

BRCAPRO Validation, Sensitivity of Genetic Testing of *BRCA1/BRCA2*, and Prevalence of Other Breast Cancer Susceptibility Genes

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Purpose: To compare genetic test results for deleterious mutations of *BRCA1* and *BRCA2* with estimated probabilities of carrying such mutations; to assess sensitivity of genetic testing; and to assess the relevance of other susceptibility genes in familial breast and ovarian cancer.

Patients and Methods: Data analyzed were from six high-risk genetic counseling clinics and concern individuals from families for which at least one member was tested for mutations at *BRCA1* and *BRCA2*. Predictions of genetic predisposition to breast and ovarian cancer for 301 individuals were made using BRCAPRO, a statistical model and software using Mendelian genetics and Bayesian updating. Model predictions were compared with the results of genetic testing.

Results: Among the test individuals, 126 were Ashkenazi Jewish, three were male subjects, 243 had breast cancer, 49 had ovarian cancer, 34 were unaffected, and 139 tested positive for *BRCA1* mutations

and 29 for *BRCA2* mutations. BRCAPRO performed well: for the 150 probands with the smallest BRCAPRO carrier probabilities (average, 29.0%), the proportion testing positive was 32.7%; for the 151 probands with the largest carrier probabilities (average, 95.2%), 78.8% tested positive. Genetic testing sensitivity was estimated to be at least 85%, with false-negatives including mutations of susceptibility genes heretofore unknown.

Conclusion: BRCAPRO is an accurate counseling tool for determining the probability of carrying mutations of *BRCA1* and *BRCA2*. Genetic testing for *BRCA1* and *BRCA2* is highly sensitive, missing an estimated 15% of mutations. In the populations studied, breast cancer susceptibility genes other than *BRCA1* and *BRCA2* either do not exist, are rare, or are associated with low disease penetrance.

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INDIVIDUALS WITH a family history of breast and/or ovarian cancer are at increased risk of carrying deleterious mutations of susceptibility genes *BRCA1* and *BRCA2*.¹⁻⁴ Genetic testing for the presence of these mutations is becoming commonplace. The basis for testing is usually an assessment of risk of carrying a mutation based on a family history of disease. Because genetic testing has important health and cost consequences, accurate risk assessment is important. Such assessment is complex, and most people overestimate their risk, of both breast cancer and of carrying a deleterious mutation.⁵⁻⁸ Two important risk models were developed before the discovery of *BRCA1* and *BRCA2*: Gail et al⁹ incorporated the number of first-degree relatives with breast cancer into a comprehensive model of breast cancer risk; Claus et al^{10,11} estimated the risk of breast cancer caused by susceptibility genes depending on the number of familial cases of breast cancer and the ages at diagnosis of affected members. After testing became available, new models were developed using regression or classification approaches in which various family characteristics were used to predict results of genetic testing.¹²⁻¹⁵

BRCAPRO^{1,3} is a computer program that implements a statistical model for calculating an individual's probability of carrying a deleterious mutation of *BRCA1*, *BRCA2*, neither, or both on the basis of the individual's cancer status and the history of breast and ovarian cancer among her first-

and second-degree relatives. (We use "carrier probability" to mean the probability of carrying a deleterious mutation of either *BRCA1* or *BRCA2*.) The model uses the autosomal dominant Mendelian characteristics of the genes, incorporates prevalence and penetrance on the basis of the published results as described in detail in Iversen et al,¹⁶ and

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uses Bayesian updating.¹⁷ BRCAPRO has been licensed to approximately 1,000 users worldwide. It is distributed free of charge as part of the genetic counseling package CancerGene (in a Web-based format available through David M. Euhus, MD, Division of Surgical Oncology, The University of Texas Southwestern Medical Center at Dallas, at http://www.swmed.edu/home_pages/cancergene/).

In a clinical setting, BRCAPRO can be used to aid in advising individuals whether to undergo genetic testing. Testing usually has no value for someone whose carrier probability is small. However, the threshold depends on the individual's attitudes toward testing, her family's attitudes toward testing, and her attitudes about prophylactic procedures.¹⁸ Less intuitively, testing may not be worthwhile for a woman whose carrier probability is large (see Discussion). Testing will generally be informative and potentially valuable for women whose carrier probability is between these extremes.

BRCAPRO also has research uses. Family histories are usually easier and less expensive than genetic testing, and sometimes genetic testing is not possible. BRCAPRO can be helpful in two categories of application: (1) as a guide to determine who to test and to judge the utility of such testing; and (2) as a substitute for testing. Regarding the first application, a researcher who contemplates genetic testing for subjects involved in a clinical trial or subjects in a research database can use BRCAPRO to determine the expected number of mutations in each subset of study participants. This allows for judging whether the scientific question can be addressed with sufficient statistical power. It also allows for estimating the cost of testing per mutation expected. In addition, it allows for selecting the most informative subset of participants for testing when funding for genetic testing is limited. Regarding the second application, using a procedure called multiple imputation, each subject can be assigned a mutation with probability calculated using BRCAPRO and the conclusions drawn on the basis of these assignments, assuming that the assignment is actual. This procedure is repeated many times, with potentially different conclusions each time. The result is a frequency distribution of conclusions. This frequency distribution may have great variability, indicating uncertainty regarding the scientific hypothesis being addressed. However, it may have little variability, especially if the number of participants is large, thereby obviating the need to perform genetic testing.

Applications of BRCAPRO for research include the following: (1) quantifying the association between breast cancer risk and family history that is not attributable to major autosomal dominant genes¹⁹; (2) using multiple imputation to analyze the association between familial susceptibility and severity of prognosis in a large population-based case series obtained by linking Surveillance,

Epidemiology, and End-Results (SEER) follow-up to Cancer and Steroid Hormone study family history information²⁰; (3) developing a classification algorithm for determining which missense mutations have a deleterious effect²¹; (4) estimating the prevalence of nonfounder *BRCA1* and *BRCA2* mutations in Ashkenazi families at high-risk for breast and ovarian cancer (Kauff et al, manuscript submitted for publication); and (5) validating simple family history assessment tools.²²

For a carrier probability model to be useful it must be accurate and widely applicable; the substance of this article is an assessment of the limitations and practical application of BRCAPRO and other carrier probability models. Potential limitations of BRCAPRO include the following: (1) it uses published penetrance/incidence and prevalence estimates, which may be inaccurate; (2) it considers only first- and second-degree relatives; (3) it accounts for breast and ovarian cancer only; and (4) it considers only the two known susceptibility genes, *BRCA1* and *BRCA2*. If there are other susceptibility genes with disease penetrances comparable to those of the two known genes, then some individuals with large BRCAPRO carrier probability will harbor mutations of the other genes but will test negative for *BRCA1* and *BRCA2*. In view of the wide applicability and potential limitations of BRCAPRO, we undertook the present study to validate its performance, extending three previous studies.²³⁻²⁵ These three studies considered subsets of data from two of the six centers that are considered here. Inferences from those studies were consistent with ours, but firm conclusions about validation, sensitivity, and so on are not possible because of the small sizes of the previous studies.

PATIENTS AND METHODS

Study Description

We collected data retrospectively from families for which at least one member was tested for mutations at both *BRCA1* and *BRCA2*. Six cancer genetic counseling centers participated: Dana-Farber Cancer Institute, Georgetown University Medical Center, Creighton University, The University of Texas Health Science Center at San Antonio, University of Pittsburgh Medical Center, and Lahey Clinic. There was no uniform set of eligibility criteria across centers, reflecting current practice. At some of the centers, models used to help guide whether to carry out genetic testing included Frank et al,¹² Couch et al,¹³ Shattuck-Eidens et al,¹⁵ and FitzGerald et al.²⁶ Characteristics of eligibility criteria from each center are listed in Table 1.^{12,13,15,26}

We included every family for which at least one member had been tested, regardless of family history. No genetic testing results were used in determining eligibility for the study. Therefore, the numbers of cancers reported in families represent the standard in these six centers. We selected one member (the proband) from each family; this was the member who had the first genetic test for both *BRCA1* and *BRCA2* in the family. A family was excluded if the proband had not completed testing of both genes. Information was reported to genetic counselors

Table 1. Eligibility Criteria for BRCA1/BRCA2 Mutation Probability Testing in Each of the Six Centers

Center/Program	Period of Eligibility	Clinic/Study or Registry Subject Criteria	Subject Demographics	Referral Method	Risk Model Used	Eligibility for Genetic Testing			
						Cancer History of Breast and/or Ovarian	≥10% Pretest Mutation Probability	Other; When Low Pretest Probability	Fee for Genetic Test
Creighton Hereditary BC and OC studies	Completed by May 1998 validation	All families BRCA1/2 tested at Creighton	Most white; throughout United States	Self and physician*	Nonquantitative consensus of experts	Self + family; available to test	Not used; Risk by expert consensus	Selected only by expert consensus	No cost to participant
Dana-Farber Cancer Risk and Prevention Program	1995-1997	All patients BRCA1/2 tested	All white; HSS	Self and physician	Available published models†	Self or family with ≥ 1 case/kindred	Yes, using published models	If high risk by epidemiologic data‡	No cost to participant
Lahey Clinic Risk Assessment Program	1995-1997	All patients in program BRCA1/2 tested		Self and physician	Available published models	Self + family; pedigree analysis	Yes, using published models	Rarely: affected Jewish families	No cost to participant
Lombardi Cancer Center, Georgetown Medical Center	1995-1997	All families in CARE Program; high risk +BC or OV	Clinic-based population	Self and physician	Available published models§	Self, with family history of either; positive relative	Yes, using published models§	Rarely: presence of associated cancers	No cost to participant
UPCI Cancer genetics program	1995-1997	All patients in program BRCA1/2 tested	West PA, east OH, WV; All white; HSS	70% physician; 30% self	Available published models†	Self and family history	Yes, using published models	Rarely: Jewish or relevant cancer history	Fee paid by participant
UTHSCSA Familial BC registry	1992-1997	BC in 2 FDR; blood sample	General population; not high-risk clinic	Selected from registry	Available published models	BC, self age < 50 + FDR	Yes, using published models	None	No cost for cases in study

Abbreviations: BC, breast cancer; OC, ovarian cancer; BRCA1/2 tested, having undergone genetic testing for deleterious mutations of BRCA1 or BRCA2; HSS, high socioeconomic status; CARE, Cancer Assessment and Risk Evaluation Program; UPCI, University of Pittsburgh Cancer Institute; PA, Pennsylvania; OH, Ohio; WV, West Virginia; UTHSCSA, The University of Texas Health Science Center at San Antonio; FDR, first-degree relative.

*Most subjects were not initially referred for genetic testing.

†For models predictive of BRCA1 mutations only, 50% of the predicted risk was added to estimate the additional contribution of BRCA2 mutations.

‡High-risk determination by epidemiologic date; ie, a woman diagnosed with breast cancer at age 31, in a small family without other cancer history.²⁶

§Studies guiding criteria for genetic testing selection included Frank et al,¹² Couch et al,¹³ and Shattuck-Eidens et al.¹⁵

by family members. Errors in reporting are possible, particularly for second-degree relatives,²⁷ but these errors are also likely to occur in the practical use of BRCAPRO outside of this study. Documentation was obtained when possible.

We compared each proband's carrier probability and testing result. A better comparison of the accuracy of the program would be to compare the probability with the actual genotype, but genetic testing is imperfect and so the genotype may be unknown. "Carrier probability" refers to the probability of genotype and not to test results. Genetic alterations reported as polymorphisms and uncertain variants were scored as negative.

Description and Application of BRCAPRO

BRCAPRO uses two forms of input data: proband-specific and population-based. Proband-specific data include the proband's first- and second-degree family history of breast and ovarian cancer. Specifically, BRCAPRO uses the following information for each proband and

each first- and second-degree relative (including those not affected by cancer); sex; current age or age at death; exact relationship to the proband (such as daughter of sister no. 3); any diagnosis of breast cancer, second primary breast cancer, and ovarian cancer; and age at each diagnosis. Whether or not the proband is Ashkenazi Jewish (AJ) is also accounted for in the model. If part of the family history information was missing, we took a conservative approach. For example, if a relative's existence was known but there was no information about her cancer status, then that relative was not considered. (This may create a bias because lack of knowledge about a relative's cancer status may be related to her cancer status. However, direction and magnitude of this bias are not always the same.) If a relative was diagnosed with breast cancer at age 35, but her current age is unknown, her age is censored at 35 with regard to ovarian and second primary breast cancers. If genetic testing results of family members are available, then this information can be included in the BRCAPRO

calculations, but each proband in our study was the first family member tested and so we did not exercise this option.

The population-based inputs of BRCAPRO are mutation prevalence and disease penetrance. The prevalence of mutations for individuals of AJ descent is estimated to be 1.22% for *BRCA1* and 1.36% for *BRCA2*.^{28,29} These figures are estimated to be 0.12% and 0.044% for non-AJ individuals.³⁰ Penetrance is the probability of diagnosis of cancer up to and including each age. Published penetrance estimates are similar in the two ethnic groups, and the associated published standard deviations are large, especially at the two extremes of age. Therefore, we estimated penetrance for breast and ovarian cancer by combining estimates for AJ³¹ and non-AJ³⁰ individuals. For each age, the result is a weighted average of the two (specifics of the estimation method are given in Iversen et al¹⁶). Penetrances at age 70 for both AJ and non-AJ carriers of mutations of *BRCA1* and *BRCA2* are .691 and .671 for breast cancer and .296 and .191 for ovarian cancer. Differences are greater at some other ages. Penetrances for noncarriers are taken from the SEER database³² and adjusted to exclude cases estimated to be attributable to *BRCA1* and *BRCA2*. (BRCAPRO penetrance files are available at <http://biosun01.biostat.jhsph.edu/~gparmigi/brcapro.html>.) Prevalence and penetrance estimates used in BRCAPRO in the present validation study were arrived at independent of the families considered in this study.

Genetic Testing

At three of the six study centers, genetic testing was carried out by Myriad Genetic Laboratories, Inc, or Oncormed. Testing at Creighton was performed in a collaborative research protocol in the laboratories of Gilbert Lenoir (International Agency for Research on Cancer, Lyon, France) and Steven Narod (Women's College Hospital, Toronto, Ontario, Canada). Georgetown used a variety of testing laboratories, including those of Myriad, Oncormed, Steven Narod, and the University of Pennsylvania. Dana-Farber used laboratories of Myriad and the University of Pennsylvania. Both genes were fully sequenced in all cases, except that testing restricted to the three common AJ mutations was allowed (and typical) if the proband was AJ.³¹

Description of Families

We tabulate the proportions of probands and also families in our study who have breast cancer, ovarian cancer, both cancers, bilateral breast cancer, and male breast cancer. We also tabulate the numbers of familial cancers by proband carrier probability, categorized into 10 groups: 0 to 0.1, 0.1 to 0.2, and so on. We show the same categorization of carrier probability overall and for affected and unaffected probands separately.

Accuracy of BRCAPRO

Genetic testing may not be perfect, and BRCAPRO predicts genotype rather than testing result. Therefore, BRCAPRO may meet its goal and yet show up poorly when compared with testing results. For example, some individuals who carry a mutation and whose BRCAPRO probabilities are close to 100% will test negative. Nevertheless, to assess the model's predictive performance we compare BRCAPRO predictions to the results of genetic testing. We group the probands into *sextiles*, categories that each contain one sixth of the data ordered by carrier probability. Within each sextile we calculate the average carrier probability and the associated expected number of positive tests. We compare the latter with the actual number of positive tests and the associated 95% confidence interval (CI). If BRCAPRO were a perfect inferential tool, then the two would agree—up to sampling variability—within each sextile.

We repeat the above comparison for AJ and non-AJ families separately. We also compare mean carrier probabilities between the probands who test positive and those who test negative, using *t* tests.

The ability of any model to discriminate between *BRCA1* and *BRCA2* on the basis of family history is limited because both types of mutations are associated with similar increases in the incidence of breast and ovarian cancer. Therefore, we combine the two genes in most of our analyses. However, small differences in penetrances and distribution of age of onset for these two genes^{30,31,33,34} give BRCAPRO a modest ability to discriminate between them. We assess this ability by calculating the average probabilities of carrying mutations for *BRCA1* and *BRCA2* separately for those probands who tested positive for *BRCA1* and *BRCA2* and neither gene.

We assess the dependence of the accuracy of BRCAPRO in predicting testing results on the assumed penetrance of *BRCA1* and *BRCA2*. In particular, we consider fractions from 20% to 100% of the published estimates of penetrance and calculate the linear correlation coefficient between BRCAPRO and the observed testing results for each fraction. The higher the correlation, the more the evidence favors the respective penetrance, but we do not quantify the strength of this evidence.

Sensitivity and Specificity of Genetic Testing

Sensitivity of genetic testing is the proportion of carriers of mutations who test positive. Specificity is the proportion of noncarriers who test negative. Sensitivity can be estimated from our study as follows. Suppose BRCAPRO were a perfect inferential tool and consider a cohort of individuals having carrier probability greater than 99.9%. An estimate of the sensitivity of testing would be the proportion of these individuals testing positive. In another cohort with carrier probability equal to 90%, say, 90% of the tests would be expected to be positive. If only 70% actually tested positive in this cohort, then estimated sensitivity would be 70 of 90, or 78%. An estimate derived from the two cohorts combined would weight them by their sample sizes, and the variances of the individual estimates would be similarly weighted. In our study, we estimate sensitivity using maximum likelihood and derived from each proband's carrier probability and testing result. In evaluating the likelihood, the probability of a positive test is modeled as the product of carrier probability and sensitivity. Because BRCAPRO may not be a perfect inferential tool, the resulting estimate of sensitivity will have uncertainty beyond that resulting from sampling variability. In addition, mutations in genes other than *BRCA1* and *BRCA2* may be responsible for cancer in some of the families in our study. Carrier probability may well be large for probands in these families, and of course genetic testing would not discover these mutations. Hence, our estimate of sensitivity of *BRCA1/BRCA2* testing is conservative in the sense that it is likely to underestimate true sensitivity.

RESULTS

Description of Study Sample

Our sample consisted of 301 probands and their families. Two examples that are representative of our study families are shown in Fig 1. The BRCAPRO carrier probability is 99.9% for the proband depicted in Fig 1A. This proband was found to carry a mutation on *BRCA1*. For the proband depicted in Fig 1B, the BRCAPRO carrier probability is 1%. No mutations were found on either gene for this individual.

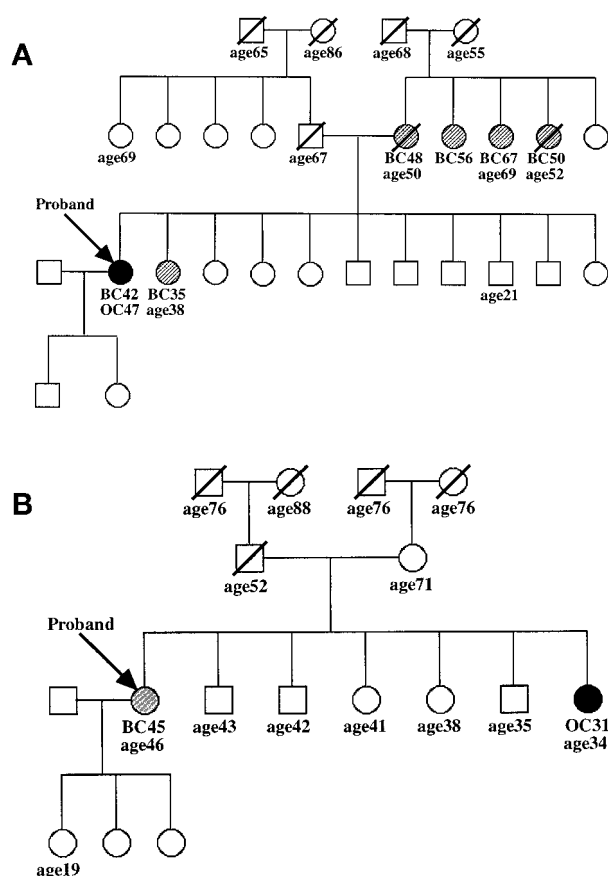


Fig 1. Example family histories. Neither family is Ashkenazi Jewish. Symbols: □, male; ○, female; /, deceased; ●, cancer; BC# (or OC#), age at breast (or ovarian) cancer diagnosis; age#, current age or age at death (when known).

Of the 301 families in our sample, 126 (42%) were AJ. Table 2 lists the distribution of breast and ovarian cancer in the probands and their families. The average number of cases (\pm SD) of breast cancer in the 301 families was 3.0 ± 1.8 , the average number of ovarian cancers was 0.8 ± 1.0 , and the average number of bilateral breast cancers was 0.5 ± 0.7 .

Table 3 lists the numbers of cancers in the families categorized by carrier probability. The numbers of cancers varied greatly among the families. The majority (216 [71%]) of the probands have three or more cases of familial breast or ovarian cancer, and might be deemed at “high risk” for carrying mutations for this reason.⁴ Conversely, a fair number of probands had rather low carrier probabilities. There was an average of 3.8 cancers (breast or ovarian) per family, including probands: 3.9 for the 267 (89%) families with affected probands and 2.8 for those with unaffected probands. As expected, there was a tendency for probands

Table 2. Distribution of Breast and Ovarian Cancers in 301 Probands and First- and Second-Degree Family Members

	Proband		Family	
	No.	%	No.	%
Breast cancer*	243	80.7	284	94.4
Ovarian cancer	49	16.3	147	48.8
Both†	25	8.3	132	43.9
Neither	34	11.3	2	0.7
Bilateral breast cancer	47	15.6	112	37.2
Male breast cancer‡	3	1.0	7	2.3

*Includes bilateral disease.

†For proband, refers to both breast and ovarian cancer in same individual; for family, refers to both types of cancer in family (including proband) but not necessarily in the same member.

‡Seven of the 301 probands were male and four were unaffected male subjects.

with extensive family histories of breast and ovarian cancer to have higher carrier probabilities. However, many probands with extensive family histories of disease had low carrier probabilities and some with only a few cancers had high carrier probabilities. This indicates that the number of familial cancers alone cannot be used to give an accurate assessment of genetic risk. It is important to consider ages of onset, types of cancers, number and ages of unaffected family members, and the exact relationships among all family members.

The distribution of carrier probabilities is listed separately for affected and unaffected probands in Table 3. Most unaffected probands had carrier probabilities of less than .5 (the probability that the proband would inherit a mutation harbored by a particular parent). Carrier probability could be greater than .5 for unaffected probands if there is cancer on both sides of the family or if the proband has both descendants and ancestors who are affected.

There were different levels of genetic risk among tested individuals at the six centers, with numbers of cancers per family averaging 2.4, 3.0, 3.5, 3.5, 3.6, and 5.2. Similarly, they differ by carrier probability, with respective averages of 32%, 24%, 65%, 58%, 71%, and 72%.

The overall proportion of probands testing positive was 168 (56%) of 301: 139 (46%) for *BRCA1* and 29 (10%) for *BRCA2*. Corresponding frequencies among AJ probands were 78 (62%) of 126: 62 (52%) for *BRCA1* and 13 (10%) for *BRCA2*. Among non-AJ probands, the frequencies were 90 (51%) of 175: 74 (42%) for *BRCA1* and 16 (9%) for *BRCA2*.

Validation of BRCAPRO

Mean carrier probability was 61%: 79% for those who tested positive and 39% for those testing negative ($P < 10^{-10}$). Figures 2A and 2B show the proportions of positive

Table 3. Numbers of Members (including proband) With Breast or Ovarian Cancer in the 301 Families by Category of the Proband's BRCAPRO Carrier Probability

	Categories of Carrier Probability										Total
	0.0-0.1	0.1-0.2	0.2-0.3	0.3-0.4	0.4-0.5	0.5-0.6	0.6-0.7	0.7-0.8	0.8-0.9	0.9-1.0	
No. of cancers											
0	2	0	0	0	0	0	0	0	0	0	2
1	7	1	2	4	1	1	2	0	0	3	21
2	20	10	2	3	10	3	4	2	1	7	62
3	10	3	5	0	11	2	3	2	5	21	62
4	8	6	1	2	5	1	2	1	3	30	59
5	1	1	1	1	2	1	2	4	3	34	50
6	1	0	0	0	1	0	1	0	1	9	15
7	0	0	0	0	0	0	0	1	2	16	19
8	0	0	0	0	0	0	0	2	1	5	8
9-14	0	0	0	0	0	0	0	0	1	2	3
Proband											
Unaffected	5	1	1	4	18	3	0	1	0	1	34
Affected	44	20	10	6	12	5	14	11	17	128	267
Total	49	21	11	10	30	8	14	12	17	129	301

tests plotted against the average BRCAPRO carrier probability. The data set is partitioned into sextiles ordered by BRCAPRO, with each circle or square in Fig 2A and Fig 2B representing a sextile. In Fig 2A, the sample size is 50 or 51 in the six intervals of carrier probability defined in Table 4. This table gives the mean carrier probability for probands within each category, labeled AC Prob %; these means correspond to the horizontal position of the solid circles in Fig 2A. Each circle's vertical position is the observed proportion of positive test results in that category, *BRCA1* and *BRCA2* combined, and the vertical lines show confidence intervals. If both BRCAPRO and testing were perfect, if there were no susceptibility genes other than *BRCA1* and *BRCA2*, and if there was no sampling variability, then the solid circles would lie on the diagonal line shown in Fig 2A. Sampling variability explains much but not all of the deviation from the diagonal line. Each of the highest three categories, in toto representing the carrier probabilities in the top half of the distribution, has its 95% CI wholly below the diagonal. At the opposite extreme, there is a suggestion that BRCAPRO may underestimate the true proportion of positive testing results because the confidence interval for the lowest sextile is wholly above the diagonal. Overall, the correspondence between carrier probabilities and proportions of positive tests is encouraging.

AJ Subgroup

Figure 2B displays the same scheme as shown in Fig 2A but separated into AJ ($n = 126$) and non-AJ ($n = 175$) subgroups, and corresponding to the data in Table 5. Each open circle in Fig 2B represents a sextile of the proband data set that is AJ, and each solid square in Fig

2B represents a sextile of the proband data set that is not AJ. The area of each circle and each square is approximately proportional to the sample size. The model fit is similar in the two subgroups. For the AJ, the correlation is .445 ($P < 10^{-10}$) and for the non-AJ it is .577 ($P < 10^{-10}$). The estimated sensitivities are not statistically different in the two subgroups: 83.3% (95% CI, 73.3% to 90.6%) among the AJ and 87.5% (95% CI, 78.1% to 93.9%) among the non-AJ.

High-Risk Families

As indicated above, 216 (71%) of the 301 probands were at high risk for carrying mutations on the basis of having three or more cases of familial breast or ovarian cancer.⁴ In these families, BRCAPRO was effective in distinguishing between carriers and noncarriers: positive tests by sextile of carrier probability were three of 25 (12% v 3% predicted), eight of 25 (32% v 26% predicted), 27 of 50 (54% v 56% predicted), 18 of 25 (72% v 87% predicted), 19 of 25 (76% v 96% predicted), and 45 of 51 (88% v 99.5% predicted).

Low-Risk Probands

Thirty-seven probands had carrier probability less than 5%. Two of these probands tested positive (5.4%; 95% CI, 1.5% to 17.7%). Mean carrier probability in these 37 probands was 2.2% and therefore the expected number of positive tests was .85.

Unaffected Probands

Of the 34 unaffected probands, 19 (56%) tested positive; average carrier probability was 39%. The fit of BRCAPRO

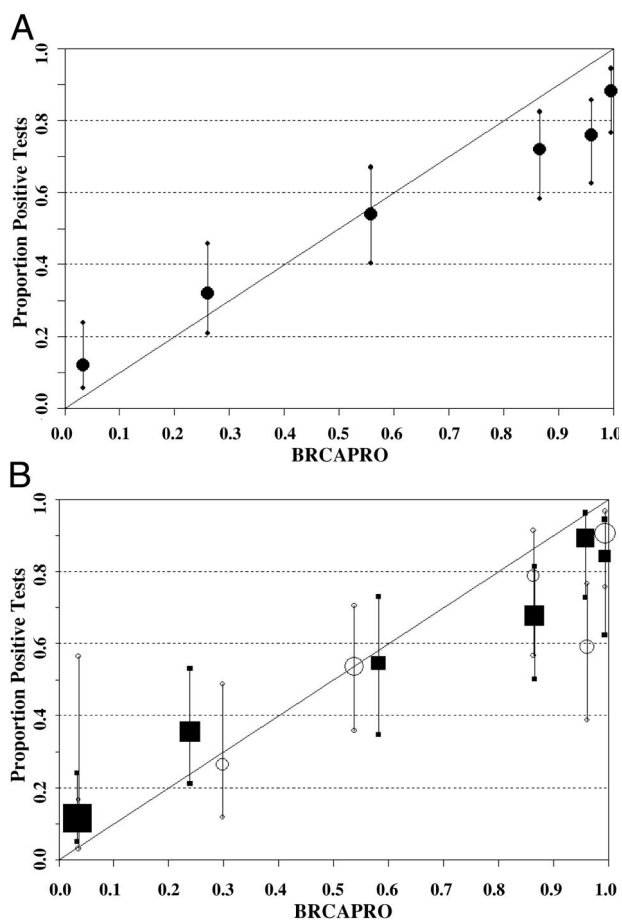


Fig 2. Comparison of BRCAPRO carrier probability and results of genetic testing: (A) *BRCA1* and *BRCA2* combined; (B) by subgroups of AJ and not AJ. Each circle/square represents a sextile of the data set; each 95% CI is shown by a vertical line with dotted end points.

is similar in unaffected and affected probands: Restricting to unaffected probands, the correlation between carrier probability and testing result was .557 ($P < 10^{-5}$) and for affected probands it was .513 ($P = .0019$).

Male Probands

There were seven male probands (2.3%) in the study, four of whom were AJ. Six of the seven tested positive and all six had carrier probabilities greater than 50%. The seventh male proband was AJ and had no family history of cancer; his carrier probability was less than 1% and, not surprisingly, he tested negative. Three of the seven male probands had breast cancer and carrier probabilities greater than 95% and all three had mutations at *BRCA2*. The other three male probands who tested positive (at *BRCA1*) had both descendants and ancestors who were affected, and these three had

the largest carrier probabilities (52.4%, 73.6%, and 99.7%) among all unaffected probands.

Discriminating *BRCA1* and *BRCA2* Mutations From Family History

Table 6 lists mean carrier probabilities for *BRCA1* and *BRCA2* separately for carriers of each type of mutation and for noncarriers. Table 6 indicates that BRCAPRO has some ability to discriminate between mutations on these two genes, but this ability is limited.

Sensitivity of Genetic Testing/Prevalence of Other Genes

The estimated sensitivity of genetic testing was 85.4% (95% CI, 78.7% to 90.5%). The undiscovered mutation proportion of about 15% includes any mutations on susceptibility genes other than *BRCA1* and *BRCA2* (see Discussion).

DISCUSSION

BRCAPRO is designed to provide the probability of carrying a mutation on the basis of family history. Our study shows that the program is effective in predicting the risk of testing positive. It is especially accurate in predicting testing results when the carrier probability is less than 70%. Larger carrier probabilities overestimate the frequency of a positive test result in our sample by about 15%. Assuming that the penetrance and prevalence functions used by BRCAPRO are accurate, we conclude that genetic testing for *BRCA1* and *BRCA2* is highly sensitive, missing at most an estimated 15% of mutations. Included are mutations of other breast and ovarian cancer susceptibility genes that have approximately the same penetrances as *BRCA1* and *BRCA2*.

The fit of the actual testing results to carrier probability in Fig 2A is good but not perfect. Individuals with small carrier probabilities are unlikely to carry mutations at *BRCA1* or *BRCA2*: among the 37 probands having carrier probability less than 5%, only two (5.4%) were carriers. Conversely, individuals with high carrier probabilities are likely to carry mutations: among the 90 probands having carrier probability more than 95%, 75 (83%) were carriers. For predicting whether an individual tests positive for *BRCA1* or *BRCA2*, these calculations and Fig 2 suggest that carrier probability is a good estimate unless it is large—greater than 70%. For such large carrier probabilities, taking 85% of the carrier probability to account for imperfect test sensitivity improves the estimated probability of a positive test result.

Estimated sensitivity of genetic testing in our study was at least 85%. This is an average in the sense that it applies over the spectrum of testing methods and laboratories used; individual methods may have higher sensitivity and others may have lower sensitivity.³⁰ Our estimate of sensitivity of testing

Table 4. BRCAPRO Carrier Probability and Expected and Observed Test Findings

Carrier Prob %	No.	AC Prob %	Exp Pos	Obs Pos		Obs 95% CI
				No.	%	
0-11.0	50	3.4	1.7	6	12.0	5.6-23.8
11.0-43.0	50	26.1	13.1	16	32.0	20.8-45.8
43.0-73.1	50	55.8	27.9	27	54.0	40.4-67.0
73.1-94.9	50	86.6	43.3	36	72.0	58.3-82.5
94.9-98.88	50	96.0	48.0	38	76.0	62.6-85.7
98.88-100	51	99.5	50.7	45	88.2	76.6-94.5
0-100	301	62.2	184.7	168	55.8	50.2-61.3

Abbreviations: Carrier Prob %, range of carrier probability for each sextile of the proband data; No., number of probands in the sextile; AC Prob %, average carrier probability; Exp Pos, expected number of positive tests based on the average carrier probability; Obs Pos (%), observed number of positive tests, *BRCA1* plus *BRCA2* (% of n); Obs 95% CI, 95% confidence interval for the positive tests observed.

is substantially greater than the 63% of Ford et al.³⁰ A likely reason is that they used estimated odds of linkage and their testing methodology was less sensitive than full sequencing.

Our results lead to the conclusion that any undiscovered breast cancer genes in the population studied are likely to have low prevalence or low penetrance. Genes having penetrance similar to *BRCA1* and *BRCA2* are probably rare, with total prevalence no greater than approximately one quarter that of *BRCA1* and *BRCA2* combined. Figure 3 is a schematic showing the trade-off between false-negatives in testing for *BRCA1* and *BRCA2* and the existence of other moderately penetrant susceptibility genes, with the sum being 15%. If the sensitivity of testing for *BRCA1* and *BRCA2* is 85%, then there is no room for other such genes in our study populations. If the sensitivity of testing is

100%, then other susceptibility genes could have total prevalence one quarter that of the total of these two genes.

BRCAPRO uses published estimates of penetrance. Population-based evidence regarding a particular mutation of *BRCA1*³⁵ suggests that these estimates may be too high. Our study has little ability to address penetrance. However, to investigate the effect of overestimating penetrance, we recalculated all carrier probabilities after lowering penetrance input to the model to various proportions of published estimates. Mean carrier probability dropped and estimated sensitivity increased, as shown in Table 7. Cases with carrier probability near 100% have the most influence in estimating sensitivity. Large values of carrier probability tend to decrease more in noncarriers, resulting in increased sensitivity if a smaller penetrance is assumed. Of the 90

Table 5. BRCAPRO Carrier Probability, Expected and Observed Test Findings by Subgroups

Carrier Prob %	No.	AC Prob %	Exp Pos	Obs Pos		Obs 95% CI
				No.	%	
Ashkenazi Jewish						
0-11.0	6	3.6	0.2	1	16.7	3.0-56.4
11.0-43.5	19	29.8	5.7	5	26.3	11.8-48.8
43.5-78.0	28	53.8	15.1	15	53.6	35.8-70.5
78.0-94.9	19	86.4	16.4	15	78.9	56.7-91.5
94.9-98.88	22	96.2	21.2	13	59.1	38.7-76.7
98.88-100	32	99.5	31.8	29	90.6	75.8-96.8
0-100	126	71.7	90.4	78	61.9	53.2-69.9
Not Ashkenazi Jewish						
0-11.0	44	3.4	1.5	5	11.4	5.0-24.0
11.0-43.5	31	23.9	7.4	11	35.5	21.1-53.1
43.5-78.0	22	58.2	12.8	12	54.5	34.7-73.1
78.0-94.9	31	86.6	26.9	21	67.7	50.1-81.4
94.9-98.88	28	95.9	26.8	25	89.3	72.8-96.3
98.88-100	19	99.4	18.9	16	84.2	62.4-94.5
0-100	175	53.9	94.3	90	51.4	44.1-58.7

Abbreviations: Carrier Prob %, range of carrier probability for each sextile of the proband data; No., number of probands in the sextile; AC Prob %, average carrier probability; Exp Pos, expected number of positive tests based on the average carrier probability; Obs Pos (%), observed number of positive tests, *BRCA1* plus *BRCA2* (% of n); Obs 95% CI, 95% confidence interval for the positive tests observed.

Table 6. Means (and 95% CI) of Probability of Carrying a Mutation on BRCA1 (BRCAPRO1), BRCA2 (BRCAPRO2), and Either (total carrier probability), Shown by Result of Genetic Testing

Test Result	No.	%	BRCAPRO1		BRCAPRO2		Total Carrier Probability	
			Mean	95% CI	Mean	95% CI	Mean	95% CI
Negative	133	44	0.26	0.21-0.32	0.14	0.10-0.17	0.40	0.34-0.45
BRCA1	139	46	0.65	0.60-0.70	0.16	0.12-0.20	0.80	0.75-0.85
BRCA2	29	10	0.48	0.37-0.59	0.32	0.24-0.40	0.79	0.68-0.91
Total	301	100	0.46	0.43-0.50	0.16	0.14-0.19	0.62	0.59-0.66

probands having carrier probability more than 95% when using published penetrance, 75 (83%) tested positive. Decreasing penetrance to 50% of the published estimates means that only 47 had carrier probability more than 95%, and 43 (91%) of these tested positive. Decreasing the estimate of penetrance to 20% of published figures means that only 14 probands had carrier probability more than 95%, and all tested positive. The correlation coefficient is reasonably high and nearly constant over the range of penetrances considered, which means that Table 7 provides little evidence concerning the accuracy of published estimates.

Our results suggest that genetic testing is highly specific. Although the slight excess in the proportions of positives we found for probands having low carrier probability could be because of wrongly calling a case positive, other explanations are more plausible. One is ascertainment bias. For example, families with affected third-degree relatives, relatives with colon cancer, and so on, may be more likely to present at clinics, and this information is not used in BRCAPRO. Conversely, the excess may be due to sampling variability, incorrect omission of deleterious missense mutations, inaccurate penetrance and prevalence estimates, or inaccurate family histories. The family history in Fig 1A illustrates incomplete information, which is a type of inaccuracy that is common in our study. The current ages of many unaffected relatives were not reported. Ignoring unaffected relatives in BRCAPRO overestimates carrier

probability. The effect can be substantial but is not great in this particular family: If all unknown ages of siblings of the proband were assumed to be 42 and all aunts were assumed to be age 69, then the proband's carrier probability would drop to 99.8%, only slightly reduced from the value 99.9% indicated in Fig 1.

We compared BRCAPRO with an easy-to-use model for predicting testing results that was developed by Myriad Genetics, Inc.^{12,15} We used the updated version of the model,¹² available at <http://www.myriad.com>. The Myriad model is not based on Mendelian inheritance but instead uses logistic regression fitted to various characteristics of family history: whether any relatives have been diagnosed with ovarian cancer, whether the proband has a second primary cancer, and an interaction term between diagnosis at age less than 40 and whether any relative had early-onset breast cancer. The Myriad model applies only for women with early-onset breast cancer (age < 50) and at least one first- or second-degree relative with ovarian or early-onset breast cancer. In our study, the Myriad model applied for 144 (48%) of the 301 probands. Of these, 91 (63%) tested positive, which compares with a proportion of 46% positive tests predicted by the Myriad model (50% among positive tests and 39% among negative tests; $r = .29$; $P = .0003$).

The Myriad probability tends to be smaller than that of BRCAPRO, in part because the former predicts results of testing rather than carrier status. However, the Myriad probability is larger than BRCAPRO when many relatives are unaffected (unaffected relatives are not considered by Myriad) and when a family's cancers are not consistent with a heredity pattern. An example of the latter is member 1 of family 4 of Berry et al³: BRCAPRO carrier probability is 2.4% and Myriad's is 59%.

The Myriad model is not as accurate as BRCAPRO. For the 144 probands where Myriad applied, the mean BRCAPRO probability was 78% (90% among those testing positive and 58% among those testing negative; $r = .49$; $P = 10^{-10}$). BRCAPRO more accurately predicted testing result than did Myriad for 110 (76%) of the 144 probands: of the 25 probands for which BRCAPRO was less than Myriad, 22 (88%; $P = .0002$) tested negative; of the 119 probands for

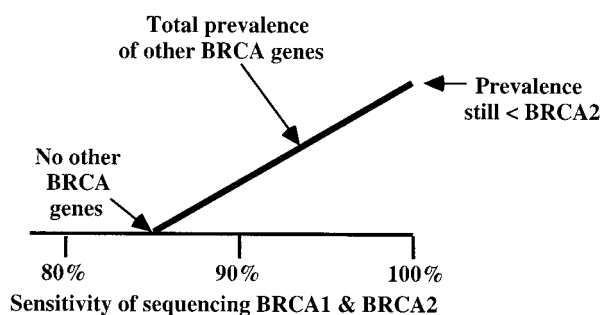


Fig 3. Trade-off between estimated sensitivity of genetic testing and estimated prevalence of other susceptibility genes that have penetrance characteristics similar to BRCA1 and BRCA2.

Table 7. Estimated Sensitivity of Testing and the Correlation Coefficient Between Testing Results and Carrier Probability Assuming Reduced Overall Penetrance of Breast and Ovarian Cancer in Both AJ and Non-AJ Populations

Penetrance, × Published:	100%*	90%†	80%†	70%†	60%†	50%†	40%†	30%†	20%†
Average carrier probability	.614	.609	.593	.571	.543	.507	.460	.390	.276
Estimated sensitivity‡	.854	.866	.879	.896	.916	.938	.964	.993	1.000
Correlation coefficient	.534	.539	.540	.539	.536	.527	.511	.479	.412

*Published results; default values used by BRCAPRO.

†Reductions (90% to 20% of the published results) with all estimates reduced simultaneously.

‡Estimated by means of maximum likelihood.

which BRCAPRO was more than Myriad, 88 (74%; $P = 10^{-7}$) of them tested positive. Therefore, BRCAPRO was more accurate whether it pointed more in the negative direction or more in the positive direction. Also, BRCAPRO applies generally, whereas Myriad's application is restricted. Of the 157 probands for which the Myriad model did not apply, the BRCAPRO fit to the genetic testing results was just as good ($r = .56$) as for the 144 cases for which Myriad did apply.

The utility of BRCAPRO as compared with simply counting the number of familial cancers is evinced by the cross-tabulation in Table 3. It is easy to assess genetic risk in families that are cancer-free and those that have more than six cancers. For such families, computer programs are of little use. However, when a family has from one to six cancers, finding carrier probability can be difficult, and it is not necessarily intuitive. For a given number of familial cancers, carrier probabilities range from small to large. For example, for probands with three familial cancers, about one in six had probabilities smaller than 10%, whereas one in three had probabilities greater than 90%. The spread is not as large for unaffected probands, who constituted a small proportion (11%) of our sample. As indicated above, 50% is usually the upper limit of carrier probability in unaffected women. Most unaffected probands in our study were at high genetic risk, with about two thirds having carrier probability greater than 40% (Table 3). However, there is still substantial variability, with about 15% of unaffected probands having probability less than 10%.

We indicated in the Introduction that most people overestimate their risk of carrying mutations. This overestimation can be substantial. For example, in the Bluman et al study,⁶ and restricting to the 78 women whose carrier probability as assessed by BRCAPRO was less than 10%,

the women estimated their carrier probability to be 65% on average. Moreover, none of the 78 women thought that their probability was less than 10% and 16 thought that it was 90% or more.⁶ Using BRCAPRO can provide a service to women by helping to correct unreasonable overestimates. In the opposite direction, BRCAPRO can also correct underestimates. Of the 31 women in this study whose BRCAPRO carrier probability was greater than 90%, their own assessment of their probability averaged only 79%; 19 of the 31 thought that their probability was less than 90% and one estimate was as low as 20%.

The importance and clinical application of BRCAPRO depends on the individual's carrier probability, but it also depends greatly on the individual's attitudes. If she will not make changes in her life as a result of learning her carrier probability, then the information has no value. However, some women will make decisions on the basis of the level of associated risk. A low probability might not prompt any changes in lifestyle or health care decisions, whereas a probability in the range of 5% to 10% might prompt the individual to seek genetic counseling and a high probability might lead to prophylactic surgery. An individual with a 10% probability might base subsequent health care treatment options on the outcome of genetic testing, opting for a surgical solution if the test finds a deleterious mutation, and avoiding surgery otherwise. The benefit of testing depends on the individual's attitudes and carrier probability, and for some it can result in additional life expectancy.

Genetic counseling should include the ramifications of positive genetic test results and of negative test results. BRCAPRO facilitates counseling by addressing the probabilities of both types of results. It also elucidates the individual's circumstances in the case of a negative genetic test. If the test has 100% specificity, then an individual

Table 8. Carrier Probability After a Negative Genetic Test for a BRCA1/BRCA2 Mutation ("negative predictive value"), Assuming the Test Sensitivity Equals 85%

	Carrier Probability (%)												
	0	10	20	30	40	50	60	70	80	90	95	99	100
Before test (BRCAPRO)	0	10	20	30	40	50	60	70	80	90	95	99	100
Negative predictive value	0	2	4	6	9	13	18	26	38	57	74	94	100

whose test is positive has a 100% probability of carrying a mutation. However, if her test is negative, then her carrier probability is not 0; it depends on the test's sensitivity and on her carrier probability before the test (eg, from BRCAPRO). Assume sensitivity equals 85%. Her carrier probability after a negative test ("negative predictive value") is shown in Table 8.

A woman with a 20% pretest carrier probability will go to 100% with a positive test and 4% with a negative test. However, a woman with a large carrier probability will still have a large carrier probability even after a negative test. Such women with a negative test will be difficult to counsel, and our study shows that they are not rare (15 probands had carrier probabilities > 95% and yet tested negative). Is it a case of a missed mutation? A mutation at another susceptibility gene? A woman with a pretest probability of 99% would reasonably consider prophylactic interventions even if her test is negative. If her decisions will be the same for both positive and negative results, then the test has little value.

Probands of special interest in counseling are those unaffected by disease. Unaffected women usually have carrier probabilities less than 50%. Moreover, for any given family history, a woman's carrier probability gets smaller with increasing age as long as she is disease-free. As Table 8 shows, testing is most informative for women who have moderate carrier probabilities, and because unaffected women with moderate carrier probabilities tend to be young, they also have the most to gain from genetic testing in terms

of expected incremental quality-adjusted life-years,¹⁸ depending on their attitudes toward prophylactic procedures.

The average carrier probability over the entire population is the sum of the prevalences of *BRCA1* and *BRCA2*. Therefore, in the general population, most women's carrier probabilities are less than 1%. These women would probably be advised to not have genetic testing, at least in part because of their low carrier probability. However, the number of such women is large and so many who have been advised against testing are indeed carriers. Some will discover their carrier status after being diagnosed with disease. This is an inescapable consequence of genetic counseling, with or without providing carrier probabilities.

We conclude, first, that for individuals who present at genetic counseling clinics, BRCAPRO provides an accurate assessment of probability of carrying a deleterious mutation of *BRCA1* and *BRCA2*. Multiplying this probability by the sensitivity of the testing method used gives an accurate estimate of the probability of testing positive. Moreover, although an individual's carrier probability is affected by the estimates of penetrance and prevalence used, the accuracy of BRCAPRO is not dependent on having accurate estimates of these quantities. Second, methods for genetic testing for *BRCA1* and *BRCA2* used in our study have high sensitivity, which we estimate to be at least 85%. Finally, if there exist breast cancer susceptibility genes with penetrance comparable to those of *BRCA1* and *BRCA2* in the population we studied, then mutations at these genes are rare.

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