Limited Family Structure and BRCA Gene Mutation Status in Single Cases of Breast Cancer

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Context  An autosomal dominant pattern of hereditary breast cancer may be masked by small family size or transmission through males given sex-limited expression.

Objective  To determine if BRCA gene mutations are more prevalent among single cases of early onset breast cancer in families with limited vs adequate family structure than would be predicted by currently available probability models.

Design, Setting, and Participants  A total of 1543 women seen at US high-risk clinics for genetic cancer risk assessment and BRCA gene testing were enrolled in a prospective registry study between April 1997 and February 2007. Three hundred six of these women had breast cancer before age 50 years and no first- or second-degree relatives with breast or ovarian cancers.

Main Outcome Measure  The main outcome measure was whether family structure, assessed from multigenerational pedigrees, predicts BRCA gene mutation status. Limited family structure was defined as fewer than 2 first- or second-degree female relatives surviving beyond age 45 years in either lineage. Family structure effect and mutation probability by the Couch, Myriad, and BRCAPRO models were assessed with stepwise multiple logistic regression. Model sensitivity and specificity were determined and receiver operating characteristic curves were generated.

Results  Family structure was limited in 153 cases (50%). BRCA gene mutations were detected in 13.7% of participants with limited vs 5.2% with adequate family structure. Family structure was a significant predictor of mutation status (odds ratio, 2.8; 95% confidence interval, 1.19-6.73; \(P\) = .02). Although none of the models performed well, receiver operating characteristic analysis indicated that modification of BRCAPRO output by a corrective probability index accounting for family structure was the most accurate BRCA gene mutation status predictor (area under the curve, 0.72; 95% confidence interval, 0.63-0.81; \(P<.001\)) for single cases of breast cancer.

Conclusions  Family structure can affect the accuracy of mutation probability models. Genetic testing guidelines may need to be more inclusive for single cases of breast cancer when the family structure is limited and probability models need to be recreated using limited family history as an actual variable.

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Identifying appropriate candidates for GCRA is challenging. The general consensus (eg, American College of Medical Genetics, National Comprehensive Cancer Network) is that BRCA testing is not appropriate for unaffected women in the general population, but there is less clarity in this re-
February 2007 within the Duarte, Calif–based City of Hope Cancer Screening & Prevention Program Network high-risk clinics for GCRA. At their initial GCRA consultation, all women are invited to participate in an institutional review board–approved prospective hereditary cancer registry, and 98% enroll and provide written informed consent. Of the 1543 women who had been BRCA gene mutation testing through the Cancer Screening & Prevention Program Network, we identified 306 diagnosed as having breast cancer prior to age 50 years who did not have a family history of breast or ovarian cancers in first- or second-degree relatives.

Estimation of Prior Probability of BRCA Gene Mutation
A detailed 3- to 5-generation family history was obtained by an experienced cancer genetics clinician during the initial GCRA session. Based on the participant’s reported family history and available medical records, the probability that she carried a deleterious BRCA gene mutation was calculated using the 3 most commonly used predictive models, Myriad, Couch, and BRCAPRO.

The Myriad model is a set of mutation probability tables categorized by age at onset (<50 or ≥50 years old) of breast cancer, ovarian cancer incidence in the patient and/or first- or second-degree relatives, and Ashkenazi Jewish ancestry, based on test data from a commercial laboratory (Myriad Genetic Laboratories Inc, Salt Lake City, Utah). Originally published by Frank et al,21 the tables are periodically updated online (available at http://www.myriadtests.com/provider/braa-mutation-prevalence.htm; the version used for this study, Myriad BRCA1/2 Mutation Prevalence Guide, version 1.1, was updated June 28, 2005).

BRCA1 gene mutation probability in the Couch model is based on mean age at breast cancer onset in a family, presence or absence of ovarian cancer, and Ashkenazi Jewish ancestry.22 Although the original Couch model only considered BRCA1, a subsequent publication presented BRCA2 genotyping data for the same cohort, wherein BRCA2 represented one third of the mutations.23 For this study, to account for BRCA2 we modified the BRCA1 predicted probability by a factor of 1.33 (representing published data from the combined analyses for the original cohort). Although suboptimal, this adjustment is commonly used in GCRA clinic settings.

BRCAPRO is a computer-based Bayesian probability model that uses first- and second-degree family history of breast and/or ovarian cancers to determine the probability that a BRCA1 or BRCA2 gene mutation accounts for these cancers.22 Key variables include the population prevalence of mutations, age-specific penetrance, and Ashkenazi Jewish heritage. The BRCAPRO version contained in CaGene version 4.0 (University of Texas Southwestern Medical Center at Dallas, Dallas, Tex) was used for the calculations in this study. If either parental lineage was of Ashkenazi Jewish ancestry, the respective tables (Couch or Myriad) or calculations (BRCAPRO) for individuals of Ashkenazi Jewish descent were used.

Classification of Family Structure as Limited or Adequate
To develop a family structure variable, we evaluated each participant’s family history to determine if she had a limited family structure in either the maternal or paternal lineage. Limited family structure was defined as fewer than 2 first- or second-degree female relatives surviving past age 45 years in either lineage; otherwise the participant was deemed to have an adequate family structure (FIGURE 1). Age 45 years was selected based on the expected age-specific penetrance of disease in BRCA gene mutation carriers.1,2 Participants without information about their birth parents (eg, because of adoption) were classified as limited in both parental lineages. The definition of family structure was derived prior to any analyses and did not vary during the course of the study.
**BRCA Gene Mutation Testing**

Genetic testing was performed by Myriad Genetic Laboratories Inc according to their standard commercial techniques. Testing for 261 participants consisted of full sequencing of all BRCA1 and BRCA2 exons and flanking intronic segments and, beginning in 2004, 5 specific BRCA1 genomic rearrangements (154delAG and 5382insC in BRCA1 and 6174delT in BRCA2) and 16 had partial sequencing, 10 because of partial Ashkenazi Jewish descent and 6 after a negative founder mutation panel result.

**Data Analysis**

Statistical analyses were conducted using SPSS software, version 11.0 (SPSS Inc, Chicago, Ill). Descriptive statistics were analyzed using independent sample t tests or 1-way analysis of variance. Categorical data were analyzed using the χ² statistic (with or without correction) or the Fisher exact test. All tests were 2-sided with α=.05. For the purpose of analyses, participants were classified as having limited family structure if either lineage was limited; adequate structure required that both lineages have adequate family structure. The ability of each model and of family structure to predict mutation status was determined using stepwise multiple logistic regression, with family structure (adequate=0 and limited=1), Myriad probabilities, Couch probabilities, and BRCAPRO probabilities included as covariates while controlling for age group (<40 or ≥40 years at breast cancer diagnosis) and Ashkenazi Jewish ancestry (no=0 and yes=1).

Receiver operating characteristic (ROC) curves were generated to evaluate the quality or performance of each model. Generally, the greater the area under the curve, the better the model performance characteristics.

Given that single cases of early onset breast cancer without affected first- or second-degree relatives were selected for this study, none were classified empirically as having a hereditary breast and ovarian cancer phenotype. Therefore, participants with uninformative test results (noncarriers and carriers of unclassified variants of uncertain significance) were combined for the χ² tests, stepwise multiple logistic regression analyses, and generation of ROC curves.

A multiple linear regression analysis was conducted, regressing mutation (no mutation or variants of uncertain significance=0 and mutation=1) on BRCAPRO probability and family structure (adequate=0 and limited=1) to derive corrective factors to adjust BRCAPRO output for limited family structure. The regression was conducted separately for 4 subgroups of the sample: non–Ashkenazi Jewish younger than 40 years at breast cancer diagnosis; non–Ashkenazi Jewish aged 40 years or older at diagnosis; Ashkenazi Jewish younger than 40 years at diagnosis; and Ashkenazi Jewish aged 40 years or older at diagnosis. The unstandardized regression coefficients (β) and constant (origin) were used to create a corrected probability index (CPI) customized to each subgroup by multiplying the original value of BRCAPRO (ranging from 0.1–87.6) and family structure (categorized as 0=adequate and 1=limited) by its regression coefficient and adding them together along with the constant.

Parental country of origin and ancestry was determined by participant self-report during their GCRA consultation. Non-Latina European non–Ashkenazi Jewish ancestry was categorized as non-Latina white. Ashkenazi Jewish ancestry in either or both parental lineages was categorized as Ashkenazi Jewish. Native Hawaiian/Pacific Islander, Near/Middle Eastern, and Native American ancestry were categorized as other. Differing parental ancestry was categorized as mixed.

Based on the distribution of deleterious mutation within the overall sample and each subgroup of interest, a power of at least 80% with 95% confidence (P=.05) was achieved for contingency table analysis of association with family structure for the total sample (N=306) and the non–Ashkenazi Jewish subsample (n=245). The group younger than 40 years is 15 participants short (n=185) of achieving a power of 81%. The group aged 40 years or older (n=121) is 39 participants short of achieving a power of 82%.

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**Figure 1. Limited and Adequate Family Structure**

Limited Paternal Family Structure

- 88 y d. 73 y
- 62 y 55 y d. 53 y

Adequate Family Structure for Both Maternal and Paternal Lineage

- 88 y d. 73 y
- 62 y 55 y 60 y

MVA indicates motor vehicle accident. Age at cancer risk assessment, breast cancer onset, or death is provided below each individual.
RESULTS
Characteristics
Sample characteristics are described in Table 1. The majority (n=161 (53%)) of the sample was non-Latina white; 20% indicated Ashkenazi Jewish background. For the entire cohort, mean age at ascertainment (GCRA consultation) was 40.7 years. As is typical in a high-risk clinic referral–based population, the mean age at ascertainment was 37.7 years (SD, 5.9 years; range, 22-49 years). Nineteen participants (6.2%) had bilateral breast cancer. There was no statistically significant difference in age at first breast cancer diagnosis when examined by mutation status.

BRCA Gene Mutation Prior Probability
For the entire cohort, the mean probability of a BRCA gene mutation was more than twice as high using the Couch model (20.4%; SD, 10.9%; range, 6.7%-63.7%) compared with both the Myriad model (8.0%; SD, 2.1%; range, 6.9%-12.2%) and the BRCAPRO model (7.3%; SD, 14.1%; range, 0.1%-87.6%) (Table 2).

The mean mutation probability among non–Ashkenazi Jewish participants (n=245) was 6.9% using the Myriad model (SD, 0%; range, 6.9%-6.9%), 16.4% (SD, 5.8%; range, 6.7%-23.1%) using the Couch model, and 3.4% (SD, 7.8%; range, 0.1%-59.9%) using BRCAPRO. For participants of Ashkenazi Jewish descent (n=61), the predicted mean mutation probability was 12.2% by the Myriad model (SD, 0%; range, 12.2%-12.2%), 36.4% (SD, 11.7%; range, 24.9%-63.7%) by the Couch model, and 23.3% (SD, 21.0%; range, 0.3%-87.6%) by BRCAPRO. Predicted prior probabilities were significantly higher for participants of Ashkenazi Jewish ancestry compared with non–Ashkenazi Jewish participants using the Myriad model (12.2% vs 6.9%; t(49)=-7.27; P<.001), the Couch model (36.4% vs 16.4%; t(48)=-19.05; P<.001), and the BRCAPRO model (23.3% vs 3.4%; t(47)=-7.27; P<.001) (n=306 for each test, but the unequal variances test had to be applied, reducing the degrees of freedom).

BRCA Gene Mutation Testing
Overall, 29 participants (9.5%) had a deleterious mutation (18 in BRCA1 and 11 in BRCA2), 23 (7.5%) had 1 or more unclassified variants, and 254 (83.0%) had negative test results (Table 1). Of the 45 participants tested for the Ashkenazi Jewish founder mutation panel, 6 were found to carry a founder BRCA gene mutation. Two of the 10 participants who had full BRCA gene sequencing because of partial Ashkenazi Jewish heritage were found to have a deleterious BRCA gene mutation. A deleterious mutation was not identified in the 6 participants of Ashkenazi Jewish ancestry who had full sequencing of the BRCA genes following a negative founder mutation panel, although 1 had a variant of uncertain significance in BRCA2.

Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)* (N = 306)</th>
<th>Distribution of Mutation by Race/Ethnicity, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at breast cancer diagnosis, mean (SD) [range], y†</td>
<td>37.7 (5.9) [22-49]</td>
<td></td>
</tr>
<tr>
<td>Family structure:‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>153 (50)</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>153 (50)</td>
<td></td>
</tr>
<tr>
<td>BRCA test results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deleterious BRCA1 mutation</td>
<td>18 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Deleterious BRCA2 mutation</td>
<td>11 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>23 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>254 (83.0)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Latina white</td>
<td>100 (32.7)</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>61 (19.9)</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Latina/Hispanic</td>
<td>73 (23.9)</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>31 (10.1)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>African American</td>
<td>4 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>10 (3.3)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Mixed§</td>
<td>27 (8.8)</td>
<td>3 (10.4)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.
†The proportions of adequate and limited family structure were approximately equal for each subset used in subsequent analyses.
‡Combination of 1 or more of the races/ethnicities listed.

Table 2. Pretest BRCA Mutation Probabilities Using 3 Predictive Models, by Family Structure

<table>
<thead>
<tr>
<th>Predictive Model</th>
<th>Family Structure</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Limited</td>
<td>Adequate</td>
</tr>
<tr>
<td>All participants (n = 306)</td>
<td>8.11 (2.23)</td>
<td>7.80 (2.00)</td>
</tr>
<tr>
<td>Couch</td>
<td>21.12 (12.05)</td>
<td>19.61 (9.57)</td>
</tr>
<tr>
<td>BRCAPRO</td>
<td>8.59 (13.81)</td>
<td>6.06 (14.32)</td>
</tr>
<tr>
<td>Aged &lt;40 y (n = 185)</td>
<td>7.54 (1.74)</td>
<td>7.30 (1.40)</td>
</tr>
<tr>
<td>Myriad</td>
<td>23.90 (12.10)</td>
<td>21.82 (8.50)</td>
</tr>
<tr>
<td>BRCAPRO</td>
<td>9.18 (16.37)</td>
<td>5.66 (13.35)</td>
</tr>
<tr>
<td>Aged ≥40 y (n = 121)</td>
<td>8.95 (2.60)</td>
<td>8.61 (2.50)</td>
</tr>
<tr>
<td>Myriad</td>
<td>17.06 (10.83)</td>
<td>16.09 (10.18)</td>
</tr>
<tr>
<td>BRCAPRO</td>
<td>7.72 (8.66)</td>
<td>6.86 (15.84)</td>
</tr>
</tbody>
</table>

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Classification of Family Structure and Effect on Observed Mutation Status

Family structure was equally divided between limited (n = 153) and adequate (n = 153) according to our classification criteria. Including the 8 participants who were adopted, 26 (8.5%) had limited family structures in both paternal and maternal lineages. Of those with limited structure in only 1 lineage (n = 127), more had a limited paternal (n = 86 [67.7%]) vs maternal (n = 41 [32.3%]) structure (χ² = 15.95; P < .001).

The mean predicted Myriad, Couch, and BRCAPRO probabilities of detecting a BRCA gene mutation are shown in Table 2, stratified by family structure and by age at breast cancer diagnosis. The association between family structure and mutation carrier status for the entire sample was significant (χ² [with continuity correction] = 5.48; P = .02), with limited family structure being more predictive of a mutation (Table 3). This same trend (nonsignificant, possibly due to small sample sizes) was also observed for cases diagnosed prior to age 40 years and, in particular, for those aged 40 to 49 years at onset of breast cancer, in whom 7 of 9 BRCA gene mutation carriers had a limited family structure (Table 3). Similarly, when considered separately, more BRCA gene mutation carriers had a limited family structure regardless of Ashkenazi Jewish ancestry. The family structure effect remained significant (χ² = 4.368; P = .04) when the bilateral breast cancer cases (n = 19; 8 mutation-positive and 11 mutation-negative) were removed.

Based on stepwise multiple logistic regression, participants with a limited family structure were 2.8 times more likely to be carriers of a deleterious BRCA gene mutation than those with adequate family structure (odds ratio [OR], 2.8; 95% confidence interval [CI], 1.2-6.7; P = .02), primarily because of limited paternal family structure (OR, 3.0; 95% CI, 1.3-6.7; P = .007). The OR for the BRCAPRO model was not impressive (OR, 1.03; 95% CI, 1.01-1.05; P = .002). The other 2 predictors tested (age group and Couch model) were not significant.

The positive predictive value, negative predictive value, sensitivity, and specificity of having limited family structure were compared by each model (Myriad, Couch, and BRCAPRO) using a 10% probability threshold (Table 4). Family structure and BRCAPRO demonstrated comparable positive and negative predictive values among Ashkenazi Jewish participants, and both were superior to the Couch model in all subsets. From a clinical perspective, the balance between sensitivity (66.7%) and specificity (53.6%) was most favorable for family structure in non–Ashkenazi Jewish participants (Table 4), where BRCAPRO showed the least sensitivity (23.8%).

For our sample, the Myriad, Couch, and BRCAPRO models tended to overestimate the likelihood of a mutation if...
the family structure was adequate and to underestimate the likelihood of a mutation if the family structure was limited (Table 2). The area under the ROC curve (Figure 2) was similar for family structure and BRCAPRO, and both models were statistically significant for mutation prediction compared with chance (area under the ROC curve for family structure, 0.62; 95% CI, 0.52-0.73; \( P = .03 \) and for BRCAPRO, 0.67; 95% CI, 0.57-0.78; \( P = .003 \)).

**Derivation of Corrective Factors to Adjust BRCAPRO Based on Family Structure**

A multiple linear regression analysis was then conducted, regressing mutation (no or variant of uncertain significance=0 and yes=1) on BRCAPRO probability and family structure (adequate=0 and limited=1).

The regression was conducted separately for 4 sample subgroups: non–Ashkenazi Jewish younger than 40 years at breast cancer diagnosis; non–Ashkenazi Jewish aged 40 years or older at diagnosis; Ashkenazi Jewish younger than 40 years at diagnosis; and Ashkenazi Jewish aged 40 years or older at diagnosis. The 2-variable model significantly explained mutation status in each of the 4 subgroups. Each variable had a significant standardized regression coefficient (\( \beta \) weight) only for the non–Ashkenazi Jewish patients with breast cancer diagnosed before age 40 years. No other \( \beta \) weights were significant. The CPI computations are shown in Table 5.

The CPI is not a literal probability ranging from 0 to 1 but is a relative index of likelihood of having a BRCA gene mutation. Based on examination of \( \beta \) weights, BRCAPRO was weighted most heavily for the Ashkenazi Jewish participants with breast cancer diagnosed before age 40 years, whereas family structure was weighted most heavily in the Ashkenazi Jewish participants aged 40 years or older at diagnosis.

The CPI ranged from −0.20 to 0.62 (mean=0.10; SD=0.08) and correlated \((r=0.73; P < .001)\) with BRCAPRO. Mutation-positive participants had a significantly higher CPI (mean=0.17; SD=0.13) compared with mutation-negative participants or those with variants of uncertain significance \((\text{mean}=0.08811; \text{SD}=0.13)\) compared with mutation-negative participants or those with variants of uncertain significance \((\text{mean}=0.08811; \text{SD}=0.13)\) compared with mutation-negative participants or those with variants of uncertain significance \((\text{mean}=0.08; \text{SD}=0.06)\) \((t_{50}=−3.22; P = .003)\) \((n=304; \text{equal variances not assumed})\). Ashkenazi Jewish participants had a significantly higher CPI \((\text{mean}=0.14; \text{SD}=0.13)\) than non–Ashkenazi Jewish participants \((\text{mean}=0.09; \text{SD}=0.06)\) \((t_{50}=−2.94; P = .004)\) \((n=304; \text{equal variances not assumed})\). Participants with breast cancer diagnosed prior to age 40 years had a significantly higher CPI \((\text{mean}=0.11; \text{SD}=0.09)\) than did those who had diagnoses at age 40 years or older \((\text{mean}=0.08; \text{SD}=0.06)\) \((t_{50}=3.50; P = .001)\).

The area under the ROC curve (Figure 2) for the CPI was 0.72 \((P < .001)\) for the whole sample and ranged from 0.68 to 0.79 for the subgroups.

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The corrected probability index model incorporates factors to correct for limited family structure. Only the latter 3 models have an area under the receiver operating characteristic curve significantly greater than chance.

**Table 5. Family Structure Corrective Factors for Modification of BRCAPRO**

<table>
<thead>
<tr>
<th>Age Subgroup, y</th>
<th>Constant</th>
<th>Multiply Family Structure Code (0 or 1) by</th>
<th>Multiply BRCAPRO Probability by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non–Ashkenazi Jewish, &lt;40</td>
<td>0.048</td>
<td>0.059</td>
<td>0.006</td>
</tr>
<tr>
<td>Non–Ashkenazi Jewish, ≥40</td>
<td>0.010</td>
<td>0.041</td>
<td>0.013</td>
</tr>
<tr>
<td>Ashkenazi Jewish, &lt;40</td>
<td>−0.214</td>
<td>0.225</td>
<td>0.007</td>
</tr>
<tr>
<td>Ashkenazi Jewish, ≥40</td>
<td>0.016</td>
<td>0.119</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Sample regression equations: (1) a 49-year-old Ashkenazi Jewish woman with a limited family history and a BRCAPRO probability of 15 would have a corrected probability index (CPI) of 0.15 + (0.119 x 0.048) + (0.007 x 15) = 0.156; (2) the same patient with an adequate family history would have a lower probability (CPI = 0.046); (3) a 33-year-old Ashkenazi Jewish woman with limited family history and the same BRCAPRO probability would have a CPI of −0.214 + (0.225 x 1.0) + (0.007 x 15) = 0.116; (4) the same woman with adequate family history would have a CPI of 0.109.*
LIMITED FAMILY STRUCTURE AND BRCA MUTATION STATUS IN BREAST CANCER

COMMENT

Using the largest published series of BRCA–tested women with a history of breast cancer who did not have any first- or second-degree relative with breast or ovarian cancers, we showed that the probability of a BRCA gene mutation is greater when family structure is limited—that is, when there are fewer than 2 female relatives surviving beyond age 45 years in either parental lineage. This practical observation is consistent with autosomal dominant inheritance of a trait with sex-limited expression. Although statistically intuitive, limited family structure is akin to the problem of “missing values” and is a limitation of all common mutation probability models. Consequently, absent better models, cancer risk assessment practices and genetic testing guidelines need to be more inclusive of single cases of breast cancer when there is limited family structure.

Although earlier high-risk clinic populations tended to have strong family cancer histories, this contemporary cohort was more inclusive with respect to offering genetic testing to single cases of early onset breast cancer. Some practice guidelines and policy statements cite a 10% mutation probability as a threshold for recommending BRCA gene mutation analysis; however, the National Comprehensive Cancer Network guidelines suggest that even a single case of early onset breast cancer may be sufficient justification for GCRA, especially in the setting of Ashkenazi Jewish ancestry.11 Furthermore, the updated American Society of Clinical Oncology policy statement emphasizes that medical necessity and clinical judgment of an experienced cancer genetics clinician regarding BRCA genetic susceptibility testing should be the critical deciding factor, rather than a specific numerical threshold.12 Our findings provide important evidence to support more inclusive guidelines.

The observed 13.7% rate of mutations in cases with limited family structure exceeds typically applied thresholds for offering genetic testing. The dichotomous variable of family structure may be most applicable to cases in which the indications for testing are borderline, such as single cases of breast cancer between ages 40 and 50 years. The Couch and BRCAPRO models were developed when there were more restrictive high-risk clinic referral guidelines, resulting in a preponderance of multicase families in the model’s underlying populations. Although other predictive models exist,17-19 the 3 used herein are the most commonly used and widely accepted risk probability models in cancer risk counseling clinics. Although our results may not be generalizable and warrant validation in other high-risk clinic populations, there are no other predictive models for single cases.

The problem of limited family structure is not uncommon, in part because of smaller family sizes, premature mortality (eg, accidental death), and loss of family information from events such as the Holocaust. Factors that reduce breast or ovarian cancer penetrance, such as risk reduction surgery, may also obscure recognition of hereditary traits.

The fact that commonly used models for estimating BRCA gene mutation probability were insensitive to family structure as a predictive factor is a cautionary note for community practitioners. Not surprisingly, the Myriad model estimates did not vary by family structure because all of our cases were women diagnosed as having breast cancer prior to age 50 years who did not have a first- or second-degree relative with breast cancer prior to this age or with ovarian cancer. The Couch model estimates, which are stratified by 5-year increments of age at breast cancer onset, were closest to the observed rate of mutations only in the families with limited structure and overestimated the rate in the families with adequate structure. Although the Bayesian adjustment in the BRCAPRO model may increase the accuracy of mutation prediction in a family with multiple women (regardless of their cancer history), our study demonstrates that this model does not appear to be well calibrated to single cases of breast cancer.

While family structure was highly predictive of mutation status, all tested models used in isolation had suboptimal ROC characteristics. The CPI, which incorporated a corrective adjustment in BRCAPRO for limited family structure, had better characteristics than either model alone, though even the CPI did not have optimal predictive performance for clinical use. The influence of family structure on the performance of predictive models as well as the CPI should be confirmed in other high-risk clinic populations.

Other, less commonly used predictive models,17-19 including the Manchester Scoring System and the BOADICEA (Breast and Ovarian Analysis of Disease Incidence and carrier Estimation Algorithm) model would also be expected to be insensitive to limited family structure because they primarily use positive selection criteria (eg, sum number of relatives with cancer), with no adjustment for the missing value problem inherent in a lack of at-risk women in a given lineage. If relatives do not exist, the probability models make the erroneous assumption of a zero rather than a missing value. The Manchester model uses a scoring system to determine whether a family exceeds a 10% probability of a BRCA mutation threshold.27-28 Female and male breast cancer, ovarian, pancreatic, and prostate cancer are calculated in the score, with adjustment based on age at diagnosis. A single case of breast cancer does not meet the threshold for testing, regardless of family structure. The BOADICEA model was developed using complex segregation analysis and uses the Bayesian theorem to estimate mutation probability from evaluation of family cancer history.29-31 Although the model considers breast and ovarian cancer status in more distant relatives (up to third-degree), it is still subject to the missing-data problem noted above.

Given the significant effect of family structure, illustrated by limited accuracy of probability models for single
cases of breast cancer, and the commonality of the missing-data problem, the databases of currently available probability models should be reanalyzed and limited family history recoded as a separate variable.

Recent data suggest that BRCA1 gene mutations are more prevalent than predicted by the models among women with “triple-negative” breast cancers (ie, negative immunostaining for estrogen and progesterone receptors and HER-2/neu nonamplified).32 The addition of pathologic characteristics (eg, grade and hormone receptor status) was reported to improve the performance characteristics of the BRCAPRO model for BRCA1 gene mutations in a sample that included only 15 breast cancer cases without additional family history of the disease.19 Formal analysis of family structure in addition to pathologic characteristics may be of interest in future studies.

Although experienced geneticists and cancer risk counselors know to assess more-distant relatives (third- and fourth-degree) for potential clues to support a recommendation for BRCA gene testing, busy oncology or primary care clinicians rarely have the time to obtain and qualify a pedigree beyond 1 or 2 generations. In addition, a recent survey study found that less than one quarter of health care professionals and medical students knew the importance of paternal family history in evaluation of hereditary breast cancer, highlighting the need for continuing professional education.33 Along with continued emphasis on the importance of obtaining a family history, as technology such as BRCA gene testing enters the realm of community care it is important to highlight the limitations of the available models, which use only first- and second-degree relatives. Community clinicians need to understand the inherent limitations of all the models with respect to family structure.

Given the documented efficacy of risk-reducing surgery in BRCA gene carriers with limited-stage breast cancer,7,9,34-38 the influence of BRCA gene mutation status in decision making for patients with newly diagnosed breast cancer,8,9 and the sensitivity of enhanced surveillance with magnetic resonance imaging,39,40 our findings support BRCA gene mutation testing for women with early onset breast cancer when the results will influence medical management, regardless of mutation estimates from existing models.12

This report demonstrates the effect of family structure on mutation probability models, highlighting the need for clinicians to consider family structure when deciding whether to offer BRCA gene mutation testing to a “single case” of early onset breast cancer.

Author Contributions: Dr Weitzel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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You are an artist if you pay homage through one medium to all that you feel from another. The scientific training permits of reliability and accuracy, not of adequacy. Thus from these it follows that medicine may be both a science and an art.
—Alan Gregg (1890-1957)