



Health Matrix: The Journal of Law-Medicine

Volume 7 | Issue 1

1997

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CLINICAL IMPLICATIONS OF BRCA1 GENETIC TESTING FOR ASHKENAZI-JEWISH WOMEN

Georgia L. Wiesner, MD[†]

THE COMPLEX ISSUES SURROUNDING genetic testing for breast cancer susceptibility were recently highlighted when a single mutation in a major breast cancer susceptibility gene was found to exist with remarkably high frequency within the Ashkenazi-Jewish population.¹ This genetic alteration, 185delAG, is easily identified by standard molecular techniques and is one of over one hundred reported mutations in the Breast Cancer 1 (BRCA1) gene.² A major consequence of this genetic discovery is that widespread testing and screening is now possible for all women regardless of their previous risk profile for developing breast cancer. Indeed, a commercial testing company, Genetics and In-Vitro Fertilization (IVF) Institute of Fairfax, Virginia, is currently marketing the BRCA1, 185delAG test to general physicians and oncologists for patients outside of scientific research protocols. As a result, a debate about the merits of breast cancer susceptibility testing gained national prominence.³

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1. See Jeffrey P. Struewing et al., *The Carrier Frequency of the BRCA1 185delAG Mutation is Approximately 1 Percent in Ashkenazi Jewish Individuals*, 11 NATURE GENETICS 198, 198 (1995) (stating that the observed cancer frequency of BRCA1 in Ashkenazi individuals is several times higher than the expected frequency of all BRCA1 mutations combined in the general population).

2. See Francis S. Collins, *BRCA1-Lots of Mutations, Lots of Dilemmas*, 334 NEW ENG. J. MED. 186, 186 (1996) (noting that the 185delAG is a frame-shift mutation at position 185 in exon 2 and involves a deletion of an adenine (A) and guanine (G) nucleotide); Donna Shattuck-Eidens et al., *A Collaborative Survey of 80 Mutations in the BRCA1 Breast and Ovarian Cancer Susceptibility Gene: Implications for Presymptomatic Testing and Screening*, 273 JAMA 535, 537-39 (concluding that the high frequency of protein-terminating mutations found in the diverse eighty mutation survey could lead to a relatively simple diagnostic test for BRCA1 mutations).

3. See Laurie Goodman, *Breast Cancer Mutation Screening*, 13 NATURE GENETICS 17, 17 (1996) (stating that although some researchers agree that women have a right to know about

Offering BRCA1 genetic testing on a commercial basis is controversial. Several national groups have strongly recommended a cautious approach to incorporating genetic testing into medical practice,⁴ and have published guidelines for BRCA1 testing which propose that it be limited to high-risk women under scientific protocols. This will ensure that the benefits and limitations of testing are adequately understood before it is offered to the general public. Clearly, genetic testing for cancer susceptibility can have a profound and positive impact on high-risk individuals and families.⁵ However, providing unrestricted cancer susceptibility testing to the general population raises several important questions about the risks and benefits involved as well as how testing should be integrated into the health care for all Americans.⁶

The high frequency of the 185delAG mutation in Ashkenazi-Jewish women also raises questions about the potential ethical and social impact on that community. How will

genetic disposition, many researchers feel that this information may cause the patient more harm than good); Gina Kolata, *Breaking Ranks: Lab Offers Test To Assess Risk of Breast Cancer*, N.Y. TIMES, Apr. 1, 1996, at A1 (stating that a private commercial institute that was not part of any agreement to hold back the breast cancer test decided to offer the test despite the still-remaining unanswered questions); Open Letter from the Genetic & IVF Institute (Apr. 1996) (on file with author) (announcing the Institute's Plan to begin offering 185delAG BRCA1 mutation testing).

4. See generally American Society of Clinical Oncology, *Statement of the American Society of Clinical Oncology: Genetic Testing for Cancer Susceptibility*, 14 J. CLINICAL ONCOLOGY 1730 (1996) (setting forth the American Society of Clinical Oncology's position on genetic testing and the ethical and psychological impact of these tests). See also National Advisory Council for Human Genome Research, *Statement on Use of DNA Testing for Presymptomatic Identification of Cancer Risk*, 271 JAMA 785, 785 (1994) [hereinafter National Advisory Council] (proposing a series of questions that must be addressed before incorporating genetic testing into medical practice); American Society of Human Genetics, *Statement of the American Society of Human Genetics on Genetic Testing for Breast and Ovarian Cancer Predisposition*, 55 AM. J. HUM. GENETICS i, i (1994) [hereinafter ASHG] (recommending that testing should initially be offered and performed on an investigational basis by appropriately trained health care professionals who have a therapeutic relationship with the patient and are fully aware of the genetic, clinical, and psychological implication of testing, as well as the limitations of testing).

5. See Barbara B. Biesecker et al., *Genetic Counseling for Families with Inherited Susceptibility to Breast and Ovarian Cancer*, 269 JAMA 1970, 1971 (1993) (reporting the dramatic impact which early detection of breast cancer susceptibility has had on women who were tested for the BRCA1 mutation).

6. See Goodman, *supra* note 3, at 17 (stating that many researchers believe that the information obtained from genetic screening may be harmful given the uncertain consequences of a positive test); Judy E. Garber & Deborah Schrag, *Testing for Inherited Cancer Susceptibility*, 275 JAMA 1928, 1928-29 (1996) (discussing the need for physicians to become aware of psychological, behavioral, and logistical impacts of genetic testing).

members of the Jewish community utilize this genetic information? Is this genetic mutation found solely in the Jewish population? Should genetic testing be available to all persons who want to be tested? Will genetic testing be required by employers and third-party payers for health insurance? Who will have access to the test results? What are the limitations of genetic tests? With what accuracy does BRCA1 testing predict the occurrence of breast cancer? This Article will provide a framework for understanding the impact of genetic testing for breast cancer risk in Ashkenazi-Jewish women by reviewing the scientific basis for cancer susceptibility testing as well as essential concepts of inheritance and the genetics of breast cancer.

I. A TALE OF TWO WOMEN: THE TESTING DILEMMA

In order to appreciate the potential impact of genetic testing for a community or society, we must first understand the clinical process of susceptibility testing for cancer. The following two clinical histories from the Center for Human Genetics at University Hospitals of Cleveland illustrate the complex issues facing women who are considering predictive and diagnostic genetic testing for BRCA1.⁷ These case studies also demonstrate that the decision to have testing must be made carefully. Each woman deliberated the benefits and risks of testing over an extended period of time before reaching a final decision.

A. Case One

BET was a forty-two-year-old Jewish woman who was referred by her surgeon to the Cancer Genetics Clinic for consultation prior to prophylactic mastectomy. She had questions about her risk for developing breast cancer and whether she

7. A combined program in Cancer Genetics was established in October, 1994 in the Center for Human Genetics and the Department of Genetics in Case Western Reserve University and University Hospitals of Cleveland. Specialized clinics to evaluate patients for familial breast and colon cancer were begun in March, 1995. The cases provided here have been slightly modified to protect the identity of the patients and their families. The patient abbreviations are fictitious as are minor details about the family structure as shown in the pedigrees in Figure 1 and 2.

should consider removal of her normal breast tissue as a preventative measure for breast cancer. Her older sister, who is now fifty-two years old, had developed breast cancer twelve years before at the age of forty-one (Figure 1). In addition, her mother and maternal grandmother had both developed ovarian cancer late in life and her father had died of colon cancer. A distant cousin on her mother's side had also developed ovarian cancer. She was not concerned about her risk for ovarian cancer since her uterus and ovaries had been surgically removed because of an unrelated medical condition. In addition to her own health-related issues, she wondered what could and should be done to predict cancer in her fourteen-year-old daughter.

Figure 1.
Center for Human Genetics
CGC- Family 041

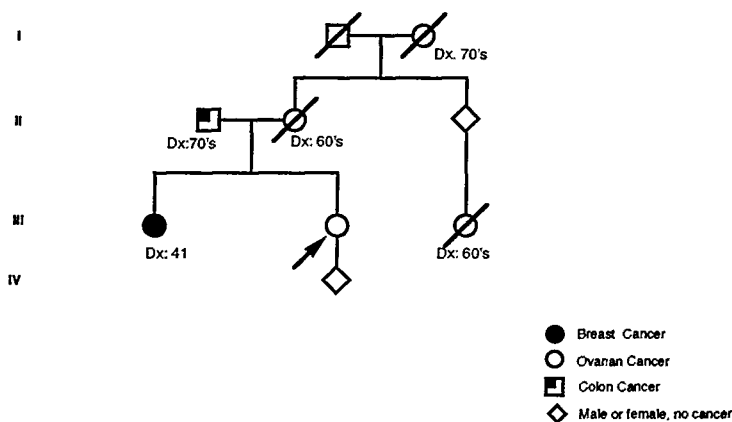


Figure 1
Pedigree "MCT/BET" Case

Initial review of her family medical tree showed that while several members had developed cancer, it was not the "classic" scenario for the hereditary breast ovarian syndrome. This determination was made despite the small size of BET's family and her lack of detailed information on distant relatives. However, the fact that her sister developed breast cancer prior to menopause coupled with the fact that their mother had ovarian cancer concerned the genetics team that met with BET.⁸ After a

8. Genetic evaluation and counseling sessions consist of a support person (if the patient

complete discussion of the risks and benefits of testing, she was advised that predictive genetic testing for the BRCA1 gene was possible for her. Most importantly, the counselor felt that BRCA1 testing could assist her in making her decision about prophylactic breast surgery. If she did carry a BRCA1 genetic alteration, then BET felt that she would have a prophylactic mastectomy in order to markedly reduce her risk of breast cancer. In contrast, if she did not carry a BRCA1 genetic alteration, then her risk for developing breast cancer would be much smaller, comparable to the population risk for all women, and she felt that she would avoid breast surgery.

The process of predictive testing was discussed with BET. The first step in the process was to analyze the pedigree by reviewing the surgical and pathology reports on all family members with cancer. Secondly, it was explained that for predictive testing to be useful for BET, the genetic test for the BRCA1 gene should first be performed on an individual in the family who was suspected of developing cancer because of an inherited susceptibility. This step is necessary because it confirms that a genetic mutation is identifiable in the patient's family. In BET's case, it was suggested that the BRCA1 test should be performed on her older sister. If her sister's genetic test was positive for a BRCA1 mutation, then BET could choose to have predictive testing.

After her initial visit, BET was faced with unanticipated decisions. While she understood that genetic testing would help her with her decision for prophylactic surgery, she was not prepared to approach other family members with what she felt was a private decision. In particular, she was concerned about her sister's well-being. She was hesitant to discuss genetic testing with her sister because BET did not want to cause her additional emotional distress. Thus, BET agreed to supply medical records on her mother's cancer diagnosis while she considered her choices.

Approximately five months after her initial visit, BET returned to the clinic with her sister, MCT. BET and MCT

wishes) a genetic counselor, and a medical geneticist. Both genetic counselor and physician have expertise in cancer genetics. Review of family information and final recommendations are done in conjunction with the patient's primary physician, oncologist, or surgeon.

were told the limitations of testing, as well as the actual testing procedure prior to collecting their blood samples. The BRCA1 185delAG mutation was also specifically discussed because of their Ashkenazi-Jewish heritage. They were aware that in order for BET to have predictive testing, MCT would undergo diagnostic genetic testing with the intention of sharing the results with BET. The test was performed after receiving each sister's informed consent.

BET and MCT both returned to the clinic to learn their results approximately one month later. MCT, the sister who had developed breast cancer when she was forty-one years old, had the BRCA1 mutation, 185delAG. This mutation is commonly found in Ashkenazi-Jewish women. BET also learned that she shared the same 185delAG mutation with her sister. The implications of the gene test were discussed with each sister and plans for cancer screening and surgery were made. For BET, the process of genetic testing had taken approximately six months and required prolonged deliberation of her personal beliefs. While saddened by the result of her genetic test, she was determined to use the information as a preventative measure.

B. Case Two

JB is a forty-seven-year-old Jewish woman who developed cancer of the right breast when she was forty-six years old. She was referred to the Cancer Genetics Clinic for a discussion about prophylactic surgery for her left breast. Her family tree has numerous members with cancer including breast, ovarian, and stomach cancers. Her mother had bilateral breast cancer at age forty-six and her maternal grandmother had ovarian cancer in her fifties. The family tree is illustrated in Figure 2. In discussing her concerns with the genetic counselor and medical geneticist, JB was most concerned about her chances of developing a second cancer in her left breast. Her family pedigree was consistent with an inherited cancer family syndrome, including the hereditary breast-ovarian syndrome. All of these factors made BRCA1 testing possible.

Center for Human Genetics
CGC- Family 005

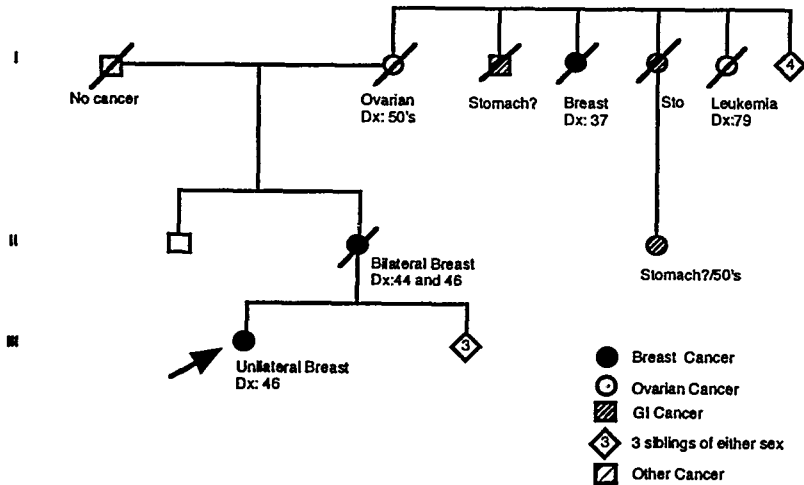


Figure 2
Pedigree "JB" Case

Counseling involved a review of JB's family pedigree and a discussion of the risk of developing additional cancers in carriers of BRCA1 mutations, such as ovarian and contralateral breast cancer. The potential risk for developing ovarian cancer was surprising to JB, who was initially concerned about developing bilateral breast cancer as her mother had. In considering testing, JB also needed to consider the technical limitations of genetic testing. Since her personal and family history was suggestive of an inherited cancer family syndrome, it was most likely that her previous breast cancer was caused by an inherited susceptibility gene.

Before continuing with JB's case study, it is important to note that there are two separate factors that can decrease the chance of identifying a specific mutation in a cancer predisposition gene. First, the BRCA1 test is approximately ninety percent sensitive.⁹ Therefore the test could possibly yield a

9. Sensitivity is defined as the proportion of people with the disease who do have a

negative result because of technological complexities of the laboratory performance. Second, there are several genes that can cause familial breast cancer (see Table 1) and not all genes currently can be tested.

With this in mind, one possible explanation for the clusters of cancer in her family could be a BRCA1 mutation, however, it also could be due to other breast cancer susceptibility genes such as those that cause the Hereditary Non-polyposis Colorectal Cancer syndrome or other unidentified genes. In addition, consideration had to be given to a chance occurrence of a cluster of common cancers occurring in her family.

JB was also faced with decisions that she had not anticipated prior to meeting with the genetics team. She was surprised that she had an elevated risk for ovarian cancer and, furthermore, that BRCA1 testing was not one hundred percent accurate. In addition, JB was concerned about insurance discrimination and did not want the genetic testing to put her health insurance coverage at risk. Therefore, she declined to have the test after careful deliberation over a three-month period of time. However, because of her elevated risk for developing ovarian cancer, she was receptive to having a prophylactic removal of her ovaries. JB explained that she based her decision on the analysis of her family tree during her clinic visit. At that time she had been told that she probably carried a cancer susceptibility gene, since she had developed breast cancer at an early age. Therefore, JB felt that the genetic test result would not clarify her risk for other cancers. Rather, she feared that it might impose a larger burden by potentially resulting in the loss of her health insurance coverage.

II. THE AGE OF GENETIC DISCOVERY

A quiet revolution has taken place in our understanding of the genetic mechanism of disease over the last forty-three years since James Watson's and Francis Crick's discovery of the

positive test and measures the accuracy of a specific laboratory test. See MARCUS HERMANSEN, *BIOSTATISTICS: SOME BASIC CONCEPTS* 172-73 (1990) (defining the relationship between predictive value, sensitivity, and specificity). Thus, for BRCA1 families, testing would yield a true positive result 90% of the time. *Id.*

double helical structure of DNA.¹⁰ Indeed, over the last 130 years, medical science has moved from the notion of units of heredity, as proposed by Gregor Mendel in 1865,¹¹ to the first description of a genetic disease, alkaptonuria, in 1909.¹² Genes were physically mapped to chromosomes in 1910,¹³ and DNA was discovered as the molecule of inheritance in 1944.¹⁴ When the ambitious Human Genome Project was initiated in 1990, mapping and sequencing the entire human genome was a dream.¹⁵ Now, in 1996, the physical mapping project is nearly complete,¹⁶ and genetic scientists are focused on locating each of the estimated 100,000 genes located on the twenty-three human chromosome pairs.¹⁷

In a relatively short time span, this information has enormously impacted our understanding of the biochemical and molecular basis of disease and has led to the development of new paradigms for medical science.¹⁸ Clinical laboratory testing has focused on the diagnosis of disease after a patient develops characteristic signs and symptoms of illness. Health care delivery now includes identifying high-risk patients, prior to the development of symptoms, by searching for specific genetic alterations known to cause diseases.¹⁹ Prior knowledge of potential illness can be advantageous because specific health

10. See GUNTHER S. STENT & RICHARD CALENDAR, *MOLECULAR GENETICS: AN INTRODUCTORY NARRATIVE* 202-08 (1978).

11. See *id.* at 1-7.

12. See HARRY HARRIS, *THE PRINCIPLES OF HUMAN BIOCHEMICAL GENETICS* 187 (A. Neuberger & E.L. Tahim ed., 2nd ed., 1975) (discussing Garrad's concept of pathogenesis and the genetic disorder alkaptonuria).

13. See STENT & CALENDAR, *supra* note 10, at 17-21 (discussing T. H. Morgan's experiments which establish a genetic map of the *drosophila* chromosomes).

14. See *id.* at 23 (noting Oswald Avery's discovery that genes are embodied in DNA).

15. See James D. Watson, *The Human Genome Project: Past, Present, and Future*, 248 *SCIENCE* 44, 47 (1990) (discussing some of the scientific strategy and methodology needed to be worked out to achieve the goals of the 1990 plan).

16. See Francis Collins & David Galas, *New Five-Year Plan for the U.S. Human Genome Project*, 262 *SCIENCE* 43, 43 (stating that in 1993, progress toward achieving the first set of goals for the genome project was on schedule, and in some instances, even ahead of schedule).

17. See MARGARET W. THOMPSON ET AL., *GENETICS IN MEDICINE* 31 (1991) (discussing the organization of the human genome).

18. See Victor A. McKusick, *The New Genetics and Clinical Medicine: A Summing Up*, *HOSP. PRAC.*, July 15, 1988, at 177, 181 (summarizing some of the more striking aspects of the biochemical and molecular basis of disease and the remarkable possibilities this approach has opened up).

19. See Arno G. Motulsky, *Predictive Genetic Diagnosis*, 55 *AM. J. HUM. GENETICS* 603, 603 (1994) (discussing various applications of genetic screening prior to the onset of the disease).

screening measures can be instituted to minimize morbidity and mortality.²⁰ While predictive or presymptomatic testing can currently identify only a small fraction of human disorders,²¹ the direct incorporation of genetic discoveries from basic science into the practice of medicine is at the forefront of a new medical model of health care.

III. GENETIC BASIS OF CANCER

The advances in molecular biology and human genetics over the last two decades have led to a greater appreciation of the underlying cellular and genetic mechanisms of the neoplastic process. The current model of carcinogenesis is that both inherited and sporadic cancers are due to genetic alterations in the nucleus of a single cell.²² However, the development of a tumor is not an instantaneous event. Rather, a cell becomes cancerous after a series of genetic and cellular alterations that disable the normal mechanisms that control how the cell grows and divides.²³ In this view, a neoplastic tumor can be thought of as a disorder of cell regulation which leads to an expansion of the initial malignant cell with numerous clonal malignant daughter cells that eventually metastasizes to other tissue sites.

Except in extremely rare situations, the presumption is that no single genetic alteration is adequate to produce malignant transformation and tumor development. The accumulation of several mutations in key regulatory genes, however, results in loss of control over the normal cell cycle checkpoints and other regulatory steps.²⁴ Thus, there is an increase in abnormal cel-

20. See Biesecker et al., *supra* note 5, at 1971.

21. See generally Howard Markel, *The Stigma of Disease: Implications of Genetic Screening*, 93 AM. J. MED. 209 (1992) (discussing the concept of "quarantine mentality" and the desire of society to separate itself from those labeled "ill" within the context of new advances in genetic technology). See also Goodman, *supra* note 3, at 17 (discussing ethical issues raised by genetic screening).

22. See J. Michael Bishop, *Molecular Themes in Oncogenesis*, 64 CELL 235, 238 (1991) [hereinafter Bishop, *Molecular Themes*] (discussing the inheritance of cancer); J. Michael Bishop, *The Molecular Genetics of Cancer*, 235 SCIENCE 305, 305, 310 (1987) (reviewing the means by which proto-oncogenes have been identified and the evidence that damage to these genes may be involved in the genesis of cancer).

23. See Andrew W. Murray, *Creative Blocks: Cell-Cycle Checkpoints and Feedback Controls*, 359 NATURE 599, 603-04 (1992) (concluding that failures in feedback control mechanisms, which regulate the cell cycle, can contribute to the generation of cancer).

24. See *id.* See also Bert Vogelstein et al., *Genetic Alterations During Colorectal-Tumor*

lular proliferation with the development of a malignant tumor. Instability of the genetic material in the cell nucleus is a hallmark of neoplasia and is exhibited by cytogenetic and molecular abnormalities in many tumor types.²⁵ As the tumor progresses, there are increasing non-random alterations in several regions of the genome.

An important conceptual model which explains the occurrence of inherited and sporadic cases of cancer was first proposed by Alfred G. Knudson in 1971.²⁶ Using familial and isolated cases of retinoblastoma, a rare childhood eye tumor, he suggested that a somatic mutation occurs in each copy of a putative gene before a tumor can form in the immature retina cell, or retinoblast. Since each cell carries two copies of each gene, such mutations occur as a rare event in the life of a cell and are seen as a sporadic, rare case of retinoblastoma. However, if a mutation is inherited from a parent with retinoblastoma, the child carries an altered germline susceptibility gene. In other words, the specific mutation is found in the genetic material in all cells of the body. In this case, one additional somatic mutation in the corresponding allele²⁷ of a single cell initiates the neoplastic process. This model was shown to be accurate in subsequent investigations showing cytogenetic abnormalities in retinoblastoma tumor cells, the identification of the retinoblastoma gene on human chromosome 13, and family studies of retinoblastoma.²⁸

Development, 319 NEW ENG. J. MED. 525, 525 (1988) (finding that the colorectal-tumor developmental model often involves the mutational activation of an oncogene coupled with the loss of several genes that normally suppress tumorigenesis).

25. See Russell F. Jacoby et al., *Genetic Instability Associated with Adenoma to Carcinoma Progression in Hereditary Nonpolyposis Colon Cancer*, 109 GASTROENTEROLOGY, 73, 73, 81 (1995) (correlating genetic instability to the pathogenesis of carcinoma in hereditary nonpolyposis colon cancer); Vogelstein et al., *supra* note 24, at 529-31. See also Floyd Thompson et al., *Clonal Chromosome Abnormalities in Human Breast Carcinomas*, 7 GENES, CHROMOSOMES, CANCER 185, 191-93 (1993) (illustrating the frequent finding of clonal chromosome abnormalities in human primary breast cancers).

26. Alfred G. Knudson, Jr., *Mutation and Cancer: Statistical Study of Retinoblastoma*, 68 PROC. NAT'L ACAD. SCI. 820, 820 (1971) (suggesting the possibility that tumors are distributed in accord with a Poisson distribution).

27. See THOMPSON ET AL., *supra* note 17, at 373 (comparing Mendelian and sporadic forms of cancer). An allele is one of a pair of genes located at a specific chromosomal site or locus. See *id.* at 53.

28. See W.K. Cavenee et al., *Expression of Recessive Alleles by Chromosomal Mechanisms in Retinoblastoma*, 305 NATURE 779, 780 (1983) (confirming the two-step mechanism of tumorigenesis whereby a subsequent event in a predisposed retinal cell results in homozygosity

The Knudson hypothesis was a crucial step in our understanding of inherited cancers and has provided a framework for cancer research and discovery. Other tumor types, such as colon cancer and breast cancer, follow the more complex model of multi-stage carcinogenesis where mutations in several regulatory genes must occur before malignant transformation of the cell.²⁹ In addition, environmental factors influence the development of cancer and there may be gene-environmental factors that cause transformation or progression of cancer.³⁰

It must be remembered that for the majority of individuals, cancer is a sporadic event, occurring in the absence of an inherited predisposition to malignancy. However, a small proportion of adults and children carry an inherited, germline mutation in a cancer predisposition gene.³¹ This genetic alteration places them at an increased risk of developing cancer over their lifetimes. Such genetic susceptibility does not mean that all mutation carriers will develop cancer. In fact, the causative genes for most family cancer syndromes, including breast cancer, are not fully penetrant.³² The expression of the cancer, therefore, depends upon a complex chain of events where mutations in a major predisposition gene interact with mutations in other modifier genes and with other environmental factors.

The explosion of information about the molecular basis of human disease and genetic susceptibility has been most pronounced in the study of breast cancer. Several genes causing breast cancer have been recently located and cloned.³³ Fur-

for the mutant allele). See generally Veronique Blanquet et al., *Spectrum of Germline Mutations in the RB1 Gene: A Study of 232 Patients with Hereditary and Non-Hereditary Retinoblastoma*, 4 HUM. MOLECULAR GENETICS 383 (1995) (reporting novel germline mutations in the retinoblastoma gene of hereditary and non-hereditary RB patients).

29. See Vogelstein et al., *supra* note 24, at 531.

30. See Bishop, *Molecular Themes*, *supra* note 22, at 237 (noting that many of the experimentally documented carcinogens may act indirectly as mutagens by stimulating cellular proliferation that, in turn, increases the probability of converting endogenous DNA damage into mutations); Mark H. Skolnick & Lisa A. Cannon-Albright, *Genetic Predisposition to Breast Cancer*, 70 CANCER 1747, 1749 (1992) (diagramming a model of how environmental factors impact inherited cancer predispositions).

31. See Struewing et al., *supra* note 1, at 198.

32. Penetrance is the proportion of gene carriers that express, or show signs or symptoms, of the genetic trait in question. See THOMPSON ET AL., *supra* note 17, at 83. For family cancer syndromes, a penetrance level of .90 indicates that 90% of individuals known to carry the abnormal gene will develop cancer.

33. See generally Kinneret Savitsky et al., *A Single Ataxia-Telangiectasia Gene with A*

thermore, it is estimated that approximately five to ten percent of all cancers are caused by an inherited susceptibility gene.³⁴ This has had a tremendous impact on breast cancer prevention by potentially identifying women at risk for breast cancer prior to the development of disease. However, there are several unanswered questions about how to appropriately integrate cancer risk assessment into clinical health care.

IV. THE GENETICS OF BREAST CANCER

Breast cancer is a substantial national health concern because it is the most common cancer in American women today. Approximately 180,000 women are diagnosed with breast cancer each year, and another 46,000 women will die of the disease.³⁵ Current estimates suggest that nearly one out of eight

Product Similar to PI-3 Kinase, 268 SCIENCE 1749, 1749 (1995) (identifying the ATM gene which is believed to be involved in the autosomal recessive disorder ataxia-telangiectasia); Ethan Lange et al., *Localization of an Ataxia-Telangiectasia Gene to an ~500-kb Interval on Chromosome 11q23.1: Linkage Analysis of 176 Families by an International Consortium*, 57 AM. J. HUM. GENETICS 112, 112-15 (1995) (localizing the gene for Ataxia-Telangiectasia); Fredrick S. Leach et al., *Mutations of a mutS Homolog in Hereditary Nonpolyposis Colorectal Cancer*, 75 CELL 1215, 1215 (1993) (discussing the mutS homolog in HNPCC); Richard Fishel et al., *The Human Mutator Gene Homolog MSH2 and its Association with Hereditary Nonpolyposis Colon Cancer*, 75 CELL 1027 (1993) (explaining that gene MSH2 has been mapped and found to be associated with hereditary nonpolyposis colon cancer); Jean Feunteun et al., *A Breast Ovarian Cancer Susceptibility Gene Maps to Chromosome 17q21*, 52 AM. J. HUM. GENETICS 736 (1993) (confirming the location of a dominant gene that confers susceptibility to breast and ovarian cancer); Yushio Miki et al., *A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1*, 266 SCIENCE 66 (1994) (identifying a strong candidate for the BRCA1 gene); Elizabeth Culotta & Daniel E. Koshland, Jr., *P53 Sweeps Through Cancer Research*, 262 SCIENCE 1958, 1959 (1993) (noting that in 1993 several teams of scientists cloned a gene that carries out at least a part of p53's tumor suppression activity); Nicholas C. Nicolaides et al., *Mutations of Two PMS Homologues in Hereditary Nonpolyposis Colon Cancer*, 371 NATURE 75, 75 (1994) (reporting the nucleotide sequence, chromosome localization, and mutational analysis of hPMS1 and hPMS2, which were found to be mutated in the germline of HNPCC patients); C. Eric Bronner et al., *Mutation in the DNA Mismatch Repair Gene Homologue hMLH1 is Associated with Hereditary Non-polyposis Colon Cancer*, 368 NATURE 258, 258 (1994) (proposing that hMLH1 is the HNPCC gene located on 3p because of the similarity of the hMLH1 gene product to yeast DNA mismatch repair protein, MLH1).

34. See Mary-Claire King et al., *Inherited Breast and Ovarian Cancer: What are the Risks? What are the Choices?*, 269 JAMA 1975, 1975 (1993) (stating that the goal of identifying genes responsible for breast cancer is to learn biological features of the disease that can be studied for the development of preventive strategies); Ruth Ottman et al., *Familial Breast Cancer in a Population-Based Series*, 123 AM. J. EPIDEMIOLOGY 15, 15 (1986); Mary-Claire King, *Breast Cancer Genes: How Many, Where and Who are They?*, 2 NATURE GENETICS 89, 89 (1992) (stating that it is important to determine which compounds are most effective against each tumor genotype).

35. See Craig Henderson, *Breast Cancer*, in AMERICAN CANCER SOCIETY TEXTBOOK OF

to ten women will develop breast cancer at some point in their lives.³⁶ Breast cancer is etiologically and genetically heterogeneous.³⁷ For most women, a combination of family history and reproductive factors, such as age at menarche, age at first birth, and parity, are important for the development of breast cancer.³⁸ Large epidemiologic studies have consistently demonstrated that family history is an independent risk factor for the development of breast and other cancers.³⁹ Approximately twenty to thirty percent of all breast cancers occur in women with a family history of the disease in a close female relative.⁴⁰ For a woman with a mother, sister, or daughter with breast cancer, the odds of developing breast cancer are mildly elevated, two to three times over the general population risk.⁴¹ However, this risk can be as high as nine to ten times the population risk when more than one relative is affected, or if the cancer developed at a young age in the family member.⁴²

There are several rare family cancer syndromes that have

CLINICAL ONCOLOGY 198, 198-99 (Gerald P. Murphy et al. eds., 1995).

36. See Graham A. Colditz, *Epidemiology of Breast Cancer: Findings from the Nurses' Health Study*, 71 *CANCER* 1480, 1480 (1993) (noting that the average years of life lost by those with breast cancer (twenty years) is higher for American women than the average of all cancers combined (sixteen years)); Kathy A. Fackelmann, *Refiguring The Odds: What's a Woman's Real Chance of Suffering Breast Cancer?*, 144 *SCI. NEWS* 76, 76 (1993) (translating statistical risks of breast cancer in women to reflect age and to compare with other common health problems).

37. See generally King, *supra* note 34, at 89-90.

38. See generally King et al., *supra* note 34, at 1975.

39. See James St. John et al., *Cancer Risk in Relatives of Patients with Common Colorectal Cancer*, 118 *ANNALS INTERNAL MED.* 785, 788 (1993) (examining risk for colorectal cancer in first-degree relatives of patients with common colorectal cancer); Gary D. Steinberg et al., *Family History and the Risk of Prostate Cancer*, 17 *PROSTATE* 337, 343 (1990) (relating the risk of developing prostate cancer with a family history of the disease); Lisa A. Cannon-Albright et al., *Familiality of Cancer in Utah*, 54 *CANCER RES.* 2378, 2382-84 (1994) (discussing the familial component of both rare and common cancers in Utah).

40. See Skolnick & Cannon-Albright, *supra* note 30, at 1751.

41. See Ottman et al., *supra* note 34, at 18-20.

42. See Elizabeth B. Claus et al., *Genetic Analysis of Breast Cancer in the Cancer and Steroid Hormone Study*, 48 *AM. J. OF HUM. GENETICS* 232, 236-39 (1991) (investigating the ability of a number of possible genetic models to fit the observed patterns of transmission of breast cancer in a population-based, case-controlled study); Elizabeth B. Claus et al., *Autosomal Dominant Inheritance of Early-Onset Breast Cancer: Implications for Risk Prediction*, 73 *CANCER* 643, 644-46 (1994) (illustrating the importance of appropriate screening for patients with a family history of breast cancer); Henry T. Lynch et al., *Familial Risk and Cancer Control*, 236 *JAMA* 582, 583 (1976) (demonstrating a significant correlation between family and personal history of cancer in a 4,515 patient study); Ann Grossbart Schwartz et al., *Risk of Breast Cancer to Relatives of Young Breast Cancer Patients*, 75 *J. NAT'L CANCER INST.* 665, 667 (1985).

an associated risk for breast cancer.⁴³ Family cancer syndromes are recognized by a detailed analysis of the family tree and are characterized by the occurrence of cancers at an unusually early age. In addition, families can have many members affected with cancer over many generations. Multiplex families can have a variety of both common and rare tumor types, such as breast, colon, ovarian, and prostate cancer.⁴⁴ A complete review of the family medical tree is important to characterize the type of familial breast cancer. Only then can the appropriate testing and cancer screening be performed.⁴⁵ The major forms of familial breast cancer include site specific breast cancer, the hereditary breast-ovarian syndrome, Li-Fraumeni syndrome, the Hereditary Non-Polyposis Colon Cancer syndrome, and breast cancer in relatives of patients with the ataxia-telangiectasia syndrome.⁴⁶ Many genes responsible for these disorders have been identified and are listed in Table 1.

The Hereditary Non-Polyposis Colon Cancer, or Lynch syndrome, is a family cancer syndrome where family members develop colon, rectal, and other cancers.⁴⁷ Like other familial syndromes, the types of cancers in the family are variable so that relatives are also seen with uterine, ovarian, gastric, and breast cancers. While the chance of developing colon cancer approaches eighty to ninety percent over a patient's lifetime, the risk for developing breast cancer in these families is only mildly elevated over that of the general population.⁴⁸

43. D.G.R. Evans et al., *Familial Breast Cancer*, 30 BRIT. MED. J. 183, 184-85 (1994).

44. Lynch et al., *supra* note 42, at 58 (listing several types of mendelian-transmitted cancers); Cannon-Albright et al., *supra* note 39, at 2379-80.

45. See Lisa Sclafani, *Management of the High-Risk Patient*, 7 SEMINARS SURGICAL ONCOLOGY 261, 261-266 (1991); John J. Mulvihill, *Genetic Counseling of the Cancer Patient*, in 2 CANCER: PRINCIPLES AND PRACTICE OF ONCOLOGY 2529, 2530-31 (Vincent T. DeVita, Jr. et al. eds., 1993) (describing a paradigm for genetic counseling of cancer patients).

46. See King et al., *supra* note 34, at 1975; Michael Swift et al., *Incidence of Cancer in 161 Families Affected by Ataxia-Telangiectasia*, 325 NEW ENG. J. MED. 1831, 1831 (1991) [hereinafter *Incidence of Cancer*] (demonstrating that persons heterozygous for the ataxia-telangiectasia gene have an excess of cancer, particularly breast cancer in women).

47. See Henry T. Lynch et al., *Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndromes I and II)*, 56 CANCER 939, 939 (1985) (describing biomarker findings that show variable association with the cancer-prone genotype in patients with hereditary non-polyposis colorectal cancer).

48. See Piero Benatti et al., *Tumor Spectrum in Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and in Families with "Suspected HNPCC": A Population-Based Study in Northern Italy*, 54 INT'L J. CANCER 371, 374 (1993) (describing the tumor spectrum and most relevant clinical features of twenty-eight kindreds of HNPCC and of sixty-one "suspected"

A link between breast cancer and a rare genetic childhood disease was first described in 1987.⁴⁹ This study focused on ataxia-telangiectasia, a devastating autosomal recessive neurodegenerative disease that strikes young children.⁵⁰ Characteristic findings in homozygous patients include progressive cerebellar ataxia, loss of developmental milestones, vascular abnormalities of the skin, and a striking increase in risk of cancer. Blood relatives also have an increased risk of developing cancer. Although the study was criticized for the statistical methods employed for analysis,⁵¹ Michael Swift, et al. reported that female relatives have a risk⁵² for breast cancer of 5.1 times over the general population.⁵³

Other rare family syndromes are associated with breast cancer. Bilateral breast cancer in young women is also seen in families with the Li-Fraumeni syndrome.⁵⁴ This family cancer syndrome is characterized by a striking cluster of early onset breast cancer plus other tumors including osteosarcoma, leukemia, brain tumors, and adrenal cortical tumors.⁵⁵ Cowden syndrome, which is an autosomal dominant disorder of thyroid dysfunction, thyroid cancer, and intestinal polyposis is also associated with an elevated risk of breast cancer.⁵⁶

HNPPCC).

49. See Michael Swift et al., *Breast and Other Cancers in Families with Ataxia-Telangiectasia*, 316 *NEW ENG. J. MED.* 1289, 1289 (1987) (demonstrating that breast cancer in women is clearly associated with heterozygosity for ataxia-telangiectasia).

50. See Johns Hopkins University, *Online Mendelian Inheritance in Man*, (last modified Aug. 22, 1996) <<http://www3.ncbi.nlm.gov/omim>> [hereinafter *Mendelian Inheritance in Man*].

51. See Lewis H. Kuller & Baruch Modan, *Risk of Breast Cancer in Ataxia-Telangiectasia*, 326 *NEW ENG. J. MED.* 1357, 1357 (1992) (raising methodologic problems presented by the control group chosen by Swift et al.).

52. Relative risk is the risk of developing a disease if you have an exposure or specific factor compared with the risk of developing a disease if the exposure or specific factor is not present. See HERMANSEN, *supra* note 9, at 164-65 (describing how to approach correlations using nominal data as compared with correlations using continuous and ordinal data). As such, a relative risk of 5.1 indicates a five hundred percent increase in breast cancer incidence over the expected population rate.

53. See *Incidence of Cancer*, *supra* note 46, at 1833.

54. See Curtis C. Harris, *P53: At the Crossroads of Molecular Carcinogenesis and Risk Assessment*, 262 *SCIENCE* 1980, 1981 (1993) (discussing the mutational spectra associated with the tumor suppressor gene p53).

55. See David Malkin et al., *Germ Line P53 Mutations in a Familial Syndrome of Breast Cancer, Sarcomas, and Other Neoplasms*, 250 *SCIENCE* 1233, 1237 (illustrating that alterations of the p53 gene occur not only as somatic mutations in human cancers, but also as germline mutations in some cancer-prone families).

56. See M. Starink et al., *The Cowden Syndrome: A Clinical and Genetic Study in 21*

Table 1: Chromosomal Location and Cancer Risk for the Common Breast Cancer Susceptibility Genes:

Family Cancer Syndrome	Gene ⁵⁷	Cytogenetic Location	Selected Cancers
Hereditary Breast-Ovarian Syndrome ⁵⁸	BRCA1*	17q21	early-onset breast, ovarian, prostate, colon
Hereditary Breast-Ovarian Syndrome ⁵⁹	BRCA2*	13q	early-onset breast (both male and female breast), ovarian
Li-Fraumeni Syndrome (LFS) ⁶⁰	p53*	17p13	breast, prostate, lung, colon, bladder, liver, brain, adrenal, lymphomas/leukemia
Hereditary Non-Polyposis Colorectal Cancer (HNPCC) ⁶¹	hMSH2*	2	colon, bladder, ovarian, breast
Hereditary Non-Polyposis Colorectal Cancer (HNPCC) ⁶²	hMLH1*	3p21.2-23	colon, bladder, ovarian, breast
Hereditary Non-Polyposis Colorectal Cancer (HNPCC) ⁶³	PMS1	2q31-33	colon, bladder, ovarian, breast
Hereditary Non-Polyposis Colorectal Cancer (HNPCC) ⁶⁴	PMS2	7p22	colon, bladder, ovarian, breast
Ataxia Telangiectasia Heterozygote ⁶⁵	ATM	17q21	early-onset breast, ovarian, prostate, colon
Cowden Syndrome ⁶⁶	not identified	10q22	thyroid cancer, intestinal polyposis, breast cancer

Patients, 29 CLINICAL GENETICS 222, 222 (1986).

57. Gene names marked with an * are available for predictive genetic testing on a commercial or research basis. (Copies of testing literature are on file with author).

58. See Csilla I. Szabo & Mary-Claire King, *Inherited Breast and Ovarian Cancer*, 4 HUM. MOLECULAR GENETICS 1811, 1811, 1813 (1995).

59. *Id.* at 1811.

60. See Harris, *supra* note 54, at 1981 (stating that germline p53 mutations are missense and occur frequently in the cancer-prone individuals with Li-Fraumeni syndrome); Culotta & Koshland, *supra* note 33, at 1958.

61. See John C. D'Emilia et al., *The Clinical and Genetic Manifestations of Hereditary Non-polyposis Colorectal Carcinoma*, 169 AM. J. SURGERY 368, 368-70 (1995) (discussing the clinical characteristics, pathology, genetics, management, and surveillance of hereditary non-polyposis colorectal cancer). See generally Henry T. Lynch et al., *Genetics, Natural History, Tumor Spectrum, and Pathology of Hereditary Non-polyposis Colorectal Cancer: An Updated Review*, 104 GASTROENTEROLOGY 1535 (1993) (summarizing current knowledge on hereditary non-polyposis colorectal cancer (HNPCC) and the manner in which this knowledge can be employed effectively for diagnosis and management of the disease).

62. See generally D'Emilia, *supra* note 61, at 369-70; Lynch et al., *supra* note 61.

63. See generally D'Emilia, *supra* note 61, at 371; Lynch et al., *supra* note 61.

64. *Id.*

65. See generally *Mendelian Inheritance in Man*, *supra* note 50.

66. See Starink et al., *supra* note 56, at 225.

Perhaps the most common inherited form of breast cancer is hereditary breast-ovarian syndrome, or familial premenopausal breast cancer. This is an autosomal dominant condition where female family members can develop cancer of the breast at a young age, often in the fourth decade, and have a high incidence of bilateral breast cancer and ovarian cancer.⁶⁷ This syndrome can also affect male members of the family since men have an increased risk for prostate cancer and, in some families, breast cancer as well. The evidence for an elevated risk for breast cancer is primarily from epidemiologic studies of families with multiple members with breast cancer.⁶⁸ For these women, the lifetime risk for cancer can be as high as eighty to one hundred percent.⁶⁹

While longitudinal and genetic studies of high-risk families suggested the hereditary nature of some breast cancers, it was not until 1990 that researchers identified the chromosomal location of BRCA1 on 17q21.⁷⁰ Four years later, the long search culminated in the identification and cloning of the BRCA1 gene.⁷¹ This discovery was quickly followed by the

67. See King, *supra* note 34, at 89; Biesecker et al., *supra* note 5, at 1970 (noting that more than fifty percent of the breast cancers in studied individuals occur before age fifty).

68. See M.C. King & R.C. Elston, *Genetic Epidemiology of Breast Cancer: A Comment on Heterogeneity*, 2 GENETIC EPIDEMIOLOGY 167, 168 (1985) (clarifying that segregation of analysis estimates of susceptibility gene frequencies based only on high-risk families do not reflect the gene frequencies in the population containing high-risk families); Mary-Claire King et al., *Genetic Epidemiology of Breast Cancer and Associated Cancers in High-Risk Families II Linkage Analysis*, 71 J. NAT'L CANCER INST. 463, 463 (1983). See generally Thomas A. Sellers et al., *Epidemiologic and Genetic Follow-up Study of 544 Minnesota Breast Cancer Families: Design and Methods*, 12 GENETIC EPIDEMIOLOGY 417 (1995) (concluding that the collection of detailed information on epidemiologic risk factors will facilitate careful analysis of genetic and environmental interaction, which will increase our understanding of how BRCA1, BRCA2, and other genes influence risk).

69. See King et al., *supra* note 34, at 1978.

70. See Jeff M. Hall et al., *Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21*, 250 SCIENCE 1684, 1684 (1990).

71. See Elisabeth Steichen-Gersdorf et al., *Familial Site-Specific Ovarian Cancer is Linked*

identification of a second major breast cancer susceptibility gene called Breast Cancer 2 (BRCA2) on chromosome 13⁷² which was cloned a few months later.⁷³ While the exact function of these genes is still unknown, mutations in BRCA1 and BRCA2 predispose gene carriers to develop breast and other cancers at an early age. The cumulative breast cancer risk for putative BRCA1 carriers is extremely high, nearly fifty percent by age fifty and eighty-five percent by age seventy.⁷⁴ In addition, the risk for ovarian cancer is also greatly elevated to about thirty to forty percent by age sixty, in contrast to the average lifetime risk of 1.4% for American women.⁷⁵ Molecular linkage studies have shown that approximately fifty to eighty percent of breast cancers in high-risk families are caused by BRCA1.⁷⁶

The BRCA1 gene is a large, novel gene of unknown function that extends over 100,000 bases of genomic DNA.⁷⁷ Numerous mutations and polymorphisms⁷⁸ have been identified

to BRCA1 on 17q-12-21, 55 AM. J. HUM. GENETICS 875, 875 (1994) (establishing a linkage of families with site-specific ovarian cancer to the breast-ovarian cancer susceptibility gene (BRCA1) on chromosome arm 17q). See also Miki et al., *supra* note 33, at 66-67.

72. See Richard Wooster et al., *Localization of a Breast Cancer Susceptibility Gene, BRCA2, to Chromosome 13q12-13*, 265 SCIENCE 2088, 2088-89 (1994) [hereinafter Wooster et al. 1994] (noting the different phenotypes between BRCA1 and BRCA2 include a lower risk of ovarian cancer attributable to BRCA2 and a higher risk of male breast cancer attributable to BRCA2).

73. See Richard Wooster et al., *Identification of the Breast Cancer Susceptibility Gene BRCA2*, 378 NATURE 789, 790 (1995) (identifying the BRCA2 gene as localized to chromosome 13q12-q13).

74. See Douglas F. Easton et al., *Breast Ovarian Cancer Incidence in BRCA1 Mutation Carriers*, 56 AM. J. HUM. GENETICS 265, 267 (1995) (estimating the age-specific risks of breast and ovarian cancer in BRCA1 mutation carriers).

75. See Deborah Ford et al., *Risks of Cancer in BRCA1-Mutation Carriers*, 343 LANCET 692, 694 (1994) (providing estimates of breast and ovarian cancer risks that may be useful for counseling BRCA1 mutation carriers).

76. See Simon A. Gayther et al., *Germline Mutations of the BRCA1 Gene in Breast and Ovarian Cancer Families Provide Evidence for a Genotype-Phenotype Correlation*, 11 NATURE GENETICS 428, 428 (reporting the identification of germline BRCA1 mutations in 32 families with a history of breast and/or ovarian cancer); Ford et al., *supra* note 75, at 692.

77. See Miki et al., *supra* note 33, at 67.

78. See THOMPSON ET AL., *supra* note 17, at 436, 438 (defining mutation and polymorphism). Mutations and polymorphisms are identified by differences in the order of nucleotide base pairs in a segment of the gene. A mutation is a sequence alteration that may incapacitate or severely alter the normal function of a gene. A polymorphism is a sequence alteration that has no impact in the function of the gene. Mutations may have a severe effect on genetic function and can cause human disease. Polymorphisms are benign changes in the genetic code that have no discernible effect on the individual. Polymorphisms are frequently identified by genetic researchers and must be differentiated from true mutations.

in families previously linked to the BRCA1 region. This demonstrates that alterations in the gene have profound effects on breast cell growth.⁷⁹ Early studies of breast tumors showed that the BRCA1 region was frequently deleted in approximately twenty percent of breast tumors during the process of tumorigenesis thereby indicating that it may function as a tumor suppressor gene.⁸⁰ Tumor suppressor genes are essential for normal cell processes and act as negative regulators of cell growth.⁸¹ In fact, BRCA1 gene expression has been shown to be altered in breast epithelial cells in sporadic tumors.⁸² Molecular clues for BRCA1's specific role within the breast epithelial cell are provided by recent studies that identified two separate nucleotide base pair sequence motifs.⁸³ Analysis of the BRCA1 sequence in the initial portion of the gene has located a motif called a "ring finger" commonly found in genes that function as transcription factors.⁸⁴ The second sequence motif is deep within the gene and is homologous to other se-

79. See Szabo & King, *supra* note 58, at 1815 (suggesting that BRCA1 may regulate mammary epithelial growth and be somatically inactivated in breast cancer by a direct mutation or by alterations in gene expression).

80. See S.A. Smith et al., *Allele Losses in the Region 17q12-21 in Familial Breast and Ovarian Cancer Involve the Wild-Type Chromosome*, 2 NATURE GENETICS 128, 128 (1992) (showing that allele losses in the tumors of affected family members also affect the wild-type chromosome).

81. See Gary R. Skuse & Peter T. Rowley, *Tumor Suppressor Genes and Inherited Predisposition to Malignancy*, 16 SEMINARS ONCOLOGY 128, 128, 133 (1989) (discussing the roles of various tumor suppressor genes in tumorigenesis). See generally Christopher J. Marshall, *Tumor Suppressor Genes*, 64 CELL 313, 313 (1991) (stating that multistage carcinogenesis involves a cooperation between activated oncogenes and tumor suppressor genes).

82. See Sandra T. Marquis et al., *The Developmental Pattern of BRCA1 Expression Implies a Role in Differentiation of the Breast and Other Tissues*, 11 NATURE GENETICS 17, 17, 22, 24 (1995) (supporting that BRCA1 is involved in the process of proliferation and differentiation of multiple tissues, notably in the mammary gland in response to ovarian hormones); Marilyn E. Thompson et al., *Decreased Expression of BRCA1 Accelerates Growth and is Often Present During Sporadic Breast Cancer Progression*, 9 NATURE GENETICS 444, 444, 448-49 (explaining that decrease of activity of BRCA1 measured by BRCA1 mRNA is associated with accelerated growth of both normal and malignant mammary cells); Yumay Chen et al., *Aberrant Subcellular Localization of BRCA1 in Breast Cancer*, 270 SCIENCE 789, 791 (1995) (stating that the subcellular mislocation of BRCA1 protein suggests that abnormalities in BRCA1 are fundamental to the genesis or progression of most breast cancers).

83. Genes are composed of deoxyribonucleic acid, or DNA. The molecular structure of DNA is a linear array of four specific building blocks, or nucleotide bases. A basepair is formed when a base specifically lines-up (pairs) with its partner on a complementary strand of DNA. The two complementary strands form the DNA double helix. The specific sequence, or order, of the basepairs form the genetic code. In addition, analysis of a gene segment can reveal functional units of the gene called sequence motifs. THOMPSON ET AL., *supra* note 17, at 33.

84. See Miki et al., *supra* note 33, at 70.

quence motifs, called granins, which may guide the movement of proteins within the cell architecture, thereby suggesting that BRCA1 may be secreted from the breast cell.⁸⁵

A second locus has been linked, in multiplex families with early-onset breast cancer, to an area of chromosome 13.⁸⁶ The gene, BRCA2, is associated with pre-menopausal female and male breast cancer, suggesting that BRCA1 and BRCA2 have different biologic functions in the breast epithelial cell. The gene was recently located on human chromosome 13 and early studies have suggested that it accounts for a significant proportion of pre-menopausal breast cancer.⁸⁷ BRCA2 is a large gene with numerous mutations and polymorphisms.⁸⁸ Researchers have suggested that the cancer risk for female breast and ovarian cancer is also unusually high in both BRCA1 and BRCA2; however, families with breast cancer linked to BRCA2 are distinguished by a high incidence of male breast cancer.⁸⁹

V. CLINICAL IMPLICATIONS OF GERMLINE BRCA1 MUTATIONS

While predisposition testing is an emerging theme in modern medicine, most experts agree that the medical community should exercise caution when introducing new genetic tests into patient care. Laboratory based molecular tests are relatively new and BRCA1 mutations are particularly challenging because of the large number of mutations and polymorphisms in the gene.⁹⁰ Other issues have slowed the integration of

85. See Patricia S. Steeg, *Granin Expectations in Breast Cancer?*, 12 NATURE GENETICS 223, 223-24 (1996) (proposing that BRCA1 performs the novel function of being a member of the Granin family, a family of acidic proteins that bind calcium and aggregate in its presence).

86. See Wooster et al. 1994, *supra* note 72, at 2088-89. The BRCA2 gene is located on a part of chromosome 13 which shows loss of heterozygosity in sporadic breast and ovarian cancers. *Id.* at 2089. Although this suggests that BRCA2 is inactivated during oncogenesis, the tumor suppressor gene RB1 is also located in this region of chromosome 13 and may explain the observed loss of heterozygosity. *Id.*

87. See Wooster et al., *supra* note 73, at 789; Wooster et al. 1994, *supra* note 72, at 2088-89.

88. See Susan Neuhausen et al., *Recurrent BRCA2 6174delT Mutations in Ashkenazi-Jewish Women Affected by Breast Cancer*, 13 NATURE GENETICS 126, 126 (1996).

89. See Szabo & King, *supra* note 58, at 1811. Stephen H. Friend, *Breast Cancer Susceptibility Testing: Realities in the Post-Genomic Era*, 13 NATURE GENETICS 16, 16 (1996) (summarizing studies which link BRCA2 alterations to increased cancer risks).

90. See Miki et al., *supra* note 33, at 71; Struewing et al., *supra* note 1, at 198; Lori S.

BRCA1 testing into clinical practice,⁹¹ such as proper interpretation of the test, appropriate medical management and cancer screening recommendations, as well as adequately trained health professionals to perform testing.⁹² A better understanding of the mechanisms of the genes that cause susceptibility for breast cancer, as well as the potential interaction between genes are essential, yet unanswered, questions.

The attributable risk, or proportion of breast cancers in the general population due to BRCA1 mutations, is a very important issue in cancer susceptibility testing. Mutations in the gene may be relatively common in the population, approximately 1/500 to 1/1000, but gene frequency estimates have primarily been based on information collected from high-risk families.⁹³ Early reports suggested that there is a low proportion of BRCA1 mutations in women who have sporadic breast cancer unselected for a strong family history.⁹⁴ However, one recent study from the National Cancer Institute and the National Center for Human Genome Research identified a specific mutation, 185delAG,⁹⁵ in 0.9% of Ashkenazi-Jewish individuals.⁹⁶ This

Friedman et al., *Confirmation at BRCA1 by Analysis of Germline Mutations Linked to Breast and Ovarian Cancer in Ten Families*, 8 NATURE GENETICS 399, 400 (1994) (confirming that the BRCA1 gene is responsible for inherited predisposition to breast and ovarian cancers in some families); Steven A. Narod et al., *An Evaluation of Genetic Heterogeneity in 145 Breast-Ovarian Cancer Families*, 56 AM. J. HUM. GENETICS 254, 254 (1995) (finding evidence for heterogeneity of the breast-ovarian cancer syndrome). See generally Shattuck-Eidens, *supra* note 2.

91. See Garber & Schrag, *supra* note 6, at 1928-29 (discussing the current transition period for inherited cancer predisposition in which the health care professional is forced to integrate the rapidly evolving technology and expanding knowledge base of cancer genetics into patient care paradigms).

92. See American Society of Clinical Oncology, *supra* note 4, at 1731-35.

93. See D. Ford et al., *Estimates of the Gene Frequency of BRCA1 and Its Contribution to Breast and Ovarian Cancer Incidence*, 57 AM. J. HUM. GENETICS 1457, 1459-60 (1995) (providing evidence that the frequency of BRCA1 mutation carriers in the general population is low); Skolnick & Cannon-Albright, *supra* note 30, at 1749-50 (noting that traditionally, studies have focused on families with breast cancer and although this approach is a poor method for determining the mode of inheritance, it has been useful in collecting families for linkage studies); Claus et al., *supra* note 42, at 232, 241.

94. See Andrew Futreal et al., *BRCA1 Mutations in Primary Breast and Ovarian Carcinomas*, 266 SCIENCE 120, 120, 122 (1994) (concluding that BRCA1 has a role in early-onset breast and ovarian cancer, but may only have a minor role in sporadic breast and ovarian tumor formation).

95. This designation indicates that the mutation occurs at codon 185 of the BRCA1 gene (185), the mutation is a deletion, or loss, of genetic material (del), and that the two deleted bases are an adenosine (or A) and a guanine (or G) nucleotides.

96. See Struewing et al., *supra* note 1, at 199 (noting that the observed .9% prevalence of the 185delAG mutation is higher than the prevalence of many genetic diseases for which routine

study was performed on DNA previously collected, in a separate research protocol, from 858 blood samples from donors of Ashkenazi-Jewish descent,⁹⁷ and 815 donors of a mixed ethnic background. Using a molecular protocol that only tested for the 185delAG mutation in exon 2 of the BRCA1 gene, eight of the Ashkenazi-Jewish group and none of the mixed ethnic group had an abnormal BRCA1 test. Other researchers noticed a higher prevalence of the 185delAG mutation in Ashkenazi-Jewish breast cancer families,⁹⁸ but this was the first study that directly examined presumably healthy individuals from a specific ethnic background.

Calling this proportion of germline BRCA1 carriers an "unexpectedly high frequency," the authors proposed simplified genetic screening for a specific ethnic group. However, the authors,⁹⁹ and others¹⁰⁰ acknowledge that longitudinal studies are required to clarify the cancer risk for individuals who are tested without knowledge of their family history. This finding has highlighted the profound uncertainties of molecular genetic testing for cancer susceptibility.

The central issue for the health care provider is determining the attributable risk for cancer from a specific cancer susceptibility gene. One approach that has been used to determine risk for breast cancer is to estimate the proportion of breast cancers that are associated with germline BRCA1 mutations as a function of age at cancer diagnosis. Using prevalence figures and age-dependent incidence figures for the observed risk of breast cancer in families with BRCA1, D. Ford, et al. calculat-

screening is conducted).

97. *Id.* at 198. These samples were previously collected in an unrelated study of families with Tay-Sachs disease and were not selected for family history of cancer. *Id.*

98. See Patricia Tonin et al., *BRCA1 Mutations in Ashkenazi-Jewish Women*, 57 AM. J. HUM. GENETICS 189, 189 (1995) (noting that six of the seven Ashkenazi families in the study were found to carry the 185delAG mutation); David E. Goldgar & Philip R. Reilly, *A Common BRCA1 Mutation in the Ashkenazim*, 11 NATURE GENETICS 113, 113 (1995); Szabo & King, *supra* note 58, at 1813-14 (noting that the 185delAG mutation illustrates a "striking example" of the founder effect among BRCA1 mutations).

99. See Struewing et al., *supra* note 1, at 199 (noting however that further research will be required to determine whether screening reduces morbidity and mortality from these diseases).

100. See Collins, *supra* note 2, at 187 (stating that the value of a negative test is minimal unless an affected relative is known to carry a particular BRCA1 mutation that can be shown to be absent in the person at risk); Gerber & Schrag, *supra* note 6, at 1929 (stating that physicians should encourage their patients to participate in research studies).

ed that 7.5% of women less than thirty years of age from mixed ethnic groups, are expected to have a germline BRCA1 mutation.¹⁰¹

Genetic analysis of blood samples from young breast cancer cases has confirmed these estimates. Two papers recently published in the *New England Journal of Medicine* directly tested the frequency of BRCA1 mutations in young women with breast cancer. Using a DNA sequencing approach that is estimated to identify approximately ninety percent of known mutations, Amelia A. Langston, et al. studied eighty women from a larger population based cohort who were less than thirty years of age at diagnosis. About ten percent of this selected group had BRCA1 germline defects¹⁰² which is in accordance with previous epidemiologic estimates. Limited family history information was known, but none of the cases were members of large, high-risk breast cancer families.

The proportion of young Ashkenazi-Jewish women with breast cancer was reported in Michael G. FitzGerald, et al.'s accompanying article.¹⁰³ Using a combination of automated DNA sequencing and protein-truncation assays,¹⁰⁴ this study examined the germline BRCA1 status of 418 women of mixed ethnicity with breast cancer including thirty-nine Jewish women under age forty. Eight (twenty-one percent) of the young Ashkenazi-Jewish women had a germline 185delAG mutation of the BRCA1 gene. The study also found that a minority (thirteen percent of thirty) of women of mixed ethnicity under the age of thirty also had identifiable BRCA1 mutations. While the two study populations are not directly comparable, both groups of researchers demonstrated that a significant proportion of young Ashkenazi-Jewish woman with breast cancer carried the

101. See D. Ford et al., *Estimates of the Gene Frequency of BRCA1 and its Contribution of Breast and Ovarian Cancer Incidence*, 57 AM. J. HUM. GENETICS 1457, 1457-62 (1995).

102. See Amelia A. Langston et al., *BRCA1 Mutations in a Population-Based Sample of Young Women with Breast Cancer*, 334 NEW ENG. J. MED. 137, 137, 141 (1996).

103. Michael G. FitzGerald et al., *Germ-Line BRCA1 Mutations in Jewish and Non-Jewish Women with Early-Onset Breast Cancer*, 334 NEW ENG. J. MED. 143, 144 (1996) (finding a one percent prevalence of the BRCA1 mutation in Ashkenazi-Jewish women).

104. *Id.* at 144-45. Genetic analysis is performed using a wide variety of molecular techniques. DNA sequencing involves chemically determining the order of nucleotide bases in a segment of DNA and can be performed using automated machinery. The protein-truncation assay specifically identifies mutations that prevent the synthesis of a functional protein from a gene. *Id.*

185delAG mutation. These investigators also illustrated that BRCA1 mutations are not limited to women with a strong family history of breast cancer.

The multiplicity of genes that may cause breast cancer has contributed to the difficulties of BRCA1 predictive testing. Recent studies have shown that there is a specific mutation, 6174delT, in the BRCA2 breast cancer susceptibility gene in a significant proportion of Ashkenazi women who have developed early-onset breast cancer.¹⁰⁵ However, as suggested by S.V. Tavtigian, et al. the 6174delT (BRCA2) and 185delAG (BRCA1) mutations may account for a significant proportion of breast cancer in the Ashkenazi-Jewish population.¹⁰⁶ The increase in specific mutations in BRCA1 and BRCA2 is a reflection of a founder effect¹⁰⁷ and has been noted in other ethnic populations.¹⁰⁸

In a recent *New England Journal of Medicine* editorial, Dr. Francis Collins, the Director of the National Center for Human Genome Research, noted that there is growing interest in BRCA1 genetic testing within the Ashkenazi-Jewish community. He also announced a larger study of the 185delAG mutation in approximately five thousand Ashkenazi-Jewish individuals who were unselected for cancer or a family history of cancer.¹⁰⁹ By using this method, the prevalence of the genetic mutation can be correlated to the clinical histories of the study participants. Therefore, the attributable risk of this muta-

105. See S.V. Tavtigian et al., *The Complete BRCA2 Gene and Mutations in Chromosome 13q-Linked Kindreds*, 12 *NATURE GENETICS* 333, 335 (1996) (discussing a mutational analysis of the BRCA2 gene with mutations mapped to chromosome 13q); Neuhausen et al., *supra* note 88, at 127 (stating that the frequency of the 6174delT mutation in Ashkenazi women can be estimated to be 3 per 1,000; however, if the penetrance of this mutation is lower than BRCA1, then the frequency of this mutation will be higher).

106. Tavtigian et al., *supra* note 105, at 335.

107. A founder effect is defined as "high frequency of a mutant gene in a population founded by a small ancestral group when one or more of the founders was a carrier of the mutant gene." THOMPSON ET AL., *supra* note 17, at 432.

108. See Steinunn Thorlacius et al., *A Single BRCA2 Mutation in Male and Female Breast Cancer Families from Iceland With Varied Cancer Phenotypes*, 13 *NATURE GENETICS* 117, 117-18 (studying BRCA2 in twenty-one Icelandic families); Friend, *supra* note 89, at 16 (discussing mutations in the BRCA2 gene in Icelandic families); Szabo & King, *supra* note 58, at 1811-17.

109. See Collins, *supra* note 2, at 187 (stating that more definitive answers as to whether it is unlikely that the risk of early-onset breast cancer in women with BRCA1 mutations will be markedly lower than that observed in previously well-studied families, will be provided by the announced study).

tion can be better understood.

Dr. Collins called for restraint in pursuing genetic testing in an unregulated environment and concluded that genetic testing should continue to be performed on a research basis where full informed consent and genetic counseling can be provided to the patient.¹¹⁰ Other groups have closely examined these issues and have published recommendations for cancer susceptibility testing.¹¹¹ For example, the American Society of Human Genetics published a series of recommendations soon after the BRCA1 gene was identified in 1994. These recommendations encouraged the establishment of protocols to research the clinical models for genetic testing. The American Society of Human Genetics stated that "it is premature to offer population screening until the risk associated with specific BRCA1 mutations are determined and the best strategies for monitoring and prevention are accurately assessed."¹¹² Likewise, the National Advisory Council for Human Genome Research urged that "it is premature to offer testing of either high-risk families or the general population as part of general medical practice until a series of crucial questions has been addressed."¹¹³

The American Society of Clinical Oncology (ASCO) published recommendations for clinical oncologists in February, 1996.¹¹⁴ In particular, ASCO stated that "to the greatest extent possible, genetic testing for cancer susceptibility should be performed in the setting of long-term outcome studies." These types of outcome studies are necessary to understand the probable risk of cancer for a given gene mutation.¹¹⁵ Additionally, these studies are essential to explore the issues surrounding a patient's desire to know their genetic diagnosis when coupled

110. See Collins, *supra* note 2, at 188 (stating that the possible clinical application of BRCA1 testing presents an interesting dilemma: on the one hand the uncertain risks and benefits require that testing be conducted only under strict protocol; on the other hand, interest in such studies is growing, but such studies can accept only a limited number of women).

111. See generally National Advisory Council, *supra* note 4; American Society of Clinical Oncology, *supra* note 4. See also ASHG, *supra* note 4.

112. *Id.*

113. National Advisory Council, *supra* note 4.

114. See American Society of Clinical Oncology, *supra* note 4, at 1730.

115. See Arthur Schatzkin et al., *What Does it Mean to be a Cancer Gene Carrier? Problems in Establishing Causality From the Molecular Genetics of Cancer*, 87 J. NAT'L CANCER INST. 1126, 1130 (1995) (concluding that further epidemiological studies must be conducted before results from studies of cancer-prone families can be applied to the general population).

with potential employment and insurance discrimination.¹¹⁶

Although these issues are more fully discussed in this issue of *Health Matrix*,¹¹⁷ the ramifications of patient decision making is provided by Caryn Lerman, et al.¹¹⁸ This study investigated the attitudes and concerns of 279 male and female members of families that were previously linked to the BRCA1 gene as they progressed through predictive testing for BRCA1 germline mutations. One surprising result was that only forty-three percent¹¹⁹ of study's subjects requested their BRCA1 mutation results. This was striking when contrasted to the author's previous research that suggested that ninety-one percent of family members in high-risk families would want testing for BRCA1 mutations.¹²⁰ This study also showed that there was significant concern about potential loss of health insurance.¹²¹

116. See Katherine A. Schneider et al., *Testing for Cancer Genes: Decisions, Decisions*, 1 NATURE MED. 302, 302-03 (1995) (stating that health care providers should not assume that all individuals at risk for hereditary cancer predisposition on the basis of family history will be interested in testing at the moment it is offered); Nancy J. Nelson, *Caution Guides Genetic Testing for Hereditary Cancer Genes*, 88 J. NAT'L CANCER INST. 70, 71-72 (1996) (discussing the role psychological factors and insurance concerns have on an individual's decision to be tested); Kathy L. Hudson et al., *Genetic Discrimination and Health Insurance: An Urgent Need for Reform*, 270 SCIENCE 391, 391-92 (1995) (arguing that genetic-based exclusion of high-risk candidates from insurance coverage will make individuals less likely to participate in genetic research and to share genetic information with health care providers or family members); Biesecker et al., *supra* note 5, at 1973 (stating that it is not advantageous for women who have BRCA1 to have their insurance companies learn the results of their screening; however, if an insurance company emphasizes preventive care, it may be willing to reimburse for preventive medical intervention such as screening).

117. See generally 7 HEALTH MATRIX 1 (compiling articles from the April 1996 Symposium regarding the social, ethical, religious, scientific, and legal implications of genetic testing for the BRCA1 gene).

118. See generally Caryn Lerman et al., *BRCA1 Testing in Families with Hereditary Breast-Ovarian Cancer: A Prospective Study of Patient Decision Making and Outcomes*, 275 JAMA 1885 (1996) (identifying predictors of utilization of breast-ovarian cancer susceptibility BRCA1 gene testing) [hereinafter *BRCA1 Testing in Families*].

119. *Id.* at 1888. The author states that the primary goals of the study were: "(1) to examine predictors of decisions to receive BRCA1 test results, including sociodemographic factors, knowledge, and preceptors of the benefits, limitations, and risks of testing; (2) to evaluate the effects of BRCA1 testing on psychological and functional health status; and (3) to evaluate how testing influences participant's medical decisions." *Id.* at 1886.

120. See Caryn Lerman et al., *Interest in Genetic Testing Among First-Degree Relatives of Breast Cancer Patients*, 57 AM. J. MED. GENETICS 385, 387 (1995) (stating that the most commonly cited reasons for being tested were the following: to learn about one's children's risks; to increase the use of cancer screening tests; and, to take better care of oneself).

121. *BRCA1 Testing in Families*, *supra* note 118, at 1891 (suggesting that the concern stems from possible discrimination in enrollment, discontinuation of insurance, or increased premium rates).

The issues and concerns presented by Caryn Lerman, et al. parallel the reactions of the two Center for Human Genetics patients presented earlier. Both of these Ashkenazi women were deeply concerned about their own health, but also feared the effect the test might have on the well-being of their families and the larger community. How we address their concerns for BRCA1 testing will be debated and studied on a national level. However, it is imperative that molecular analysis for BRCA1 and other cancer predisposition genes be performed within the context of scientific protocols in order to determine the predictive value of such testing. Only through a combined approach of genetic, medical, ethical, and legal research can we truly determine whether the risks for genetic testing are too great, or the benefits too small for the entire community.