBCS). The CFRBCS was initiated by the NCI (NCI 5 U01 CA69631) to provide to the scientific community a resource for multidisciplinary studies of breast cancer and includes a large computerized database with both genetic and environmental risk information from a racially and ethnically diverse set of families with a history of breast cancer. Along with FCCC the participating institutions include Northern California Cancer Institute, Huntsman Cancer Institute, Memorial Sloan-Kettering Cancer Center, Ontario Cancer Treatment and Research Foundation and the University of Melbourne Department of Public Health. Additionally, the Department of Defense has funded an "Ovarian Cancer Consortium for Research and Surveillance." This project will recruit women at risk for ovarian cancer and include a study exploring decision-making regarding prophylactic oopherectomy and a chemoprevention trial for women prior to oopherectomy and molecular study exploring ovarian biologic markers post oopherectomy. Both studies will continue to recruit cancer patients and high-risk individuals from the Network hospitals participating in the DOD Breast Cancer High Risk Registry.

Discussion

The work of this project has provided a structured and effective way to study the diverse aspect of breast cancer. The Breast Cancer High Risk Registry has expanded the database of epidemiologic and biologic information from which research can be done. It has stimulated interventions on the optimal way of delivering breast cancer risk information, and the true impact of counseling programs on participants' risk comprehension, psychological adaptation, and adoption of recommended health practices. With new NCI registry and DOD consortium funding, the foundational work of this project will continue to grow and stimulate progress in the understanding of the genetic events which accompany the carcinogenic process, and to transfer this information to the public health realm.

5. Advisory Committee

The Breast Cancer Risk Advisory Panel brought together experts in the field of genetics, ethics, health care, as well as lay consumers. The panel and its working groups were key to the development of counseling protocols, ethical issues, and training strategies for health professionals. The consumers and community-based health professionals broadened the understanding of the impact of this research. Their input regarding the managed care influence on our current health care environment led to greater involvement of medical staff from the Network hospitals in the working groups of the Advisory Group. These working groups provided direction related to physician consultation in the genetic counseling process, continuing education needs of medical staff in the genetic counseling process, and medical management of high risk populations.

Discussion

The work of the FCCC Network Breast Cancer Risk Registry has provided the opportunity to develop and evaluate educational and psychological strategies to optimize breast cancer risk counseling in the community setting. It also provided important information on relevant issues to transferring genetic knowledge into community-based practice. We recommend that future genetic research involving community-based setting, utilize the approach of an advisory panel. Cancer genetic services requires a multi-disciplinary approach, therefore, research in this field needs to be guided by experts from a variety of disciplines. This type of

approach will guide future research on the optimal way of delivering breast cancer risk information, and the true impact of counseling programs on participants' risk comprehension, psychological adaptation, and adoption of recommended health practices.

Conclusions

This project has demonstrated that it was feasible to create an infrastructure within the community setting to identify breast cancer patients and women at risk in view of their family history of breast cancer. The program has established a framework for recruitment into this registry and on-going research whereby we will learn more about the carcinogenesis process of breast cancer. Participation in genetic research or a registry has informed consent issues for which prior research studies have not needed to address. Genetic research with both individual and family implications requires academic centers and government agencies to consider a programmatic design that has a broader accrual scope. The need for education and counseling prior to genetic research testing with individuals and extended family members, although labor intensive, is imperative to the informed consent process.

With appropriate training, educational resources and supervisory support, the transfer of genetic knowledge into community-based practice can be accomplished. To ensure that health professionals are prepared to meet future patient demands for genetic information, professional societies and health education researchers need to make continuing education in genetics a priority.

The FCCC Network Breast Cancer Risk Registry has provided the opportunity to further epidemiologic and molecular research related to breast cancer risk and to develop and evaluate educational and psychological strategies to optimize breast cancer risk counseling in the community setting. The registry database has also established significant collaborations with other academic institutions. These efforts are contributing to further clinical research to help identify the most suitable medical management, surveillance and chemopreventive therapies for high-risk populations.

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Appendices from Past Reports

1995

Appendix A	SSCP analysis results for a family
Appendix B	High Risk Registry Advisory Panel Steering Committee
Appendix C	Genetic Counseling Protocol & IRB approved Informed Consent
Appendix D	Health History Questionnaire
Appendix E	Training Manual
Appendix F	Oncology Nursing Society Abstract
Appendix G	Flip Chart
Appendix H	Procedures for Implementation

1996

Appendix A	Recruitment Procedures Manual
Appendix B	Pretest (for Training Course)
Appendix C	Post Session Evaluation (for Training Course)
Appendix D	Baseline & Six-Month Follow-Up Survey (for Training Course)
Appendix E	High Risk Registry Advisory Panel
Appendix F	Bibliography of Abstracts
Appendix G	Toward 2000 brochure

1997

Appendix A	Toward 2000 brochure
Appendix B	Residents' Training Evaluation
Appendix C	Counseling Protocols
Appendix D	Selected marketing brochures
Appendix E	Advisory Panel

Project Staff

1995

Mary Daly Principal Investigator
Andre Rogatko Biostatistician
Agnes Masny Project Manager
Tracy Jones Health Educator
Josephine Wagner Genetic Counselor
Jane Sammons Data Entry
David Berman Lab Technician

1996

Mary Daly Principal Investigator
Agnes Masny Project Manager
Josephine Costalas Genetic Counselor
Rose Batson Data Entry
David Berman Lab Technician

1997

Mary Daly Principal Investigator
Agnes Masny Project Manager
Josephine Costalas Genetic Counselor
Colleen Sands Health Educator
Rose Batson Data Entry
Luba Petrukhin Lab Technician

1998

Mary Daly Principal Investigator
Agnes Masny Project Manager
Josephine Costalas Genetic Counselor
Rose Batson Data Entry
Luba Petrukhin Lab Technician
Joann Sicilia Research Data Coordinator

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Department of Defense Infrastructure Grant
Breast Cancer High Risk Registry
September 15, 1997 to September 14, 1998

Appendices

Appendix A	Pedigree Review Categories
Appendix B	Genetic Diagnosis

Appendix A

Pedigree Review Categories

Purpose:

To review and assign a category of sporadic, familial, putative hereditary or hereditary to each side of FRAP proband's family history. These pedigree review category assignments will be used to categorize the pattern of cancers reported in proband's family history and used **for research purposes**, not for diagnostic purposes. However, the clinical risk assessment and criteria assigned for genetic testing may or may not reflect the pedigree review category assigned to the proband's pedigree.

A: Sporadic

Definition:

A single occurrence of cancer occurring on one side of the family.

Criteria:

1. One occurrence of cancer diagnosed at any age occurring on one side of the family only.

B: Familial

Definition:

A pattern of cancers in the family seen in 1 or more generations that do not fit a known cancer family syndrome, whether or not it follows autosomal dominant type of inheritance (that is, vertical transmission).

Criteria:

1. No personal history of cancer with at least 2 first and/or second-degree relatives, diagnosed at any age, with a primary cancer;

2. No personal history of cancer with one first or second degree relative with 2 primary cancers, diagnosed at any age; (??? Environmental exposures)

3. A personal history of bilateral breast cancer, diagnosed at any age, and no other cancers occurring in family history;

4. A personal history of one primary cancer, diagnosed at any age, with at least 1 first and/or second-degree relative, diagnosed at any age, with one primary cancer (cannot be ovarian cancer).

5. No personal history of cancer and has one same type of cancer diagnosis in 2 or more first and/or second degree relatives, diagnosed at age 51 and over.

C: Putative Hereditary

Definition:

A side of the family fits a hereditary pattern of inheritance of cancers but mutation analysis (genetic testing) has not been performed in this family or is pending. The cancers in that one side of the family may fit a known cancer family syndrome.

Criteria:

1. A personal history of early onset breast cancer (less than age 50) and ovarian cancer, any age.

2. A personal history of early onset breast cancer (less than age 50) and at least one relative with early onset breast cancer (less than age 50) or ovarian cancer, any age;

3. A personal history of 3 or more primary cancers, with or without other family history, with at least one cancer being less than age 50 (excluding non-melanoma skin cancers)

4. No personal history of cancer but has one first or second degree relative with more than three reported cancers, with at least one cancer being less than age 50 (excluding non-melanoma skin cancers)

5. A personal history of breast and/or ovarian cancer, any age, and has breast and/or ovarian cancer in 2 or more first and/or second degree relative, diagnosed at any age;

6. No personal history of cancer but has breast and/or ovarian cancer occurring in 3 or more first and/or second and/or third degree relatives diagnosed at any age, and seem to fit a known cancer family pattern or syndrome.

7 No personal history of cancer and has ovarian cancer in 2 or more first and/or second-degree relatives, diagnosed at any age;

8. No personal history of cancer and has one same type of cancer diagnosis in 2 or more first and/or second degree relatives, diagnosed before age 50.

D: Hereditary

Definition:

Genetic testing performed on proband or proband's relative, mutation in BRCA1, BRCA2 and/or other cancer predisposition gene confirmed, and inheritance of mutation (paternal or maternal) has been established.

Criteria:

1. Documented mutation in proband.
2. Documented mutation in proband's first degree relative.
3. Documented mutation in proband's second degree relative.

Notes:

When there are only siblings affected with cancer, diagnosis goes to maternal side (default, but not the fault of the mom)

Appendix B

********** GENETIC DIAGNOSIS BY INDIVIDUAL ID **********

ID	Family ID	Rev. date	Mat Class	Mat Type	Pat Class	Pat Type
16121	733	05-DEC-95	FAMILIAL	BREAST	NEGATIVE	
16122	733	05-DEC-95	FAMILIAL	BREAST	NEGATIVE	
16123	733	05-DEC-95	FAMILIAL	BREAST	NEGATIVE	
16311	741	20-FEB-96	SPORADIC	BREAST	PUTATIVE HEREDITARY	PROSTATE
16312	742	20-FEB-96	SPORADIC	BREAST	SPORADIC	VARIOUS
16508	746	30-JAN-96	FAMILIAL	BREAST	SPORADIC	VARIOUS
17825	813	07-MAR-96	SPORADIC	BREAST	FAMILIAL	BREAST/OVARIAN
17825	813	03-JUL-96	SPORADIC	BREAST	FAMILIAL	BREAST/OVARIAN
17826	814	03-JUL-96	NEGATIVE		NEGATIVE	
17827	814	14-MAY-96	SPORADIC	BREAST	NEGATIVE	
17827	814	03-JUL-96	SPORADIC	BREAST	NEGATIVE	
17828	814	14-MAY-96	SPORADIC	BREAST	NEGATIVE	
17828	814	03-JUL-96	SPORADIC	BREAST	NEGATIVE	
17830	815	21-MAY-96	FAMILIAL	VARIOUS	SPORADIC	ESOPHAGUS
17830	815	03-JUL-96	FAMILIAL	BREAST	NEGATIVE	
17831	815	21-MAY-96	FAMILIAL	VARIOUS	SPORADIC	ESOPHAGUS
17831	815	03-JUL-96	FAMILIAL	BREAST	NEGATIVE	
17832	815	21-MAY-96	SPORADIC	BREAST	NEGATIVE	
17832	815	27-JAN-97	FAMILIAL	VARIOUS	SPORADIC	VARIOUS
18260	833	21-MAY-96	FAMILIAL	BREAST/PROSTATE	SPORADIC	BREAST
18261	834	21-MAY-96	SPORADIC	OVARIAN	NEGATIVE	
18660	854	03-JUL-96	HEREDITARY	BREAST	UNKNOWN	
18661	855	03-JUL-96	FAMILIAL	BREAST	NEGATIVE	
18662	856	03-JUL-96	SPORADIC	BREAST/OVARIAN	FAMILIAL	COLON
18664	859	03-JUL-96	FAMILIAL	BREAST/OVARIAN	NEGATIVE	
18666	861	03-JUL-96	HEREDITARY	BREAST	FAMILIAL	VARIOUS
18667	862	06-JUL-98	HEREDITARY	BREAST	PUTATIVE HEREDITARY	PROSTATE/VARIOUS
18812	863	03-JUL-96	FAMILIAL	VARIOUS	SPORADIC	BREAST
18812	863	10-JUN-98	FAMILIAL	BR/VAR/SQUAMOUS CELL	SPORADIC	VARIOUS
18812	863	06-JUL-98	FAMILIAL	BR/VAR/SQUAMOUS CELL	FAMILIAL	VARIOUS
18813	864	03-JUL-96	SPORADIC	BREAST	NEGATIVE	
18943	871	15-JUL-96	FAMILIAL	BREAST	NEGATIVE	
18943	871	11-JUN-98	PUTATIVE HEREDITARY	BREAST	FAMILIAL	BREAST
18943	871	06-JUL-98	PUTATIVE HEREDITARY	BREAST	FAMILIAL	BREAST
18944	872	15-JUL-96	SPORADIC	BREAST	NEGATIVE	
19031	876	12-AUG-96	FAMILIAL	BREAST	FAMILIAL	VARIOUS
19032	877	13-AUG-96	FAMILIAL	VARIOUS	FAMILIAL	VARIOUS
19093	878	13-AUG-96	SPORADIC	BREAST	FAMILIAL	VARIOUS
19539	900	12-AUG-96	NEGATIVE		SPORADIC	COLON
19540	900	15-NOV-96	SPORADIC	BREAST	FAMILIAL	COLON
19541	901	12-AUG-96	PUTATIVE HEREDITARY	BREAST	SPORADIC	VARIOUS
19542	901	12-AUG-96	PUTATIVE HEREDITARY	BREAST	SPORADIC	COLON
20554	901	15-NOV-96	PUTATIVE HEREDITARY	BREAST	SPORADIC	BR/OV/COLON
19543	902	12-AUG-96	SPORADIC	VARIOUS	PUTATIVE HEREDITARY	BREAST
19543	902	29-APR-97	SPORADIC	RECTAL	PUTATIVE HEREDITARY	BREAST
19544	903	12-AUG-96	FAMILIAL	VARIOUS	FAMILIAL	VARIOUS
19544	903	15-NOV-96	FAMILIAL	VARIOUS	FAMILIAL	VARIOUS
19545	905	12-AUG-96	SPORADIC	BREAST	SPORADIC	BREAST
19546	906	12-AUG-96	FAMILIAL	BREAST/OVARIAN	NEGATIVE	
20158	930	15-SEP-98	PUTATIVE HEREDITARY	BREAST/OVARIAN	FAMILIAL	BREAST
20555	948	03-JUL-96	SPORADIC	BREAST	NEGATIVE	
20909	963	03-JUL-96	PUTATIVE HEREDITARY	BRST/COLO	NEGATIVE	
21014	968	15-NOV-96	SPORADIC	BREAST	SPORADIC	BREAST
21014	968	29-APR-97	SPORADIC	BREAST	SPORADIC	BREAST
21052	969	15-NOV-96	FAMILIAL	BREAST	FAMILIAL	VARIOUS
21053	969	15-NOV-96	FAMILIAL	BREAST	FAMILIAL	VARIOUS
21936	1018	23-DEC-96	HEREDITARY	BREAST/OVARIAN	NEGATIVE	
21937	1019	23-DEC-96	SPORADIC	BREAST	SPORADIC	VARIOUS
21938	1020	23-DEC-96	SPORADIC	BRST/VARIOUS	SPORADIC	VARIOUS

21939	1021	23-DEC-96	FAMILIAL	BREAST	SPORADIC	VARIOUS
21940	1022	23-DEC-96	FAMILIAL	BREAST/OVARIAN	FAMILIAL	VARIOUS
22008	1022	23-DEC-96	SPORADIC	BRST/COLO	SPORADIC	VARIOUS
22059	1029	23-DEC-96	SPORADIC	VARIOUS	FAMILIAL	BREAST
22059	1029	13-JAN-98	FAMILIAL/VARIOUS	BREAST/LYMPHOMA	FAMILIAL	BREAST
22060	1030	23-DEC-96	FAMILIAL	BREAST	NEGATIVE	
22060	1030	10-JUN-98	FAMILIAL	BREAST	NEGATIVE	
22061	1031	23-DEC-96	SPORADIC	BREAST	NEGATIVE	
22062	1031	23-DEC-96	SPORADIC	BREAST	PUTATIVE HEREDITARY	BREAST/PROSTATE
22062	1031	29-APR-97	SPORADIC	BREAST	PUTATIVE HEREDITARY	BREAST/PROSTATE
22819	1060	13-JAN-97	FAMILIAL	VARIOUS	FAMILIAL/HEREDITARY	BREAST
22819	1060	29-APR-97	FAMILIAL/HEREDITARY	BREAST	FAMILIAL	VARIOUS
22820	1061	13-JAN-97	FAMILIAL	VARIOUS	NEGATIVE	
22821	1062	13-JAN-97	PUTATIVE HEREDITARY	BRST/VARIOUS	FAMILIAL	VARIOUS
22821	1062	29-APR-97	PUTATIVE HEREDITARY	BRST/VARIOUS	FAMILIAL	VARIOUS
22911	1064	13-JAN-97	SPORADIC	BREAST/UTERINE	NEGATIVE	
23664	1127	10-FEB-97	FAMILIAL	BREAST/UTERINE	NEGATIVE	
24329	1144	24-FEB-97	PUTATIVE HEREDITARY	BREAST/PROSTATE	SPORADIC	LUNG/COLON
25062	1177	10-APR-97	PUTATIVE HEREDITARY	BREAST	SPORADIC	LUNG
25063	1178	10-APR-97	SPORADIC	UTERUS	PUTATIVE HEREDITARY	VARIOUS
25063	1178	10-MAY-97	SPORADIC	UTERUS	PUTATIVE HEREDITARY	VARIOUS
25404	1192	10-APR-97	PUTATIVE HEREDITARY	BREAST/OVARIAN	PUTATIVE/FAMILIAL	VARIOUS
25602	1201	10-APR-97	FAMILIAL	BREAST/OVARIAN	SPORADIC	KIDNEY
25603	1202	10-APR-97	FAMILIAL	BRST/VARIOUS	NEGATIVE	
25604	1203	10-APR-97	NEGATIVE		PUTATIVE HEREDITARY	BREAST/OVARIAN
25953	1217	07-JUL-97	SPORADIC	LEUKEMIA	FAMILIAL	BREAST/PROSTATE
25953	1217	10-JUN-98	SPORADIC	LEUKEMIA	FAMILIAL	BREAST/PROSTATE
25969	1218	02-MAY-97	FAMILIAL	BREAST	SPORADIC	LEUKEMIA
25990	1219	02-MAY-97	FAMILIAL	BRST/COLO	SPORADIC	BREAST
25990	1219	15-JUN-98	FAMILIAL	BRST/COLO	SPORADIC	BREAST
26012	1220	02-MAY-97	PUTATIVE HEREDITARY	BRST/COLO	FAMILIAL	VARIOUS
26152	1225	07-JUL-97	FAMILIAL	BRST/COLO	NEGATIVE	
26153	1225	07-JUL-97	FAMILIAL	BRST/COLO	NEGATIVE	
26154	1225	07-JUL-97	FAMILIAL	BRST/COLO	NEGATIVE	
26192	1226	07-JUL-97	PUTATIVE HEREDITARY	BREAST	SPORADIC	COLON
26192	1226	30-SEP-97	PUTATIVE HEREDITARY	BREAST/BCC	PUTATIVE HEREDITARY	COLON
26192	1226	17-JUL-98	PUTATIVE HEREDITARY	BREAST/SKIN/VARIOUS	SPORADIC	COLON
26193	1226	17-JUL-98	PUTATIVE HEREDITARY	BRST/VARIOUS	PUTATIVE HEREDITARY	BCC
27329	1281	07-JUL-97	SPORADIC	BREAST	SPORADIC	PROSTATE
27330	1282	07-JUL-97	FAMILIAL	BREAST	NEGATIVE	
27331	1283	07-JUL-97	NEGATIVE		FAMILIAL	BREAST
27332	1284	07-JUL-97	PUTATIVE HEREDITARY	BR/OV/COLON	PUTATIVE HEREDITARY	BREAST/PROSTATE
27332	1284	06-JUL-98	PUTATIVE HEREDITARY	BREAST/OVAR/RECTAL	FAMILIAL	VARIOUS
27333	1285	07-JUL-97	SPORADIC	CERVIX	FAMILIAL	BREAST/PROSTATE
27333	1285	15-JUN-98	SPORADIC	CERVIX	PUTATIVE HEREDITARY	BREAST
27493	1288	07-JUL-97	FAMILIAL	BREAST/UTERINE	SPORADIC	BRAIN/NOSE
27494	1288	07-JUL-97	FAMILIAL	UT/GI	UNKNOWN	
27495	1288	07-JUL-97	PUTATIVE HEREDITARY	BR/UT/BLAD/GI	SPORADIC	THYROID
27496	1288	07-JUL-97	PUTATIVE HEREDITARY	BR/UT/GI	SPORADIC	THYROID
27497	1288	07-JUL-97	PUTATIVE HEREDITARY	BR/UT/GI	SPORADIC	THYROID
27498	1288	07-JUL-97	PUTATIVE HEREDITARY	BR/UT/GI	SPORADIC	THYROID
28593	1338	28-JUL-97	PUTATIVE HEREDITARY	BREAST	NEGATIVE	
28594	1339	28-JUL-97	PUTATIVE HEREDITARY	BREAST	NEGATIVE	
28595	1340	28-JUL-97	FAMILIAL	BREAST	NEGATIVE	
28596	1341	28-JUL-97	PUTATIVE HEREDITARY	BREAST	NEGATIVE	
28691	1342	18-AUG-97	FAMILIAL	BREAST	FAMILIAL	COLON
28692	1342	18-AUG-97	FAMILIAL	BREAST	FAMILIAL	COLON
28954	1356	18-AUG-97	FAMILIAL	BREAST	FAMILIAL	VARIOUS
28955	1356	18-AUG-97	FAMILIAL	BREAST	SPORADIC	BRAIN
29274	1371	18-AUG-97	PUTATIVE HEREDITARY	BREAST/OVARIAN	NEGATIVE	
28956	1384	30-SEP-97	NEGATIVE		FAMILIAL	VARIOUS
28956	1384	10-JUN-98	NEGATIVE		FAMILIAL	VARIOUS
29642	1385	30-SEP-97	FAMILIAL	VARIOUS	FAMILIAL	VARIOUS
29642	1385	06-JUL-98	FAMILIAL	VARIOUS	FAMILIAL	VARIOUS
29644	1387	29-SEP-97	PUTATIVE HEREDITARY	VARIOUS	PUTATIVE HEREDITARY	VARIOUS
30080	1406	16-DEC-97	SPORADIC	BREAST/HEADNECK	NEGATIVE	

30081	1407	16-DEC-97	SPORADIC	BREAST	SPORADIC	MELANOMA
30207	1411	16-DEC-97	FAMILIAL	VARIOUS	FAMILIAL	VARIOUS
30207	1411	15-JUN-98	PUTATIVE HEREDITARY	BREAST/OVARIAN	SPORADIC	VARIOUS
30207	1411	06-JUL-98	PUTATIVE HEREDITARY	BREAST/OVARIAN	SPORADIC	VARIOUS
30208	1412	16-DEC-97	FAMILIAL	BRST/VARIOUS	FAMILIAL	BRST/VARIOUS
30382	1419	16-DEC-97	SPORADIC	OVARIAN	FAMILIAL	BCC
30382	1419	15-JUN-98	PUTATIVE HEREDITARY	BREAST/OVARIAN	FAMILIAL	BCC
30382	1419	06-JUL-98	PUTATIVE HEREDITARY	BREAST/OVARIAN	FAMILIAL	BCC
30770	1434	16-DEC-97	FAMILIAL	BREAST	UNKNOWN	
31128	1453	16-DEC-97	PUTATIVE HEREDITARY	VARIOUS BR/OV	FAMILIAL	VARIOUS/BCC
31321	1460	16-DEC-97	FAMILIAL	VARIOUS	SPORADIC	LEUKEMIA
31321	1460	16-JUL-98	PUTATIVE HEREDITARY	BRST/OV/MELANOMA	FAMILIAL	VARIOUS/BCC
31448	1467	16-DEC-97	FAMILIAL	BREAST/PROSTATE	FAMILIAL	VARIOUS
31449	1467	16-DEC-97	FAMILIAL	BREAST/PROSTATE	FAMILIAL	VARIOUS
31492	1469	16-DEC-97	FAMILIAL	BRST/VARIOUS	FAMILIAL	BRST/VARIOUS
31493	1470	16-DEC-97	SPORADIC	VARIOUS	PUTATIVE HEREDITARY	OV/VARIOUS
31855	1489	13-JAN-98	PUTATIVE HEREDITARY	BRST/VARIOUS	SPORADIC	UNKNOWN
31855	1489	16-JUL-98	PUTATIVE HEREDITARY	BRST/VARIOUS	SPORADIC	PRIMARY SITE UNKNOWN
32030	1496	17-MAR-98	PUTATIVE HEREDITARY	BREAST/OVARIAN	NEGATIVE	
32030	1496	03-JUN-98	PUTATIVE HEREDITARY	BREAST/OVARIAN	PUTATIVE HEREDITARY	BREAST/OVARIAN
32030	1496	06-JUL-98	PUTATIVE HEREDITARY	BREAST/OVARIAN	PUTATIVE HEREDITARY	BREAST/OVARIAN
32348	1510	17-MAR-98	FAMILIAL	VARIOUS	NEGATIVE	
12228	1546	17-MAR-98	FAMILIAL	VARIOUS	FAMILIAL	VARIOUS
34386	1607	10-JUN-98	PUTATIVE HEREDITARY	BREAST	FAMILIAL	LUNG
34468	1611	17-JUL-98	FAMILIAL	VARIOUS	FAMILIAL	VARIOUS BR/OV
34804	1626	16-JUL-98	FAMILIAL	BRST/VARIOUS	NEGATIVE	
36063	1681	16-JUL-98	FAMILIAL	BREAST/BCC	NEGATIVE	
36064	1682	16-JUL-98	PUTATIVE HEREDITARY	BREAST	SPORADIC	LUNG
36066	1683	16-JUL-98	PUTATIVE HEREDITARY	VARIOUS BR/OV	NEGATIVE	
36067	1684	16-JUL-98	PUTATIVE HEREDITARY	BRST/VARIOUS	SPORADIC	LUNG
36068	1684	16-JUL-98	PUTATIVE HEREDITARY	BREAST/OVARIAN	SPORADIC	PRIMARY SITE UNKNOWN
36687	1709	23-SEP-98	FAMILIAL	BREAST	SPORADIC	LUNG
36803	1715	16-JUL-98	PUTATIVE HEREDITARY	VARIOUS BR/OV	FAMILIAL	STOMACH
37469	1747	17-SEP-98	PUTATIVE HEREDITARY	BREAST	SPORADIC	LUNG
37470	1748	28-AUG-98	FAMILIAL	BRST/VARIOUS	NEGATIVE	
38630	1811	23-SEP-98	PUTATIVE HEREDITARY	BRST/VARIOUS	SPORADIC	BCC
38631	1811	17-SEP-98	SPORADIC	BCC	PUTATIVE HEREDITARY	BRST/VARIOUS
38632	1811	16-SEP-98	SPORADIC	BREAST/BCC	PUTATIVE HEREDITARY	BRST/VARIOUS
38999	1831	23-SEP-98	SPORADIC	OVARIAN	FAMILIAL	VARIOUS/LUNG

164 rows selected.