Published in final edited form as:

Fam Cancer. 2010 December ; 9(4): 495–502. doi:10.1007/s10689-010-9348-3.

Predicting *BRCA1* and *BRCA2* gene mutation carriers: comparison of PENN II model to previous study

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Abstract

A number of models have been developed to predict the probability that a person carries a detectable germline mutation in the *BRCA1* or *BRCA2* genes. Their relative performance in a clinical setting is variable. To compare the performance characteristics of a web-based *BRCA1/BRCA2* gene mutation prediction model: the PENNII model (www.afcri.upenn.edu/itacc/penn2), with studies done previously at our institution using four other models including LAMBDA, BRCAPRO, modified PENNI (Couch) tables, and Myriad II tables collated by Myriad Genetics Laboratories. Proband and

family cancer history data were analyzed from 285 probands from unique families (27 Ashkenazi Jewish; 277 female) seen for genetic risk assessment in a multispecialty tertiary care group practice. All probands had clinical testing for *BRCA1* and *BRCA2* mutations conducted in the same single commercial laboratory. The performance for PENNII results were assessed by the area under the receiver operating characteristic curve (AUC) of sensitivity versus 1-specificity, as a measure of ranking. The AUCs of the PENNII model were higher for predicting *BRCA1* than for *BRCA2* (81 versus 72%). The overall AUC was 78.7%. PENN II model for *BRCA1/2* prediction performed well in this population with higher AUC compared with our experience using four other models. The ease of use of the PENNII model is compatible with busy clinical practices.

Keywords

BRCA1; *BRCA2*; Breast cancer; Risk prediction; Ovarian cancer

Introduction

An estimated 1 in 500 people in the USA carry deleterious mutations in the *BRCA1* or *BRCA2* genes, with higher prevalence in individuals of Ashkenazi Jewish descent for whom the prevalence is about 1 in 40. Analyses of the penetrance of mutations in *BRCA1/2* report ranges for risk of female breast cancer to age 70 of 44–68% in both *BRCA1* and *BRCA2* mutation carriers, while risk of ovarian cancer to age 70 ranges from 22 to 60% *BRCA1* carriers and 15–30% in *BRCA2* carriers. The risks to age 80 are even greater [1–5]. The female breast cancers that occur in *BRCA1* and *BRCA2* mutation carriers are diagnosed characteristically in the perimenopausal years. Increased risks are also noted for cancers of the peritoneum, fallopian tube, prostate, male breast, pancreas, biliary system, stomach, and cutaneous melanoma [6].

Recognition of the risks associated with *BRCA1/2* mutations has led to recommendations for cancer screening and management that are different in ages of initiation, modality, and frequency, than the recommendations for women with average cancer risks [7–10]. If *BRCA1/2* testing was inexpensive and if no psychosocial consequences were associated, testing might be conducted on all individuals presenting with breast or ovarian cancers. However, neither of these conditions are true, so multiple models have been developed to help identify individuals whose medical care would be impacted maximally by recognition of a *BRCA1/2* mutation.

In 2007, we reported performance characteristics of four BRCA prediction models (LAMBDA, BRCAPRO, MYRIADII, and PENNI, a modified Couch model) in women presenting for genetic risks assessment at the Mayo Clinic [11]. That study showed reasonably similar overall performance of all the models, and that certain families had drastically different risk scores based upon the data elements included in each model and their weighting in the risk scoring. Since publication of that study, the PENNII model was introduced. This is a web-based tool, and we have now re- studied the original Mayo data set plus newer families from the same population, in order to compare this model with the others.

Methods

Subjects

Between 1996 and 2005, probands (defined as the initial consultands in the families) from 322 independent families had cancer risk assessment at the Mayo Clinic and subsequently had clinical genetic testing for mutations in *BRCA1* and *BRCA2* at Myriad Genetics Laboratories, Inc, Salt Lake City Utah that included complete sequencing of both genes and, since 8/2003,

testing for a five-site rearrangement-panel in *BRCA1*. The newer BRCA Rearrangement Test (BART, Myriad Genetics), which was introduced clinically in 2006, was not performed on this group of probands as it was not available at the time their data was entered for this study. Sixteen families were excluded for having DNA variants of unknown significance (2 in *BRCA1* and 14 in *BRCA2*). A detailed family history of cancer diagnoses was collected by a certified genetic counselor or a Familial Cancer Program study coordinator trained in genealogic collection. If possible, the pedigrees were extended to all affected and unaffected third degree relatives of the consultand. Efforts were routinely made to verify the diagnoses of breast and ovarian cancers in relatives by collection of medical records and death certificates, but this was not consistently successful so risk estimates in this study were frequently based upon a verbal family history alone. For the purposes of this study, ductal carcinoma in situ was not considered to be invasive breast cancer, and peritoneal cancer was considered equivalent to ovarian cancer. No fallopian tube cancers were reported in these families. Twenty-one other families were excluded for not having appropriate data detail to use this model. All consultands studied had given permission for use of their medical records for research purposes and this study was approved by the Mayo Clinic Institutional Review Board.

The PENNII model for BRCA mutation prediction

The PENNII model can be found at this web site <http://www.afcri.upenn.edu/itacc/penn2/> and a screen shot of the data entry interface is shown in Fig. 1. The output of the model includes the consultand's probability of having a deleterious *BRCA1* or *BRCA2* gene mutation and the probability of a deleterious gene mutation in an affected family member, i.e., one with breast or ovarian cancer. If the proband has a diagnosis of breast or ovarian cancer, the risk prediction will be the same for individual and family. If the consultant is unaffected, then the family risk reflects the probability in an affected member and the consultant risk is reduced according by Mendelian logic to whether they are first or second degree relatives of the affected member. The details of this model's development have not yet been published (manuscript under review); however, co-author S. Domchek, co-developer of this model has provided information on the development of this model to us for describing the Mayo PENNII study. Pedigrees were collected from 545 families attending breast cancer risk evaluation clinics in Cambridge University (Cambridge, UK), the Royal Marsden Hospital (London, UK), Albert Einstein Medical Center (Philadelphia, PA), the University of Chicago (Chicago, IL), the University of Michigan (Ann Arbor, MI), and the University of Pennsylvania (Philadelphia, PA), in accordance to IRB protocols at each site. All families included in the study had two or more individuals affected with either breast and/or ovarian cancer and one affected individual had to be a first, second or third degree relative of the second affected individual. At least one affected individual was tested for mutations in *BRCA1* and *BRCA2* between 1994 and 2000 at one of the collaborating centers. An additional 392 families with at least one affected at the University of Pennsylvania between 2000 and May 2004 also were included, for a total of 966 families. All families included in the analysis with negative genetic testing results were tested for mutations in both *BRCA1* and *BRCA2*. Negative results from individuals of AJ descent that only were tested for the three AJ founder mutations (185delAG and 5382insC in *BRCA1*, 6174delT in *BRCA2*) also were included. Forty percent of AJ individuals negative for these three mutations went on to have full sequencing. Families having only variants of unknown significance were excluded. A set of variables were derived from factors felt to be potential predictors of *BRCA1/2* mutations including those previously associated with mutations as well as malignancies not included in previous models. In addition, groupings of multiple primary cancers, such as breast cancers and any non-ovarian cancer in the same individual, were considered as possible predictors. For further refinement, all variables were run as independent variables in three logistic regression models as: (i) univariate predictors, (ii) bivariate predictors with the number of women in the family over 19 years of age and (iii) bivariate predictors with a binary categorical UK/non-UK clinic location. Models were run with the presence of a

mutation in *BRCA1* or the presence of a mutation in *BRCA2* as dependent variables. Variables were removed as predictors if their significance level was greater than 0.25. Additionally, variables whose significance level was greater than 0.25, or increased by an order of magnitude when adjusted for by one of the non-biological variables (family size/clinic location) were removed as possible predictors. Finally, 105 families with missing values in any of the remaining possible predictors were eliminated. Thus, 861 families with complete records were included in the final modeling.

The resulting variable set was made available to a stepwise-constructed optimal model aimed at predicting the probability of detecting a mutation in *BRCA1/2* in the setting of commercial genetic testing. Using Proc Logistic (SAS version 8.2, Inc., Cary, NC), the predictive value of these models was evaluated using ROC analysis and the Hosmer–Lemeshow criterion [12]. Following the stepwise variable selection algorithm, the refined significant independent predictor set was the model was manually optimized for quality and clinical practicality. The resulting web-based tool incorporates the results of these models to generate the probability of detecting a mutation in *BRCA1* and the probability of detecting a mutation in *BRCA2* separately. The web site does not require any client downloads or fees for use.

Table 1 describes the four models used in our original study and compares with the PENNII model.

Statistical methods

The demographic data of the Mayo study were summarized with counts and percentages for nominal data and with means and standard deviations for quantitative data. Receiver-operator characteristics (ROC) curves were obtained and the areas under the curves (AUCs) were estimated. As both men and women had been assessed, summaries and computations were first performed for all subjects and then within the set of women only. The Receiver Operating Characteristic (ROC) curve is a plot of $Y = \text{sensitivity}$ (the proportion of subjects correctly classified when the subject is a carrier) against corresponding values of $X = 1 - \text{specificity}$ (the proportion of subjects incorrectly classified when the subject is not a carrier). The area under the ROC curve is can be interpreted as the probability that the model's prediction for a randomly selected carrier from the pool of probands will be greater than its prediction for a randomly selected non-carrier. The greater the area under the curve (AUC), the better the model's performance is in ranking probands by carrier probability.

Statistical analyses were performed with STATA version 9.0 and R version 2.1.0 [13].

Results

A total of 285 individuals (277 women) were assessed with the PENNII model. Their characteristics are shown in Table 1. 79% had either breast or ovarian cancer. Of the 277 women, 55 had deleterious *BRCA1* mutations (19.9%) and 27 had deleterious *BRCA2* mutations (9.7%). Thus a total of 29.6% of probands had deleterious mutations whereas PENNII overall predicted 26%. All Ashkenazi probands were women. Overall, the AUCs of the PENNII model were higher for predicting *BRCA1* than for *BRCA2* (81 versus 72%). All AUCs are shown in Table 2 with corresponding ROC curves for this overall data set are shown in Figs. 2, 3, 4, 5, 6, 7.

Discussion

No two clinical practices are quite alike so we believe it is of value to assess the performance of the available BRCA mutation prediction models in one's own clinical practice, to be sure of providing reasonable information to patients, and to help identify models that enhance the

practice efficiency. We had previously assessed four BRCA prediction models (LAMBDA, BRCAPRO, MYRIADII, and PENNI, a modified Couch model) in women presenting for genetic risks assessment at the Mayo Clinic [11], and concluded that all performed reasonably well. The BRCAPRO had a slightly higher AUC, but was too labor intensive for routine use in a brisk office practice. The LAMBDA model, which was developed for use in Ashkenazi Jewish women, was easy to use and “missed” fewer cases than the other models even in our predominantly non Jewish patient population. The yet-to-be-published PENNII model was of interest to us because of its ease of use (very simple web-based form requiring no special software) and it incorporated specific clinical features that seemed intuitively relevant (bilateral breast cancers, mother-daughter pairing, presence/absence of prostate and pancreatic cancers) that were not used in most of the other models, and allowed very rapid data entry (perhaps 15 s from start to finish). In a somewhat expanded Mayo data set (285 vs. 200 probands), we have learned that PENNII shows a slight improvement in AUC over the models assessed previously, confirming that for this practice, PENNII provides usable information. We suspect that this sort of performance is approaching the limit for models based just on family history, as there will always be phenocopies, missing data, non penetrance, small families, new mutations, adoptions, and no paternity, to interfere with creation of a uniformly highly specific and sensitive tool. It is rather impressive that these models have the favorable performance characteristics that they have given all the possible confounders. Newer models that incorporate pathology data and hormone exposure data have the promise of providing even more refined risk assessments, but presently this requires considerably more time to gather information for input, with seemingly little gain in clinical utility.

One recent study merits special mention. Five BRCA1/2 prediction models were compared and contrasted in a very large data set (1,934 families) by Antoniou et al. [14]. The web-based BOADICEA model, BRCAPRO, IBIS, Myriad tables, and Manchester scoring system had areas under the receiver operating characteristic curve (AUC) statistics of 0.77, 0.76, 0.74, 0.75, and 0.72, respectively. In our study, we found a comparable statistic of 0.79 (0.720–0.8440) suggesting the PENNII model is as clinically relevant as most other models, and in our practice, appeared to be perform slightly better (details in Table 3). We cannot rule out the possibility that our expanded Mayo data set would have given different AUC than our original study but that does not change our conclusion regarding the performance of PENNII.

Our study does not address models that project risk of developing breast cancer, a topic that is different but is an equally important aspect of providing clinical genetic risk assessment. The traditional Gail model components were merged with genotype information from 10 single nucleotide polymorphisms in a new study reported by Wacholder et al. [15]. The AUC increased modestly from 58.0 to 61.8% by addition of the genotype data. Combining information from BRCA gene mutation probability models with risk data from breast cancer prediction models is allowing greater individualization of medical decision making.

In summary, we have determined that the web based PENNII BRCA gene mutation prediction tool is easy to use and performed well in a clinic-based practice.

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The Penn II BRCA1 and BRCA2 Mutation Risk Evaluation Model Official Web Site

The Penn II Risk Model-
What is the Penn II Model?

- This model can be used to predict the pre-test probability, or prior probability, that a person has a BRCA1 or BRCA2 mutation. In general, individuals with at least a 5-10% chance of having a mutation in either gene are considered good candidates for genetic testing.
This model does not predict breast cancer risk. It focuses only on the chance that an individual has inherited a mutation in BRCA1 or BRCA2.

Instructions for use

- Please answer the following questions.
- Information from a single lineage in the family should be used and restricted to three generations.
- If there is cancer history present on both the maternal and paternal sides, each lineage should be entered separately.
- Since this model depends on the family history being accurate, attempts should be made to confirm the family history with pathology reports, especially for cases of ovarian cancer
- Further information can be found by clicking the icon

Part A. Select the Side of the Family in Question: ☐ Maternal ☒ Paternal

Part B. Please provide Following Information:

1. Presence of Ashkenazi Jewish ancestry?		☒ no ☐ yes
2. Number of women in family diagnosed with both breast and ovarian cancer?		<input type="text"/> (0-100)
3. Number of individual women in family diagnosed with ovarian or fallopian tube cancer in the absence of breast cancer?		<input type="text"/> (0-100)
4. Number of breast cancer cases in family diagnosed in individuals under the age of 50?		<input type="text"/> (0-100)
5. What is the age of the youngest breast cancer case?		<input type="text"/> (18-130)
6. Presence of mother-daughter breast cancer diagnosis in family?		☒ no ☐ yes
7. How many individuals with bilateral breast cancer in family?		<input type="text"/> (0-100)
8. Number of male breast cancer diagnoses in family?		<input type="text"/> (0-100)
9. Presence of pancreatic cancer in family?		☒ no ☐ yes
10. Number of prostate cancer diagnoses in family?		<input type="text"/> (0-100)

Part C. Closest Relative with Breast or Ovarian Cancer:

Part D. Patient Information (Optional- for use on report only):

1. Patient's first name	<input type="text"/>
2. Patient's last name	<input type="text"/>
3. Patient's age	<input type="text"/>
4. Clinic location	<input type="text"/>

[Click to Calculate Risk](#)

Fig. 1.
Screen shot of PENNII model

Fig. 2. Receiver-operating characteristic curve (ROC) for *BRCA1* prediction using PENNII in all subjects (*AUC* area under the curve)

Fig. 3.
ROC for *BRCA1* prediction using PENNII in women

Fig. 4.
ROC for *BRCA2* prediction using PENNII in all subjects

Fig. 5.
ROC for *BRCA2* prediction using PENNII in women

Fig. 6.
ROC for *BRCA1* or *BRCA2* prediction using PENNII in all subjects

Fig. 7.
ROC for *BRCA1* or *BRCA2* prediction using PENNII in women

Table 1

Comparison of five models used at authors centers to predict the probability that a woman carries a germline deleterious mutation in *BRCA1* or *BRCA2*. Adapted from Lindor et al. [11]

Model (reference)	Derivation	Input used	Comments	Output
LAMBDA[16]	Multiple Logistic Regression analysis of 424 AJ women in Australia and the UK with personal or family history of breast or ovarian cancer, tested for the three AJ founder mutations only	Work sheet with score based on point system on personal, FDR*, and SDR** family history of breast and ovarian cancer, including age at diagnosis, bilateral disease in proband	Women only; designed for use in AJ women.	Combined probability of <i>BRCA1</i> and <i>BRCA2</i> for AJ women
Myriad II [17]	Empiric data from 10,000 women on whom BRCA sequencing was conducted	On-line risk tables, updated periodically, utilizing personal and first- and second-degree family history, for breast and ovarian cancers, grouped by those over and under age 50 years at diagnosis of breast cancer.	Women only; only affected family members included; different tables for AJ and non-AJ	Combined probability for <i>BRCA1</i> and <i>BRCA2</i> for non-AJ or AJ women.
BRCAPRO [18,19]	Bayesian model assuming autosomal dominant inheritance, based on family history of FDR* and SDR** incorporating unaffected relatives, compared with SEER*** data.	Cancer type and age at diagnosis in proband, FDR, and SDR entered into free computer program; only breast and ovarian cancers used in risk assessments.	Men and women; allows for both AJ and non-AJ; utilizes number and ages of affected and unaffected relatives in risk assessment	Predicts individual and combined probabilities for <i>BRCA1</i> and <i>BRCA2</i> genes, and also provides Couch model and Myriad II model results., and individual risks for development of breast cancer
Couch [20]	Logistic regression based on 263 families of women with family history of breast cancer with or without ovarian cancer	Published tables using average age of breast cancer, and presence or absence of ovarian cancer in predicting probability of <i>BRCA1</i> mutation	Women only; different tables for AJ/non-AJ; does not predict <i>BRCA2</i> mutation probability.	Predicts probability of deleterious <i>BRCA1</i> mutation only.
PENN II	Logistic regression based on 861 pedigrees from Europe and N. America	Free web-based tool with 11 questions at answer. Presence and ages of breast cancer, presence of ovarian cancer alone or with breast ca, bilaterality, mother-daughter concordance, pancreatic and prostate cancers, AJ/non-AJ, relation to breast/ovarian case.	AJ/non-AJ. Does not provide risk for breast or ovarian cancer.	Individual and combined probabilities of <i>BRCA1</i> and <i>BRCA2</i> mutations.

* FDR first-degree relative

** SDR second-degree relative

*** Surveillance, epidemiology, and end results (SEER) program [21]

Table 2Summaries of the individuals evaluated for *BRCA1* or *BRCA2* by PENNII

	Overall (n = 285)	Women only
Women		
n (%)	277 (97.2)	277 (100)
Ashkenazi		
n (%)	27 (9.5)	27 (9.8)
Breast or ovarian cancer		
n (%)	225 (79.0)	221 (79.8)
Age at breast cancer		
n	195	191
Mean age (SD)	45.0 (10.6)	44.6 (10.3)
Age at ovarian cancer		
n	45	45
Mean age (SD)	51.7 (12.7)	51.7 (12.7)
Penn II— <i>BRCA1</i>		
Predicted chance mutation: mean (SD)	17.2 (20.3)	17.4 (20.5)
Penn II— <i>BRCA2</i>		
Predicted chance mutation: mean (SD)	8.85 (6.27)	8.56 (5.48)
Penn II— <i>BRCA1</i> or <i>BRCA2</i>		
Predicted chance mutation: mean (SD)	26.1 (22.2)	26.0 (22.3)

Table 3

Areas under the receiver operating characteristic (ROC) curves for the different models

Model	N	Area under ROC curve (95% CI)
LAMBDA	200	0.73 (0.66–0.79)
BRCAPRO	182	0.76 (0.70–0.82)
Couch1.5	170	0.72 (0.64–0.78)
Myriad II	200	0.71 (0.64–0.77)
PENNII	285	0.81 (0.741–0.874) <i>BRCA1</i>
	ROC same for women-only	0.72 (0.593–0.792) <i>BRCA2</i>
		0.79 (0.720–0.844) <i>BRCA1</i> and <i>BRCA2</i>

The first four were published previously [11] and are shown for comparison only