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Original article

Performance of BOADICEA and BRCAPRO genetic models and of empirical criteria based on cancer family history for predicting BRCA mutation carrier probabilities: A retrospective study in a sample of Italian cancer genetics clinics

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ABSTRACT

Purpose: To evaluate in current practice the performance of BOADICEA and BRCAPRO risk models and empirical criteria based on cancer family history for the selection of individuals for BRCA genetic testing.
Patients and methods: The probability of BRCA mutation according to the three tools was retrospectively estimated in 918 index cases consecutively undergone BRCA testing at 15 Italian cancer genetics clinics between 2006 and 2008.
Results: 179 of 918 cases (19.5%) carried BRCA mutations. With the strict use of the criteria based on cancer family history 173 BRCA (21.9%) mutations would have been detected in 789 individuals. At the commonly used 10% threshold of BRCA mutation carrier probability, the genetic models showed a similar performance [PPV (38% and 37%), sensitivity (76% and 77%) and specificity (70% and 69%)]. Their strict use would have avoided around 60% of the tests but would have missed approximately 1 every 4 carriers.
Conclusion: Our data highlight the complexity of BRCA testing referral in routine practice and question the strict use of genetic models for BRCA risk assessment.

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Introduction

Increasing evidence supports the notion that the timely detection of a BRCA mutation in a family may prove helpful in preventing, in many cases, its most feared consequence, death from breast or ovarian cancer at an early age, thanks to the actions taken as a

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consequence of this information [1]. However, widespread BRCA testing in unselected individuals is not feasible, not only because of the associated costs but also for the difficulty, particularly in families with a low probability of carrying a mutation, to interpret its result when novel variants of uncertain significance (VUS) are identified [2]. Since it is not yet possible to select cases for BRCA genetic testing on the basis of biological or molecular characteristics of the cancer cells suggesting the presence of a germline mutation, the assessment of the genetic risk in a woman relies on the identification of patterns of cancer family history (CFH) associated with a "reasonably high" chance of finding a germline BRCA mutation. Clinical guidelines for the identification of Hereditary Breast-Ovarian Cancer syndrome (HBOC) have been produced in many countries. These guidelines contain similar criteria, based on CFH patterns, for referral to BRCA genetic testing [3,4]. In most cases, these criteria correspond to a probability threshold of carrying a BRCA mutation. In most European countries and in North America the threshold for genetic testing referral was set at a 10% probability of carrying a BRCA mutation [5].

Over the past two decades several tools for the individual assessment of BRCA carrier probabilities have been developed and validated, based on either empirical or genetic models. Empirical models calculate the probability of mutation using some predictor variables derived from CFH. Genetic models use mathematical algorithms based on explicit assumptions about genetic effects that take into account mode of inheritance, allele frequencies and associated cancer risks. Both empirical and genetic models have been shown to suffer from a low discrimination power at the individual level [6–8].

The validity of the available models when assessed outside high-risk populations is less known. This issue is critical in a public health perspective: in Western countries, the majority of women referred for a genetic risk assessment to decide the appropriateness of BRCA genetic testing show CFH pattern that do not qualify for the high-risk category [9,10]. This large 'intermediate risk' group of women that, in absolute numbers, contains more BRCA carriers than the high-risk group, may be offered or denied or the test according to local regulations/attitudes. The decision to provide testing should consider several constrains, including the costs of genetic testing and the woman's motivation for or against testing. However, the critical information on which to base this decision is the accuracy of the available risk assessment tools when used in women at intermediate mutation risk.

To address this issue, we evaluated the performance of a set of empirical criteria commonly used in Italy for referral to BRCA genetic testing, and of BOADICEA and BRCAPRO models, in an unselected clinical series of women undergone BRCA testing at the clinical genetics centers joining the INTEF project, an Italian cancer genetics network.

Methods

Fifteen Italian cancer genetics clinics, located in different Italian regions, contributed data to this retrospective multicenter study.

During the study period, referrals for suspected HBOC from physicians were made in the absence of formal regional care pathways for familial risk assessment. Also, women worried for their CFH could directly contact cancer genetics clinics for an appointment (self-referrals). During genetic consultations, the recommendation of genetic testing was given following similar (but not identical) protocols; in all centers, CFH criteria were used to evaluate appropriateness of BRCA testing but the final decision with each patient took into account also other personal/familial factors. Genetic testing was performed by diagnostic laboratories.

Eligible for the study were all consecutive Italian index cases initiating a complete BRCA1 and BRCA2 genetic testing (i.e. family mutation status was unknown) between 01/01/2006 and 31/12/2008.

Informed consent to the use of data for research purposes had been provided by each individual within the same counseling session, following the procedures dictated by the local Ethical Committees. Exclusion criteria were: index cases not of Italian ancestry, unavailability of test results or incomplete testing, inadequate pedigree information, and lack of written informed consent to the use of clinical and genetic data for research purposes. Limitation to Italian ancestry was decided because BRCA1/2 mutation frequencies, a parameter used in genetic models, may vary among populations.

The following tools for BRCA carrier probability prediction were applied in all cases: 1) a set of empirical criteria (Table 1), referred to as "INTEF criteria", commonly used in Italy for referral to BRCA testing [12] and similar to other empirical criteria, for example National Comprehensive Cancer Network (NCCN) criteria; 2) BOADICEA Version2 (BWA 2.0) [13]; 3) BRCAPRO (CancerGene Version 5.0) [http://www.utsouthwestern.edu/utsw/cda/dept47829/files/65844.html].

INTEF criteria do not provide percent probabilities of mutation while models provide carrier probability for BRCA1 and BRCA2 genes separately. Among the available international tools, we concentrated on BOADICEA and BRCAPRO because both models were specifically developed for BRCA mutation carrier prediction and are freely available in easy-to-use computer versions. In addition, to our knowledge, BOADICEA was never evaluated in Italian families. Family history information used by the two models is more complete than INTEF criteria as 1) also healthy family

Table 1
INTEF criteria for referral to genetic testing (overlapping with the NCCN criteria is shown on the right).

INTEF		NCCN[a]
Personal or first[b] degree relative with		
1	Male BC	Yes
2	BC and OC in the same patient	Yes
3	Female BC <36 years with/without BC/OC family history	<45 years
4	≥1 female bilateral BC <50 years with/without BC/OC family history	Yes
5	≥2 females with BC <50 years in first degree relatives	Yes
6	One female BC <50 years and ≥1 first degree relative with OC any age	Yes
7	One female BC <50 years and ≥1 first degree relative with female bilateral BC any age	No
8	One Female BC <50 years and ≥1 first degree relative with male BC	Yes
9	One female BC >50 years and ≥2 first[c] degree relatives with BC/OC any age	Yes
10	One OC and ≥1 first degree relative with BC <50 years	Any OC
11	One OC and ≥1 first degree relative with OC any age	Any OC
12	One OC and ≥1 first degree relative with female bilateral BC any age	Any OC
13	One OC and ≥1 first degree relative with male BC	Any OC
14	One OC and ≥2 first[c] degree relatives with BC/OC any age	Any OC

BC = breast cancer; OC = ovarian cancer.
[a] From the 2011 update, personal or family history of pancreatic cancer in >2 close blood relatives and triple-negative breast cancer cases aged < 60 years were introduced as testing criteria.
[b] For the paternal branch of the family consider second degree relatives.
[c] One must be a first degree relative of the other two.

members (limited to first and second degree relatives for BRCAPRO, unlimited for BOADICEA) and 2) the presence of prostate and pancreatic cancers (BOADICEA) and the breast cancer hormonal receptors status (BRCAPRO), are considered.

Data collection and quality control

Participating centers provided the following data: index case characteristics (sex, date of birth, cancer site and histology, age at cancer diagnosis, if any), number and type of cancers diagnosed in the family branch suspected for HBOC, presence/absence of each of the INTEF criteria, probabilities of being a BRCA1 and BRCA2 mutations carrier calculated using the BOADICEA and BRCAPRO models, results of BRCA genetic testing. Inconsistencies were checked and amended at the coordinating center, following queries to the submitting center.

BRCA mutations and VUS were defined according to international criteria [14]; classification of mutations was revised by 4 authors (V.G., A.V., M.M., and P.R.).

Statistical analyses

The empirical INTEF criteria and the BOADICEA and BRCAPRO risk models were used to predict the probability to carry a BRCA mutation in each index case.

The calibration of the two models was evaluated by comparing the observed and predicted number of BRCA mutation carriers in 8 subgroups defined according to specific threshold probabilities and overall (sum of observed and expected BRCA mutations over threshold strata). Comparison was performed for BRCA1 and BRCA2 together and for each of the two genes. The goodness of fit was assessed by the Pearson chi square test.

Sensitivity, specificity and positive predictive value (PPV) were calculated for the models at the cut-offs of 5% and 10% BRCA mutation carrier probability. Sensitivity was defined as the proportion of the total number of mutations detected in the study population that would have been detected if a given (set of) selection criteria had been used for testing patients. Similarly, the specificity was defined as the proportion of patients without a BRCA mutation who would not have been selected for testing if the same threshold had been applied. The positive predictive value (PPV) is the proportion of patients who would have been selected for testing using a given threshold of probability to carry a BRCA mutation who were found to actually carry the mutation.

The discrimination ability of the models to distinguish between BRCA mutation carriers and non-carriers at the individual level was evaluated using the ROC curves.

Results

Between January 2006 and December 2008, 956 consecutive index cases were tested for BRCA mutations in the 15 participating cancer genetics clinics. Thirty-eight index cases were excluded: thirteen were not of Italian ancestry, 11 had incomplete testing, five had inadequate pedigree data, and nine denied consent to the use of information for research purposes. In all, 918 index cases (886 females and 32 males) were eligible and available for the analyses.

Mutation testing was performed by direct DNA sequence or dHPLC analyses; MLPA analysis was performed in 45% of cases (data not shown).

Table 2 shows the main characteristics of cases by center. Overall, 179 individuals (19.5%) carried a BRCA mutation: 104 (11.3%) carried a BRCA1 mutation, 74 (8.1%) a BRCA2 mutation and one (0.1%) carried a mutation in both genes. Variants of uncertain significance were found in 92 (89 females and 3 males) of 918 index cases (10.0%). Large variability was seen among centers in the frequency of cases with either mutations (range 6%–37%, $P = 0.031$) and VUS (range 0%–17%, $P = 0.097$%); also the relative frequency of mutations vs. VUS varied among centers (data not shown). Most cases (81.0%) were affected by breast cancer (744 cases), and only 42 (4.6%) were free from cancer. In

Table 2
Main characteristics of index cases by clinical genetics center.

Clinic	Females				Males			BC	OC	BC & OC	Other cancers	Unaffected
	Total	Tot BRCA	BRCA1/2	VUS[a]	Total	Tot BRCA	BRCA1/2	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
	N (%)	*N* (%)	*N*/*N*	*N* (%)	*N*	*N*	*N*/*N*					
1	141	16 (11)	13/3	24 (17)	3	0	0	112 (78)	10 (7)	6 (4)	–	16 (11)
2	41	15[b] (37)	9/6	3 (7)	0	–	–	26 (63)	8 (20)	4 (10)	1 (2)	2 (5)
3	72	20 (28)	11/9	6 (8)	6	3	1/2	63 (81)	8 (10)	6 (8)	1 (1)	–
4	13	3 (23)	1/2	2 (15)	1	0	0	11 (79)	2 (14)	–	–	1 (7)
5	55	8 (15)	2/6	3 (6)	1	0	0	48 (86)	2 (4)	2 (4)	–	4 (7)
6	24	6[c] (29)	4/3[c]	1 (4)	3	1	0/1	22 (82)	4 (15)	–	1 (4)	–
7	73	15 (21)	8/7	8 (11)	4	0	0	61 (79)	1 (1)	4 (5)	–	11 (14)
8	14	4 (29)	4/0	–	2	0	0	10 (63)	2 (13)	3 (19)	–	1 (6)
9	18	1 (6)	1/0	2 (11)	1	1	0/1	15 (79)	–	1 (5)	–	3 (16)
10	50	12 (24)	8/4	1 (2)	1	1	0/1	47 (92)	1 (2)	3 (6)	–	–
11	88	15 (8)	7/8	9 (10)	2	0	0	73 (81)	8 (9)	6 (7)	1 (1)	2 (2)
12	128	23 (17)	14/9	16 (13)	3	0	0	114 (87)	10 (8)	6 (5)	1 (1)	–
13	12	1 (8)	1/0	–	1	0	0	11 (85)	0 (0)	–	–	2 (15)
14	58	12[d] (21)	10/2	2 (3)	0	0	0	50 (86)	3 (5)	5 (9)	–	–
15	99	22 (22)	11/11	12 (12)	4	0	0	81 (79)	14 (14)	8 (8)	–	–
Total	886	173 (20)	104/70	89 (10)	32	6	1/5	744[e] (81)	73[f] (8)	54[g] (6)	5[h] (0.5)	42 (5)

BC = breast cancer; OC = ovarian cancer.
[a] In addition VUS were detected in 3 male cases.
[b] In 8 cases with BRCA1 mutation BRCA2 gene testing was not performed.
[c] One case carried a mutation in both BRCA1 and BRCA2 genes.
[d] In 5 cases with BRCA1 mutation BRCA2 gene testing was not performed.
[e] 47 BC in situ.
[f] 8 OC borderline.
[g] 5 BC in situ, 1 BC in situ and OC borderline. 3 OC borderline.
[h] 1 thyroid, 1 brain, 1 melanoma, 1 colon rectum, 1 pancreas.

Table 3
Frequency of BRCA mutations according to the number of INTEF criteria present in the index case.

N. of INTEF criteria[a]	*N.* BRCA (%)	*N.* Total
0	6 (4.6)	129
1	49 (11.4)	428
Male BC (criterion 1)[b]	*1 (4)*	*25*
BC and OC in the same patient (criterion 2)	*7 (29)*	*24*
Female BC < 36 years with/without BC/OC family history (criterion 3)	*14 (11)*[c]	*126*[c]
BC < 50 years without OC (criteria 4, 5, 7)[d]	*9 (11)*	*81*[d]
BC ≥ 50 years without OC (criterion 9)	*8 (7)*	*123*
BC ≥ 50 years with OC (criterion 9)	*1 (13)*	*8*
≥1 OC with or without BC < 50 years or bilateral BC (criteria 6, 10, 11,14)[e]	*9 (24)*	*38*
2	34 (21.0)	162
3	37 (38.9)	95
4	26 (46.4)	56
≥5	27 (56.2)	48
Total	179 (19.5)	918

[a] Criteria 6 and 10 were considered a single criteria as they are specular.
[b] In the present series no case with criterion 8 or 13.
[c] 4 BRCA mutation (7%) were found in the 61 cases with female BC < 36 yrs without BC/OC family history.
[d] The 3 cases with criterion 4 including OC family history were not considered.
[e] In the present series no case with criterion 12.

the family branches suspected for HBOC the mean number of breast and ovarian cancer cases was 2.6 (±1.6) and 0.4 (±0.7), respectively, with a significant heterogeneity in the distribution among centers ($P < 0{,}0001$). A remarkable heterogeneity in the proportion of cases fulfilling at least one INTEF criterion (range 62%–98%, $P < 0.0001$) was observed among centers (Supplementary Table 1).

Performance of the evaluated tools

INTEF criteria

Of 918 cases, 789 (85.9%) fulfilled at least one INTEF criterion. The distribution of the number of INTEF criteria in the study population and the corresponding frequency of BRCA mutations are shown in Table 3. Mutation frequency increased with increasing number of criteria, from 11% (49/428) among cases with only one criterion, to 40–50% among those with 4 or more criteria. Overall, 173 of 179 BRCA mutations (96.6%) were found among women with at least one criterion, and 6 in 129 cases without INTEF criteria.

Genetic models

The total number of mutations predicted by BRCAPRO ($n = 185$) and BOADICEA ($n = 170$) were very similar to the 179 observed. When the goodness of fit of the two models was evaluated in the different carrier probability classes, statistically significant underprediction in the lowest and overprediction in the highest probability classes were observed (Table 4). The two models showed similar PPV for BRCA mutation, both at the 5% and 10% thresholds. At the 5% threshold, BRCAPRO selected 482 individuals that comprised 151 carriers (PPV = 31.3%) while BOADICEA selected 494 individuals that included 147 carriers (PPV = 29.7%). At the 10% threshold, the corresponding figures were 137 of 366 (PPV = 37.4%) and 136 of 361 (PPV = 37.7%). The two models showed also similar sensitivity. At the 5% threshold, 147 (82.1%) and 151 (84.3%) of 179 carriers were identified by BOADICEA and BRCAPRO, respectively and the corresponding figures at a 10% probability of mutation were 136 (76.0%) and 137 (76.5%). Similar results were obtained for the prediction of the presence of gene-specific mutation (data not shown).

Finally, we evaluated the discrimination ability of the two models (Fig. 1). The area under the curve for BRCA1 and BRCA2 mutations combined was 0.80 (0.76–0.84) for BRCAPRO and 0.79 (0.75–0.83) for BOADICEA; both BRCAPRO and BOADICEA models discriminated better for BRCA1 than for BRCA2 mutations.

Discussion

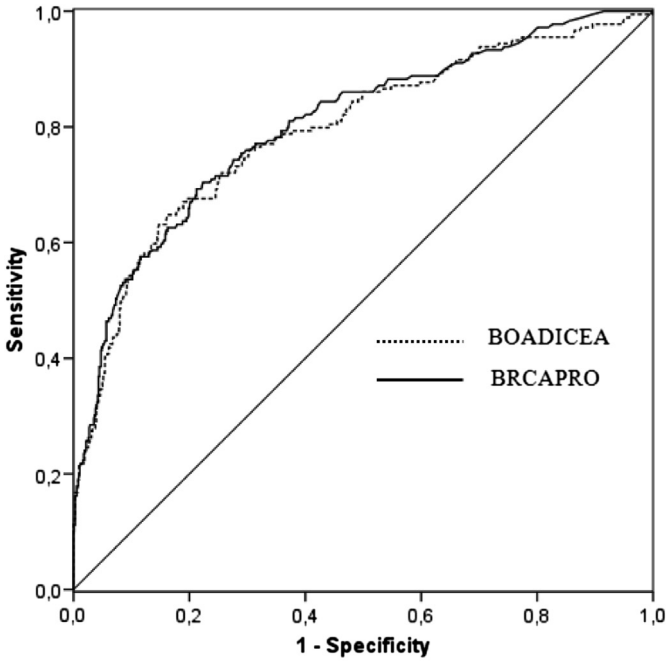
In this study we tried to assess the efficiency of the approaches used in common practice for referral for BRCA testing, and to evaluate the possible consequences deriving from a stringent use of risk assessment tools widely employed to this aim.

In total, of 918 tested individuals 179 (19.5%) were found to carry a BRCA mutation and 92 (10%) a BRCA VUS. This finding indicates that, overall, the selection process leading to offer genetic testing was efficient and in line with the international expert consensus [5]. However, a large variability was observed among the participating centers with regard to the characteristics of the tested population and to the results of genetic testing. For example, the frequency of tested individuals without any INTEF criterion ranged from 2% to 38% across centers, and the proportion of tests positive for a BRCA mutation varied accordingly, from 5% to 36%. This variability might be due to several reasons, including a) the heterogeneity of the populations referred to the clinics from which the geneticists selected the cases to test and b) the attitudes of professionals in uncertain situations (small family size, reported but not histologically confirmed ovarian cancer, etc).

Table 4
Observed and expected BRCA mutations in the predicted carrier probability classes of the BOADICEA and BRCAPRO models.

Probability	BOADICEA				χ^2_{1df}	BRCAPRO				
	Observed		Expected			Observed		Expected		
	No mutation	BRCA	No mutation	BRCA		No mutation	BRCA	No mutation	BRCA	χ^2_{1df}
<5	392	32	414.7	9.3	56.627[a]	408	28	428.2	7.8	53.759[a]
5–9.99	122	11	123.3	9.7	0.185	102	14	107.7	8.3	4.287
10–14.99	55	15	61.6	8.4	5.822[b]	49	10	51.8	7.2	1.256
15–19.99	38	4	34.8	7.2	1.742	33	11	36.4	7.6	1.776
20–29.99	39	13	39.4	12.6	0.017	43	11	40.3	13.7	0.701
30–39.99	31	14	29.2	15.8	0.321	31	9	25.9	14.1	2.854
40–49.99	12	14	14.4	11.6	0.890	22	9	16.9	14.1	3.415
≥50	50	76	30.2	95.8	17.005[a]	51	87	25.8	112.2	30.285[a]
Total	**739**	**179**	**747.6**	**170.4**	**0.527**	**739**	**179**	**733.0**	**185.0**	**0.242**

[a] $P < 0.0001$.
[b] $P < 0.01$.



Models	BRCA1 AUC (95% CI)	BRCA2 AUC (95% CI)	BRCA1-2 AUC (95% CI)
BOADICEA	0.84 (0.80-0.88)	0.71 (0.64-0.77)	0.79 (0.75-0.83)
BRCAPRO	0.87 (0.83-0.91)	0.72 (0.65-0.78)	0.80 (0.76-0.84)

Fig. 1. Receiver operator characteristic curves for BOADICEA, BRCAPRO models as predictors of an individual carrying a mutation in BRCA genes.

When we evaluated the performance in our study population, the good calibration of the two most commonly used BRCA risk assessment tools, BRCAPRO and BOADICEA, was confirmed [8]. However, the predictive power of the two models in low risk subgroups was very poor. For instance, in the group with a probability of mutation below 5% as estimated by BOADICEA, only 9 BRCA carriers were predicted while 32 were observed; the corresponding figure for BRCAPRO was 8 and 28, respectively. This finding confirms that genetic models underestimate the true proportion of positive tests at low mutation probabilities [6,7,15]. As a consequence, a strict use of commonly used probability thresholds would have caused the failure to identify a substantial proportion of the BRCA mutation carriers in the study population. At the conventional 10% mutation probability threshold, we would have avoided around 60% of the tests but we would have missed approximately 1 every 4 carriers. With the use of a more relaxed threshold, i.e. 5%, almost half of the tests could have been avoided but 1 every 6 carriers would have been missed. If confirmed, these findings would question the clinical use of current genetic models in cancer genetics clinics.

On the other hand, a strict use of clinical INTEF criteria would have produced marginal changes in comparison to what was actually observed: only 10–15% of the tests would have been avoided, and less than 5% of the BRCA carriers would have been missed. The discriminatory power of genetic models was similar to that of INTEF criteria, as for a given specificity, their sensitivity was superimposable.

Our study has several limitations. First, data were retrospectively collected from medical records and, therefore, are subjected to the bias inherent to the quality of available information that was not collected for a specific research purpose in a standardized fashion across centers. Heterogeneity in the quality of pedigree reconstruction and cancer cases documentation may, in various ways, impact on the results of the study (for example, genetic models take into account number and ages of healthy family members in the calculation of risk while empirical criteria consider only affected relatives). Second, information on the frequency of BRCA mutations in the entire population attending these clinics during the study period was not available since BRCA genetic testing was offered to selected individuals. To this regard, it must be underlined that the estimates of the sensitivity of the risk models in detecting BRCA mutations is strongly biased, in this and in similar studies. In fact, the denominator of the sensitivity should have been the total number of mutation carriers present in the population of women at intermediate familial risk undergone genetic counseling. Instead, the denominator used in the computations is the number of mutation carriers detected among those undergone BRCA testing. Since most carriers of a BRCA mutation with a low probability of carrying it (i.e. negative to the risk assessment tool) are not represented in this sample, the sensitivity of the risk assessment tools is overestimated. With a similar reasoning it can be shown that their specificity is underestimated. For these reasons, estimates of sensitivity and specificity and the performance of the ROC curves that are derived from their combination are useful only for the comparisons between risk assessment tools, while their absolute value is devoid of any meaning. Third, the study population was heterogeneous due to differences in the protocols for referral to BRCA genetic testing in the participating clinics and in the laboratory analytical methods of testing. However, this study provides a picture of the current practice in BRCA genetic testing in Italy, and possibly in most Western countries.

Recently a new version of BOADICEA that incorporates tumor pathology information (BOADICEA-Path) was validated in a large set of German families [16]. The study evaluated the performance of four models and showed that BOADICEA and BRCAPRO had significantly higher diagnostic accuracy than IBIS and CLAUS. In a subset of families a comparison among BOADICEA-Version2 and BOADICEA-Path was made. This allowed us to compare their data with ours for BOADICEA: at the conventional 10% BRCA mutation probability threshold, they would have avoided around 60% of the tests but they would have missed approximately 1 every 5 carriers, a figure somehow better than ours. The authors concluded that model calibration has to be improved.

BOADICEA and BRCAPRO models discriminate better BRCA1 than BRCA2 mutation carriers. This is probably due to the strongest association of BRCA1 mutation with ovarian cancer and triple-negative breast cancer risks.

In the future, little improvement in the predictive power of the models can be expected from country-customized versions [17], and the identification of novel BRCA mutation predictors, such as tissue-based predictors or functional tests, appears to be the only approach to substantially improve the efficiency of the selection of cases for BRCA testing.

For the moment, the answer to the question of whether women should be selected for BRCA testing using protocols based on risk evaluation tools and strict probability thresholds is a qualified no.

Of course, programs with a proactive approach including a structured triage system for the access to genetic counseling probably need to enforce rigid selection criteria based on probability thresholds, in order to contain costs, and to safeguard their feasibility and ethical sustainability. In different settings other factors, beside the mutation risk, need to be and are currently considered, including the personal motivation of the woman and the potential utility of test results for the family.

These considerations may be applicable in two different clinical settings: a) cancer genetics clinics characterized by a large proportion of consultations for suspected, but not outstanding, cancer family histories (nearly half of the cases in this study); b) centers involved in the treatment and follow-up of breast cancer cases, where the question about the heritability of the disease is frequently raised by concerned patients and their relatives.

Ethical approval

Informed consent to the use of data for research purposes had been provided by each index case during the counseling session, following the procedures dictated by the local Ethical Committees.

Conflict of interest statement

The author(s) indicated no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this chapter can be found at http://dx.doi.org/10.1016/j.breast.2013.07.053.

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