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**F**or women at increased risk of breast cancer, important opportunities exist for primary and secondary prevention. Effective medical triage requires that risk be recognized and quantified. An extensive body of literature describes the hormonal/reproductive, family history, histologic, and demographic factors that contribute to breast cancer risk. The concept that clinicians should identify women at high risk for breast cancer has come of age. The justification for practicing breast cancer risk assessment encompasses the following reasons:

\*This work was completed at the University of Pittsburgh before Ms. Peters' employment at the National Cancer Institute (NCI) and does not represent the views of the NCI, National Institutes of Health, Department of Health and Human Services, or the federal government.

# Mathematical Modeling for Breast Cancer Risk Assessment

## State of the Art and Role in Medicine

### ABSTRACT

*Women at increased risk of breast cancer have important opportunities for early detection and prevention. There are, however, serious drawbacks to the available interventions. The magnitude of breast cancer risk is a crucial factor in the optimization of medical benefit when considering the efficacy of risk-reduction methods, the adverse effects of intervention, and economic and quality-of-life outcomes. Breast cancer risk assessment has become increasingly quantitative and is amenable to computerization. The assembly of risk factor information into practical, quantitative models for clinical and scientific use is relatively advanced for breast cancer, and represents a paradigm for broader risk management in medicine. Using a case-based approach, we will summarize the major breast cancer risk assessment models, compare and contrast their utility, and illustrate the role of genetic testing in risk management. Important considerations relevant to clinical oncology practice include the role of risk assessment in cancer prevention, the logistics of implementing risk assessment, the ramifications of conveying risk information with limited genetic counseling, and the mechanisms for genetics referral. Medical professionals can embrace new preventive medicine techniques more effectively by utilizing quantitative methods to assess their patients' risks.*

(1) The importance of maintaining a high level of suspicion for clinical diagnosis, despite the young age of a patient[1]

(2) The need to begin surveillance earlier than recommended by standard guidelines[2,3]

(3) Better information about the effectiveness of prophylactic mastectomy, the ideal surgical approach, and the optimal age at surgery[4-7]

(4) The opportunity for breast cancer chemoprevention[8]

(5) Recognition of the risks of additional preventable cancers, such as ovarian cancer in BRCA1 and BRCA2 carriers

(6) The chance to treat not only high-risk patients, but also the high-risk family.

Genetic counseling for inherited cancer syndromes has grown tremen-

Table 1

**Epidemiologic Models of Breast Cancer Risk**

Model	Family History of Breast Cancer	Additional Risk Factors	Format
Gail	First-degree relatives only (maximum of 2) No paternal family history	Current age Race (statistical significance not achieved for nonwhites) Age at menarche Age at first live birth Number of breast biopsies Atypical hyperplasia on biopsy	Tables, graphs, handheld calculators, computer programs including NCI Risk Disk and CancerGene, commercially available pedigree-drawing programs
Claus	First- and second-degree relatives (maximum of 2)	Age at onset in relatives	Tables, CancerGene, commercially available pedigree-drawing programs

NCI = National Cancer Institute.

dously over the past several years, due in large part to the discovery of two genes, BRCA1 and BRCA2, mutations of which account for the majority of hereditary breast/ovarian cancer families.[9,10] Mutations in several other genes also confer susceptibility to breast cancer—namely, TP53 (aka p53) associated with Li-Fraumeni syndrome and PTEN associated with Cowden disease. These conditions account for less than 1% of hereditary breast cancer, and no available mathematical modeling incorporates them. Therefore, they will not be discussed further in this article.

Genetic testing for mutations in BRCA1 and BRCA2 can be thought of as a highly sophisticated method of risk assessment. However, for the majority of women, genetic testing is not useful in clarifying risk. Mathematical models can be used to identify families for whom testing may be beneficial and to estimate risk in the absence of genetic testing.

For most women at moderate risk (loosely defined as a non-Jewish family with one or two relatives with breast cancer and no ovarian cancer or male breast cancer), quantitative risk assessment alone may be sufficient for guiding medical decision-

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making about chemoprevention, surgical prevention, and assessment of the risk/benefit ratio for hormone replacement therapy. Using a case-based approach, we will summarize the major breast cancer risk assessment models, compare and contrast their utility, and illustrate the role of genetic testing in risk management.

#### ***Mathematical Models for Breast Cancer Risk Assessment***

Breast cancer is a common disease—the most common cancer found among women and the second major cause of cancer death. Preliminary searches for the causes or risk factors for breast cancer have been population-based. After female gender, the most important risk factor is increasing age. Composite incidence projections derived from the Surveillance, Epidemiology, and End Results (SEER) registry of the National Cancer Institute (NCI) have enabled the determination of general age-related population risks for breast cancer.[11] The next largest risk factor is family history. Early quantification of this influence consisted of empiric prevalence tables based on various configurations of affected relatives.[12-14]

Relative risks and odds ratios for various characteristics have been derived from several studies; however, an individual woman's risk is based on a combination of these factors. Therefore, statistical modeling that incorporates the relative weight of

separate risk factors is necessary to approximate an individual's unique risk. Ideally, the model is then validated in population studies. Of the models discussed here, only the Gail model[15] has been validated.[16-18]

#### **Epidemiologic Models**

The quantitative models currently used in breast cancer risk assessment can be loosely divided into two categories: epidemiologic and genetic. The Gail[15] and Claus[19] models are epidemiologic tools used to predict absolute breast cancer risk over specified intervals of time for women who have never had breast cancer. They are derived from large population-based datasets and, thus, apply to a broad range of women, particularly those without a strong family history of breast cancer (Table 1).

#### **Genetic Models**

The newest category of models estimates BRCA1 or BRCA2 mutation carrier status (and, indirectly, breast cancer risk), based entirely on family history of breast and ovarian cancer. These models were derived from small populations with a strong family history of these diseases. Specifically, the Couch (University of Pennsylvania),[20] Shattuck-Eidens,[21] and Myriad (Frank) models[22] were derived from logistic regression of risk factors predicting a positive mutation test outcome. The Berry-Parmigiani-Aguilar model (BRCAPRO)[23,24] is based on Bayesian calculations of the proba-

bility of carrying a BRCA1 or BRCA2 mutation, given the individual family pattern of affected and unaffected individuals.

The genetic models calculate mutation probabilities based on affected individuals. Risk can be adjusted by Mendelian extrapolation for unaffected relatives. Brief descriptions of each model are presented below and in Table 2; a detailed discussion of their derivations can be found elsewhere.[25]

Two other quantitative models of mutation carrier risk not detailed in this paper are worth noting. First, Ford et al provide tables predicting the probability of linkage to BRCA1 and BRCA2 for high-risk families with a minimum of four cases of breast cancer diagnosed prior to age 60 and various combinations of ovarian cancer and male breast cancer.[26] The probability of linkage (an indirect measure of whether the gene in question is involved) does

not equate with the probability of finding a mutation, because a variety of mutation types are not identified even by complete DNA sequencing of the coding region and intron/exon boundaries. Genetic testing detected BRCA1 or BRCA2 mutations in only 63% of families with linkage scores suggesting involvement of these genes.

Second, Myriad Genetic Laboratories, Inc, provides and updates a set of penetrance tables on their website ([www.myriad.com](http://www.myriad.com)), reporting the frequency of BRCA1 and BRCA2 mutations for various constellations of family history, including Jewish and non-Jewish ancestry. The data in these tables were not obtained in a controlled research study and have not been statistically modeled. Moreover, family history was not collected in a systematic, verifiable fashion. Nevertheless, the dataset includes several thousand individuals who have undergone genetic testing and is quite impressive.

### Gail Model

Using multivariate logistic regression, the following risk factors for developing breast cancer were identified in the Breast Cancer Detection Demonstration Project (BCDDP) population: age at menarche, age at first live birth, number of previous breast biopsies, number of first-degree relatives with breast cancer, and current age of the individual.[27] In addition to these characteristics, the demonstration of atypical hyperplasia on biopsy is incorporated into the original Gail model as another multiplication factor. Relative risk estimates were calculated for each of these parameters, and a woman's composite relative risk is obtained by multiplying the numbers associated with each relative risk factor. Absolute risk—defined as the probability of developing breast cancer over a specified time—is computed by multiplying the composite relative risk by the baseline proportional hazards

Table 2

### Genetic Models Used to Estimate Risk of BRCA1 and BRCA2 Mutations

Model	Relevant Variables	Output	Format
Couch (University of Pennsylvania)	Average age at diagnosis of BC in family Cancer types: BC, OC, BC and OC in same person Ashkenazi Jewish ancestry	Composite family probability of BRCA1 mutation	Tables CancerGene
Shattuck-Eidens	Proband with BC (unilateral or bilateral) or OC Age at onset in proband only (not in family members) Cancer types: BC, OC, BC and OC in the same person Ashkenazi Jewish ancestry	Probability of BRCA1 mutation in the proband	Tables Additional calculations needed if more than 1 relative affected CancerGene
Myriad (Frank)	Proband with BC at less than age 50 (required) or 40 years Proband with OC or bilateral BC Relative with BC less than age 50 Relative with OC at any age	Probability of BRCA1 and BRCA2 mutations for proband (only if affected with BC before age 50)	Table
Berry-Parmigiani-Aguilar (BRCAPRO)	All first- and second-degree relatives, affected and unaffected Current ages or ages at death Cancer types: BC (unilateral or bilateral), OC, BC and OC in same person, including age at diagnosis Includes male breast cancer Ashkenazi Jewish ancestry BRCA1 or BRCA2 mutation status: positive, negative, or not yet tested	Probability of BRCA1 and BRCA2 mutations for affected or unaffected individuals within 2 degrees of relationship of affected relatives	CancerGene: Windows-based program with database storage

BC = breast cancer; OC = ovarian cancer.

estimation derived from the BCDDP population.

The NCI website contains a breast cancer risk assessment tool in Windows format (<http://bcra.nci.nih.gov/brc/>) based on a revised version of the Gail model[28] that was used to determine eligibility for the Breast Cancer Prevention Trial.[8] It provides 5-year and lifetime risks for developing breast cancer and differs from the original model in that (1) it predicts invasive cancer only (the original predicted both invasive and in situ cancers), (2) the baseline incidence is derived from SEER data (the original Gail model used baseline data from the BCDDP population), and (3) it includes a separate baseline incidence for black women (the original applied only to white women).

The Gail model is routinely used in cancer risk counseling to derive a preliminary breast cancer risk estimate for unaffected women. It is not applicable to women who have already had either in situ or invasive cancers. Although the model has been formally validated in three studies[16-18] and can accurately predict the rate of breast cancer development in populations, it tends to overestimate risk for young women and underestimate risk for older women. Some of the overprediction in younger women results from the fact that the model was based on a population of women who were undergoing annual screening mammography.

From the standpoint of genetic risk assessment, the main limitations of the Gail model are that it does not incorporate breast cancer history for more than two first-degree relatives and does not consider age at onset of cancer. Furthermore, because second-degree relatives are not included, paternal family history is ignored. It should also be pointed out that although risk models may be accurate for populations, risk predictions for individuals may be of limited accuracy.[29]

#### **Claus Model**

A second epidemiologic model used to estimate a woman's risk of developing breast cancer over time is the Claus model.[19] Using segre-

gation analysis on data obtained from the Cancer and Steroid Hormone Study (CASH), tables were constructed that predict cumulative probabilities for the occurrence of breast cancer at different ages, depending on both the presence of breast cancer in various combinations of first- and second-degree relatives and age at onset of cancer. Although the Claus model is only useful for the subset of women with one or two relatives with breast cancer, it may be more accurate than the Gail model for this cohort, particularly in the setting of premenopausal breast cancer and minor nonfamilial risk factors, and especially when there is a paternal family history of breast cancer.

In general, the Gail and Claus models should be avoided in individuals with a strong family history of cancer and used only with caution when genetic testing has produced negative results.

#### **Couch Model**

The Couch model[20] is based on data from 169 women who were assessed at a high-risk clinic and tested for mutations in the BRCA1 gene. Risk is based on the average age at diagnosis of breast cancer in a woman's family, ethnicity (Ashkenazi Jewish descent or not), the presence of familial breast cancer only or familial breast and ovarian cancer, and whether any individual has had both breast and ovarian cancer. Risks are provided in tables.

#### **Shattuck-Eidens Model**

The Shattuck-Eidens model[21] is based on a subset of 593 women with either breast or ovarian cancer who were evaluated in 20 familial risk clinics and underwent full-sequence mutation analysis for BRCA1. Risk factors included in the final model are based on the characteristics of both the proband and her family. For the proband, the risk factors are breast or ovarian cancer status including age at onset and Ashkenazi Jewish ancestry. For the family, risk factors include breast or ovarian cancer status, but not age at onset or degree of relatedness.

Cancer status for both the proband

and family members are categorized according to the presence of breast cancer alone, ovarian cancer alone, or both cancers in the same individual. Bilaterality is also considered for the proband, who must be affected for the model to be applicable. Limited risk values are provided in graphs, but it is necessary to calculate the regression equation for many families.

#### **Myriad Model**

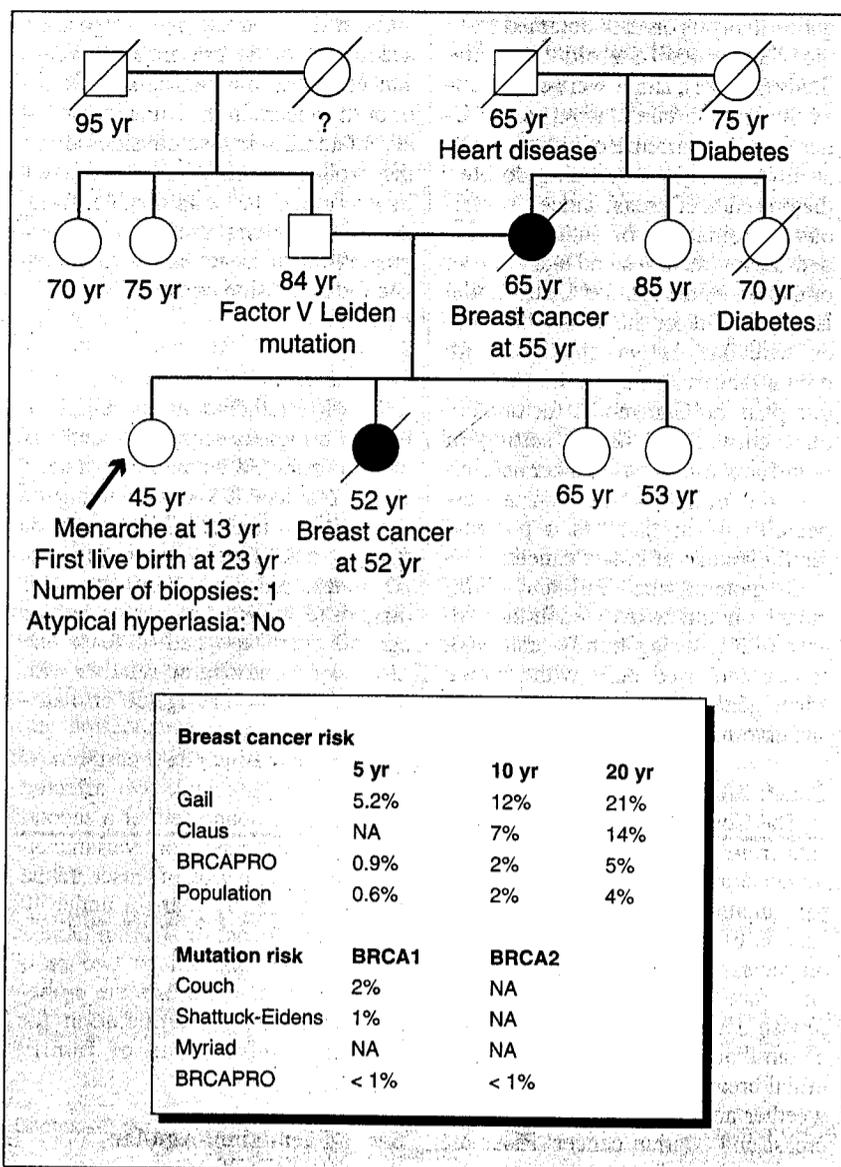
The Myriad (Frank) model[22] is based on logistic regression analysis of data from 238 women who underwent complete DNA sequencing of the BRCA1 and BRCA2 genes in familial risk clinics across the United States. All of the subjects were diagnosed with breast cancer before age 50 years and had at least one first- or second-degree relative with breast cancer before age 50 or ovarian cancer at any age.

Risk factors include breast cancer status of the proband, two affected sites in the proband (either a second primary breast cancer or ovarian cancer), categorical age of onset in the proband (under 50 years or under 40 years), and breast or ovarian cancer status in a maximum of two relatives. A simple chart lists the probabilities of carrying a mutation for varying combinations of family history.

#### **Berry-Parmigiani-Aguilar Model (BRCAPRO)**

Berry et al[23,24] devised a mathematical model using Bayesian principles to estimate the probability of carrying BRCA1 and BRCA2 mutations. The model incorporates all affected and unaffected first- and second-degree relatives and Ashkenazi Jewish ancestry. Age at onset in affected relatives and age achieved cancer-free in unaffected relatives are important components of this model. Breast and ovarian cancer histories are considered. Only the BRCAPRO and the Ford models incorporate information on males with breast cancer.

The BRCAPRO model is based on Mendelian principles and utilizes published mutation frequencies and penetrance estimates. It is computa-



**Figure 1: Extended Pedigree of Family A**—The proband is a 45-year-old white, non-Ashkenazi Jewish female of mixed European descent whose mother and sister died of breast cancer.

tionally intensive and only feasible if done by computer (in practice, using the CancerGene program, as discussed below). A validator study has recently been published.[30]

### Case Vignettes

As the following cases show, each of the models has strengths and limitations based on the purpose and setting of the risk assessment and the similarity of the patient's family to the underlying dataset. None of the

models incorporate a history of non-breast/ovarian cancers associated with BRCA1 or BRCA2, such as pancreatic cancer. The risk estimates are only as good as the quality of the medical information used with the models; verification of cancer diagnosis by record review is paramount. The models are not universally applicable, do not substitute for a careful pedigree analysis by a professional with training in genetics, and require interpretation based on experienced clinical judgment.

These cases are based on clinical experiences at the University of Pittsburgh Cancer Institute/Magee-Womens Hospital Cancer Genetics Program. The pedigree structure and clinical histories have been altered to preserve the anonymity of the patients and their relatives.

### Family A

• **Family History**—The proband in family A is a 45-year-old white, non-Ashkenazi Jewish female of mixed European descent referred to the Cancer Genetics Program because both her mother and sister died of breast cancer. An extended pedigree reveals that there have been no other cancer cases in the family, her mother and sister had postmenopausal breast cancer, and she has two unaffected sisters over age 50 (Figure 1).

• **Risk Assessment**—As expected based on pedigree analysis, the applicable mutation risk models predict a BRCA mutation risk of about 1% in this family, suggesting that genetic testing would not be beneficial. Thus, the Gail and Claus models will best approximate this woman's risk of developing breast cancer.

The Gail model predicts that this patient's risk of developing breast cancer over the next 20 years is about 21%. Her age at menarche was average, rather than late, conferring a slightly increased risk. She also had one breast biopsy before age 50, which, although benign and without atypia, is associated with an increased risk. The major component of her elevated risk is due to a family history of breast cancer in two first-degree relatives. This figures into the Gail summary relative risk as an interaction term with age at first live birth. In contrast to women with a minimal family history, in whom early parity seems to be protective, women in the BCDDP population with two or more affected first-degree relatives had higher risks of breast cancer associated with earlier parity. Similar observations have been seen in other studies.[31,32]

The Claus model predicts a 14% risk of developing breast cancer over the next 20 years. This is lower than



## Family B

• **Family History**—The proband is a 56-year-old white female of Italian descent. Her family cancer history includes a sister with bilateral breast cancer diagnosed at ages 32 and 41, who died at age 44, a paternal aunt with ovarian cancer diagnosed at age 52, and cousins with breast and ovarian cancer (Figure 2). The maternal family history is negative for cancer. Although this patient was referred to cancer genetic counseling by her gynecologist because of her immediate family history, she only learned of her extended family history after discussing her impending genetics appointment with a family member.

Further examination of this extended pedigree more strongly supports the possibility of autosomal dominant transmission of cancer. There is a direct link between the proband's immediate family members with breast and ovarian cancer and more distant affected relatives. Although this connection is through a woman who lived to age 80 without developing cancer, we know that the penetrance of BRCA1 and BRCA2 mutations is not 100%—ie, it is possible for carriers to live a long life without developing cancer.

• **Risk Assessment**—The first step is to recognize that the use of the epidemiologic Gail or Claus models would neglect significant hereditary risk factors such as bilateral breast cancer and ovarian cancer. Moreover, the Gail model ignores onset of breast cancer at a young age and all paternal family history of cancer.

The next step is to choose a relative (or relatives) for whom to calculate the probability of a having BRCA1 or BRCA2 mutation, ie, "designate a proband" for the genetic risk models. In general, it is best to base mutation probability estimates on the closest affected relative to the patient who exhibits the strongest hereditary indicators. Because the BRCAPRO calculations take into account only the first- and second-degree relatives of the designated proband, looking one or two degrees of relationship further may help to incorporate additional affected relatives.

The CancerGene program (see below) readily allows one to change the designated proband for the purposes of calculation. This helps to gauge the overall familial risk and to determine which relative has the highest probability of testing positive for a germ-line mutation. It is important to avoid testing relatives with possibly sporadic cancer, because a negative test result may mislead one to conclude that none of the familial cancers are genetic.

All of the models can be used to calculate risk for the sister with breast cancer, but only the Shattuck-Eidens and BRCAPRO models calculate risk for a proband affected with ovarian cancer alone. Since the paternal aunt in this case is alive and may be willing to provide a blood sample for genetic testing, we would want to know her pretest probability. Assuming the aunt agrees to undergo genetic counseling and testing, we will illustrate risk assessment for both the affected sister and the paternal aunt, beginning with calculations for the affected sister.

The Couch model would be inappropriate in this case because it is based on a family's average age at onset of breast cancer and only one close relative had breast cancer. (As discussed below, we would avoid including distant relatives.) In the original dataset, the mean number of affected family members was four, and only 4 of 169 families had just a single individual with breast cancer. Averaging an individual's two ages at diagnosis of bilateral disease might be misleading.

The Shattuck-Eidens model estimates that the proband's sister has a 45% probability of carrying a mutation in the BRCA1 gene, based on her age at initial diagnosis of breast cancer (32 years), her bilateral breast cancer, and the paternal aunt's ovarian cancer. Using Mendelian principles of autosomal dominant inheritance, this patient's risk of carrying a BRCA1 mutation would be half of her sister's risk, or about 22% according to this model.

The Myriad model predicts a 71% pretest probability that the affected sister carries a mutation in the BRCA1

or BRCA2 gene, based on the parameters of breast cancer diagnosis after age 40, bilateral breast cancer, and a relative with ovarian cancer. This patient's Myriad risk would be one-half of this, or about 36%.

The BRCAPRO model can be used to directly calculate risk for the patient and will also incorporate the fact that she has reached age 56 without developing cancer. It will include her affected sister's ages at both breast cancer diagnoses, the fact that her two other sisters have lived to the age of 46 and 53 without developing cancer, and her paternal aunt's age at diagnosis of ovarian cancer. The BRCAPRO combined risk for BRCA1 and BRCA2 is 16% for our proband and 61% for her affected sister. The proband's risk is not half of the affected sister's risk, as would be predicted by Mendelian laws alone, because the model has made a Bayesian adjustment to reflect the likelihood that the proband would be affected by her current age if she indeed carries a mutation.

In this case, the genetic risk models predict a range of about 16% to 36% for our proband. It should be noted that the Shattuck-Eidens risk of 22% is only for BRCA1 mutations and not BRCA2 mutations. In general, the model that can incorporate most of the salient genetic features in the family will be the most applicable. However, none of the models are likely to be as accurate when including cancer status beyond that of second-degree relatives. Although some limited third-degree history was included in the datasets used to derive the logistic regression models, the bulk of these datasets comprised first- and second-degree relatives. Also, the reporting of accurate histories becomes problematic in more distant relatives,[38] for whom it is more difficult to obtain confirming records. Therefore, without compelling reasons, we avoid the use of third-degree or more distant relatives in model input, although noting these relatives in the chart may prove useful.

• **Genetic Testing**—Recommendations from the Department of Health's

Advisory Committee on Genetic Testing advise that:

Individual and family members considering genetic testing should have access to appropriate genetic education and counseling resources to ensure their ability to make an informed decision about being tested.... Documentation of informed consent must be obtained for tests [such as BRCA] that require high scrutiny.[39]

Informed consent involves a number of components, including a discussion of the purposes of the testing, the nature and cost of the test being considered, and the risks, benefits, and limitations of testing. Many practitioners have argued effectively for the inclusion of information about the probability of finding a mutation in the gene being analyzed.

Although the probability of finding a BRCA1 or BRCA2 mutation in this patient is not extraordinarily high, testing would be reasonable under current guidelines, which advise consideration of genetic testing for pretest probabilities of 10% or greater.[40] However, the strategy that is likeliest to produce a clear result is to offer testing to an affected relative. If the proband is tested first and the result is negative (the probability of this scenario is high:  $100\% - 16\% = 84\%$ ), there would be several competing explanations for the result (see Table 3). Thus, it is essential to try to distinguish these possibilities by aiming for a testing strategy that produces a true-negative result. The paternal aunt, as the closest affected living relative, would be offered testing first. Her BRCAPRO pretest probability is 56%, making her an excellent candidate.

#### Genetic Test Interpretation and Cost

If complete DNA sequencing in her aunt is negative, the unaffected patient's risk drops from 16% to 7.5% (BRCAPRO can be recalculated using the genetic test results on the aunt). With this low risk, genetic testing for the patient would probably be fruitless. Since most hereditary breast/ovarian cancer is attributable to BRCA1 and BRCA2 mutations,[9,10] most of

Table 3

#### Competing Explanations for Negative Mutation Testing in an Unaffected Individual<sup>a</sup>

- Undetectable mutation—The cancers in the family are caused by a BRCA1 or BRCA2 mutation not detected by current testing methodologies.<sup>b</sup>
- Wrong gene—The cancers in the family could be caused by germ-line mutation of another gene, either described or unknown.<sup>b</sup>
- Not hereditary—The cancers in the family could be sporadic.<sup>c</sup>
- True negative—The family has a germ-line BRCA1 or BRCA2 mutation, but the patient did not inherit the mutation.

<sup>a</sup>No mutation yet identified in the family.

<sup>b</sup>The patient is at high risk despite a negative genetic test result.

<sup>c</sup>When testing an affected individual, another reason for a negative test result is: Wrong person tested. The person tested had a sporadic cancer; other relatives have a mutation; see text.

the proband's excess ovarian cancer risk is excluded by the aunt's negative genetic testing results. However, her risk of breast cancer remains increased based on her sister's young age at breast cancer diagnosis, and she should be managed accordingly.

The woman's 5-year risk per the Gail model is 2.8% (menarche at age 13, one previous breast biopsy, first live birth at 23), making her a possible candidate for tamoxifen chemoprevention; it seems reasonable to use this model for medical decision-making once the genetic risk has been reduced. It would also seem reasonable to use the Claus model (see Figure 2).[41]

If a BRCA1 or BRCA2 mutation were found in the aunt, the proband could be tested for that specific mutation. If the same mutation were found in the proband, her risk of developing breast cancer by age 70 is estimated at approximately 85%, with a 20% to 44% risk of ovarian cancer by age 70.[26] Screening, surveillance, and prevention strategies would be recommended based on this risk.[3,7] If the proband is negative, she can forgo enhanced cancer surveillance.

It is most cost-effective to test the aunt first. If the patient undergoes genetic sequencing first (\$2,760), has a negative result (84% chance), and the aunt is then tested to clarify the

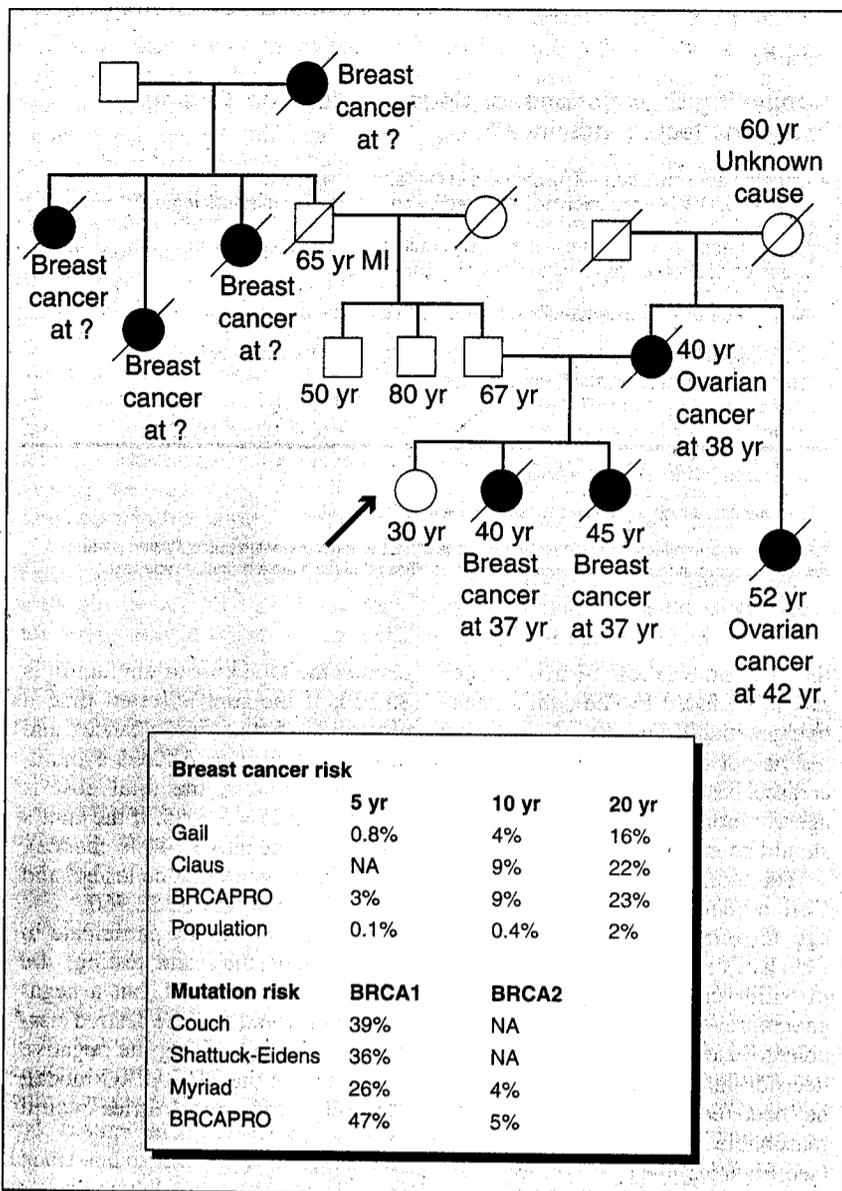
results, the total cost to the family is \$5,520. If the aunt is tested first, a mutation is found (56% chance), and the patient is then offered a mutation-specific test, the total cost is  $\$2,760 + \$325 = \$3,085$ . If the aunt's results are negative (44% chance), the proband would not be tested, and the total cost would be \$2,760.

If the aunt does not participate in genetic counseling and testing, the patient could be tested, but a negative result would lack the desired clarity (see Table 3). Using the negative test results in the BRCAPRO model, the calculated probabilities would then be only 2%.

#### Family C

• **Family History**—The proband is an unaffected 30-year-old white female of Ashkenazi Jewish descent through both parents. She had two sisters, both diagnosed with breast cancer at age 37, who are now deceased. Their mother developed ovarian cancer at age 38 and died at age 40. A maternal aunt, three paternal great-aunts, and a paternal great-grandmother also had breast cancer (Figure 3).

• **Risk Assessment**—The BRCA1 and BRCA2 mutation carrier rate for Ashkenazi Jews is about 2.5%, an order of magnitude higher than in the general white population. In other



**Figure 3: Extended Pedigree of Family C**—The proband is an unaffected 30-year-old white female of Ashkenazi Jewish descent whose two sisters died of breast cancer.

words, about 1 in 40 Ashkenazi Jewish men and women, unselected for a family history of cancer, are carriers. Three Ashkenazi founder mutations (BRCA1 185delAG and 5382insC, and BRCA2 6174delT) account for approximately 90% of carrier families,<sup>[22,42]</sup> and targeted panel testing for these mutations is relatively inexpensive. In contrast, in the general population, there are hundreds of low-frequency mutation sites. Therefore, complete DNA sequencing is required.

As shown in Figure 3, all the genetic models predict a high probability that a mutation is present in this unaffected 30-year-old proband. The Couch model is more applicable to this family than to family B because of the history of multiple cases of breast cancer. Specifically, the model predicts a BRCA1 mutation carrier risk of 77% for the family, based on an average age of breast cancer onset of 38 years, Ashkenazi Jewish descent, and a history of both breast and ovarian cancer in the family. Be-

cause she is unaffected, the proband's risk would be half of the family risk, or about 39%.

The risk of mutation as calculated by the Shattuck-Eidens model is 53% for either sister, based on unilateral breast cancer at age 37, Ashkenazi Jewish descent, two additional cases of breast cancer (the other sister and maternal aunt) and one case of ovarian cancer (the mother) in the family. The age of onset for affected relatives is not incorporated into this model.

If the Shattuck-Eidens model were calculated for the mother, her risk would be 73%, based on a diagnosis of ovarian cancer at age 38, Ashkenazi ancestry, and three additional cases of breast cancer in the family (maternal aunt and two sisters). The mother's higher calculated risk reflects the greater "genetic weight" of ovarian cancer than breast cancer, particularly for BRCA1. This proband's BRCA1 mutation carrier risk could be either 26% or 36%, depending on the relative chosen for the calculation.

The BRCAPRO model predicts a BRCA1 and BRCA2 mutation risk of 52%. Bayesian updating did not appreciably reduce this unaffected proband's risk (as it did in family B). Even with the propensity for early onset in mutation carriers, breast cancer cases by the age of 30 are uncommon. Therefore, it would be unlikely that she had already developed breast cancer, even if she were a mutation carrier.

It is also interesting that the proband's calculated BRCAPRO mutation probability is over 50%, given that she is unaffected (her maximum prior probability based on autosomal dominant inheritance is 50%). The BRCAPRO program does not incorporate relatives beyond the second degree; therefore, the paternal great-grandmother and great-aunts are not accounted for in this calculation. The > 50% probability reflects both the very high familial risk from the maternal side (approaching 100%) and the relatively high baseline carrier rate potentially also heritable from the paternal side. Indeed, Jewish families have been reported with as many as three unique BRCA1 and

Table 4

**Clinical Factors for Breast Cancer Risk Assessment**

Variable	Gail Model	Claus Model	Genetic Risk Models	Additional Medical Decision-Making
Patient age	X	X	X	X
Race	X			X
Menarche	X			
First live birth	X			
Number of breast biopsies	X			
Atypical hyperplasia	X			
First-degree relatives with breast cancer	X	X	X	
Second-degree relatives with breast cancer		X	X	
Personal history of breast cancer			X	X
Ages at onset of breast cancer		X	X	X
Bilateral breast cancer			X	X
Ovarian cancer diagnoses and ages of onset			X	X
Breast and ovarian cancer in the same individual		X	X	
Jewish ancestry			X	
Male breast cancer			X	
Ages of unaffected relatives, or age at death			X	
Family history of non-breast/ovarian cancer				X
Hysterectomy				X
Oophorectomy				X
Personal and family history of thromboembolic disease			X	
Personal and family history of osteoporosis				X
Personal and family history of cardiovascular disease			X	
Oral contraceptive use, estrogen replacement therapy, menopausal status, childbearing complete				X

BRCA2 mutations,[43] making it crucial to test for the complete three-mutation panel, even in families in which a mutation has already been identified.

• **Genetic Testing and Interpretation**—The proband underwent genetic testing for the three Ashkenazi founder mutations, and the result was negative. Although it is preferable to test an affected family member first because she has a higher probability

of carrying a mutation, all the affected relatives in this family were deceased. Her pretest mutation probability of about 50% was high enough to merit testing, but the interpretation of a negative test remains problematic, and plans for sorting out the meaning with further testing must be considered in advance. One is often faced with the decision of whether to proceed with expensive full sequencing in Ashkenazi families who receive negative results after founder

mutation testing. There are several ways to deal with this residual risk after negative testing.

Offit describes a Bayesian method of calculating remaining risk after a negative test result.[44] A simpler alternative is to recalculate the mutation risk models as if the family were not Ashkenazi Jewish, and, if the risk remains substantial, consider proceeding with full sequencing. This estimation method assumes that all the additional risk seen in Ashkenazi

Jews is related to the founder mutations. Although the accuracy of this assumption is uncertain, several studies show that Ashkenazi descent is a greater risk factor at lower levels of overall risk and loses some of its impact when the family history is highly suggestive of a BRCA1 or BRCA2 mutation.[22] When risks are thus recalculated, the Couch and Shattuck-Eidens models predict about a 20% probability that a BRCA1 mutation exists, and the BRCAPRO model combined risk drops negligibly from 52% to 48%. Proceeding with full sequencing is warranted, based on this residual risk.

Another approach would be to try to obtain tumor blocks taken from a deceased relative as a source of DNA to test for the founder mutations. Full DNA sequencing is technically difficult on paraffin blocks and generally unavailable, but the Ashkenazi Jewish founder mutations can be tested this way. If a founder mutation is identified in a tumor block, then the patient's result can be interpreted as a true-negative finding, and DNA sequencing is unnecessary.

### Conclusions

Risk assessment may be used for screening and triage, for medical decision-making about chemoprevention and prophylactic surgery, for clinical trial eligibility,[45] and in genetic counseling for pretest decision-making and posttest interpretation. The accuracy of risk predictions has different consequences for different interventions. An overestimated risk that results in triage to genetic counseling is trivial compared to one that leads to a decision to have prophylactic surgery.

Although the optimal model for clinical or research applications will be one that most closely parallels the individual's risk factors, another strategy is to calculate risk with all models and use the resulting estimates to bracket the true probability.

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ties. The discrepancies between risk estimates in these models underscore the need to develop more accurate risk-assessment tools. Validation studies of the genetic models are essential. No currently available model fully incorporates both environmental/lifestyle and genetic factors, the broad constellation of cancers that can be seen in hereditary syndromes, or the specific histologic subtypes associated with germ-line mutations. Table 4 highlights the clinical information needed to use the models discussed herein.

### Computerization

One of the most useful features of quantitative risk models is their ability to be computerized. In the clinical setting, standardization of risk factor data collection will foster the establishment of simple, number-based objective criteria for referral to more comprehensive risk assessment, tailored surveillance, and chemoprevention. In the research setting, standardized risk assessment facilitates not only the development of entry criteria, but also statistical analysis of results. It has become obvious from the sometimes conflicting results of preliminary small population studies that the ability to combine results and "meta-analyze" is a pressing need.

All of the models described in this article are available in computerized versions. The original Gail model[46] and the modified NCI Gail model[28] are available as small programs on disk. We have developed an integrated program, BRISK, that calculates Gail, Claus, and population risks[47] and are evaluating an expanded program that provides risk estimates based on the Gail, Claus, Couch, Shattuck-Eidens, Myriad, and BRCAPRO models. Patient data are entered once and automatically routed to algorithms for each model.

The CancerGene program, written by David Euhus, MD, includes these same models and can be downloaded from <http://www.isds.duke.edu/~gp/brcapro.html>. This program has a limited pedigree drawing tool, provides information and references for several hereditary cancer syndromes,

and features a "suggest a syndrome" capability.

### Ethical Considerations

Traditionally, model-based risk assessment has been performed as part of a comprehensive counseling service in cancer genetics programs, ie, as a supplement to thorough pedigree analysis.[48,49] A thorough pedigree analysis may modify or abrogate the model-based risks. Medical geneticists and genetic counselors are well versed in interpreting risks for patients, putting them into perspective, and assisting with psychological adjustment.

Issues of risk perception and communication are reviewed in depth elsewhere.[50] We have found that a brief risk assessment at the time of mammography has no measurable adverse psychological effect, and a short discussion at that time may serve to improve mood.[47] However, little is known of the psychological ramifications of providing patients with numerical risks outside of the research and counseling settings.

The ethical and medicolegal obligations of taking a family cancer history and acting upon it are becoming more explicit,[51] but the challenge to practitioners is substantial. Particular subgroups of at-risk women may benefit most from genetic counseling, and women at moderate risk experience benefits such as developing an accurate view of their risk and more realistic expectations of genetic testing.[52]

Importantly, there are various medical situations for which risk-based triage seems crucial. For example, in many institutions, Gail model risk factors are gathered at the time of screening mammography, but absolute risk is not systematically calculated, level of risk is not highlighted in the report, and opportunities for chemoprevention are probably lost.

### Evolving Field

Computerized tools may aid in the ascertainment of high-risk families and decision-making about referral. In the primary care setting, a computerized decision support system was

found to improve physicians' management decisions about familial breast and ovarian cancer, required less than a minute of additional time compared with pen and paper, resulted in significantly more accurate pedigrees than a pedigree drawing program, and was the practitioners' preferred method.[53] A touchscreen family cancer history program used in a comprehensive cancer center outpatient setting provided an effective method of gathering self-reported family history data.[54] The most time-intensive component of triage—analysis by genetics professionals—can be automated, in part, by computerized risk assessment.

As the complex interactions between low penetrance genes and environmental modifiers are elucidated, genetic risk profiling will gain more meaning in the care of patients with "sporadic" cancer. Medical professionals can more effectively embrace new methods of preventive medicine by using quantitative methods to assess their patients' risks.

*This article is reviewed  
on pages 1094 and 1098.*

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## The Rubinstein et al Article Reviewed

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Rubinstein and colleagues provide an excellent review of mathematical models for estimating breast cancer risk, including the risk of carrying inherited mutations of BRCA1 and BRCA2. Since we and others reviewed early models to predict the likelihood of inherited susceptibility to breast cancer,[1] newer quantitative tools, most notably by Parmigiani and colleagues,[2] have been developed. These models have been made available on CD-ROM, over the Internet, and in other electronic versions that are accessible to most clinicians and researchers. These quantitative resources constitute useful and important aids in genetic counseling.

With this commentary, I will provide additional perspective to the excellent overview presented by Rubinstein et al, addressing several areas that the authors did not fully touch upon. These topics include (1) the

importance of being aware of genetic testing guidelines propagated by insurers, (2) the probability of detecting missense variants of unknown significance as a result of genetic testing, (3) the psychological implications of testing unaffected probands, and (4) special aspects of testing individuals of Ashkenazi ancestry.

Finally, I will review a general caution that affects all quantitative modeling for hereditary breast cancer. This relates to the highly selected (ie, biased) nature of the ascertainment that have been used to generate risk (penetrance) information.

### Quantitative Estimates and Insurance Reimbursement

Perhaps the most clinically relevant application of quantitative risk estimates relates to the use of quantitative models by third-party carriers. In contrast to the early dire forecasts regarding insurance abuse of genetic information, several large carriers include BRCA testing in their coverage plans (without penalty) if specific family history criteria are met. For example, Blue Cross/Blue Shield has issued centralized guidelines on

BRCA testing.[3] However, Blue Cross guidelines vary according to the policies of local plans in each state.

As part of an American Medical Association conference, the Kaiser system circulated proposed criteria for BRCA testing,[4] and guidelines have also been issued by Aetna/US Healthcare.[5] These policies may be of as much interest to health-care providers as the theoretical models presented in this excellent review. Citation of the theoretical models may be useful for clinicians seeking to obtain insurance coverage for testing services provided to those insured by companies without established policies.

### Detecting Missense Mutations of Unknown Significance

A surprisingly overlooked aspect of BRCA testing relates to the frequent occurrence of "ambiguous" results. Missense mutations of unknown significance are found in up to 10%-15% of patients tested. The probability of detecting these variants depends on the ethnic origin of the proband.

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