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Performance of BRCA1/2 mutation prediction models in male breast cancer patients


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To establish whether existing mutation prediction models can identify which male breast cancer (MBC) patients should be offered BRCA1 and BRCA2 diagnostic DNA screening, we compared the performance of BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), BRCAPRO (BRCA probability) and the Myriad prevalence table (“Myriad”). These models were evaluated using the family data of 307 Dutch MBC probands tested for BRCA1/2, 58 (19%) of whom were carriers. We compared the numbers of observed vs predicted carriers and assessed the Area Under the Receiver Operating Characteristic (ROC) Curve (AUC) for each model. BOADICEA predicted the total number of BRCA1/2 mutation carriers quite accurately (observed/predicted ratio: 0.94). When a cut-off of 10% and 20% prior probability was used, BRCAPRO showed a non-significant better performance (observed/predicted ratio BOADICEA: 0.81, 95% confidence interval [CI]: [0.60-1.09] and 0.79, 95% CI: [0.57-1.09], vs. BRCAPRO: 1.02, 95% CI: [0.75-1.38] and 0.94, 95% CI: [0.68-1.31], respectively). Myriad underestimated the number of carriers in up to 69% of the cases. BRCAPRO showed a non-significant, higher AUC than BOADICEA (0.798 vs 0.776). Myriad showed a significantly lower AUC (0.671). BRCAPRO and BOADICEA can efficiently identify MBC patients as BRCA1/2 mutation carriers. Besides their general applicability, these tools will be of particular value in countries with limited healthcare resources.

KEYWORDS
BOADICEA, BRCA1, BRCA2, BRCAPRO, male breast cancer, Myriad prevalence table
1 | INTRODUCTION

Female carriers of a mutation in *BRCA1* (OMIM* 113705) or *BRCA2* (OMIM* 600185) are at increased risk of developing breast and ovarian cancer and require specific clinical management such as extra surveillance and/or preventive surgery and strategies such as platinum-based therapy* or PARP inhibitors. The cumulative risk of breast cancer at age 70 for male carriers of a pathogenic *BRCA1* or *BRCA2* mutation is estimated to be 1.2% and 6.8%, respectively. Male carriers may also be at increased risk for other types of cancer such as prostate, colon and pancreatic cancer. Although some expert groups recommend that male carriers of a pathogenic mutation should undergo regular mammography in addition to surveillance for prostate cancer, the value of these surveillance strategies is still unproven. For these reasons, male mutation carriers generally do not receive extra surveillance and rarely undergo prophylactic mastectomy of the breasts. Nonetheless, it is of vital importance to determine whether a male breast cancer (MBC) patient is a carrier of a pathogenic *BRCA1*/*2* mutation. Not only is this important as a determinant of chemotherapy choices such as treatment with platinum* or PARP inhibitors, but also it provides the opportunity to identify other mutation carriers in the family through cascade screening, thus enabling prevention.

The NICE (National Institute for Health and Care Excellence) guideline proposes that genetic testing should be offered to female probands when the combined probability of being a *BRCA1* and *BRCA2* mutation carrier is 10% or higher. However, this guideline is more ambiguous when it comes to genetic testing for MBC patients. In the Netherlands, every male affected with breast cancer is offered *BRCA1*/2 testing regardless of age or family history. Previous studies have shown that 4%-40% of MBC patients carry mutations in one of the *BRCA* genes, with *BRCA2* mutations being the most common. This obviously means that *BRCA1*/2 account for only a minority of MBC patients, and thus many individuals are tested unnecessarily. As well as being cost-inefficient against a background of limited healthcare resources, testing may also lead to adverse psychological effects, as shown for female patients offered *BRCA1*/2 diagnostic testing.

Over the last 2 decades, various algorithms, tables and more sophisticated web-based tools have been developed to calculate the prior probability of *BRCA1* or *BRCA2* mutation carriership. The performance of these models has generally been evaluated in mostly female probands with various ethnic backgrounds. We now wish to establish whether these models can also accurately select MBC probands for DNA testing. To date, this question has only been addressed in 2 small studies. In 2010, Zanna et al evaluated the discriminatory capacity of the Myriad prevalence table (*"Myriad"*), the Ontario Family History Assessment Tool (FHAT), BRCAPRO (*BRCA* probability) 4.0 and 5.0 and the Italian Consortium (IC) model in a cohort of 102 MBC cases from Tuscany, Italy. They found that BRCAPRO 5.0 showed the best combination of sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for combined *BRCA1*/2 probability. BRCAPRO 5.0 was also superior in the discrimination of *BRCA2* mutations and it was especially useful in dealing with non-familial MBC patients. More recently, Mitri et al studied the accuracy of BRCAPRO 6.0 in 146 MBC cases. They concluded that BRCAPRO is a useful aid in selecting MBC cases for mutation analysis. Both studies only evaluated the discriminatory ability of the models.

In this study, Myriad, BRCAPRO 6.0 (CaGene6) and BOADICEA 3.0 (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) were chosen for evaluation due to their ability to calculate the mutation prediction probability for an affected male proband, the frequent (international) use of these tools in both clinical and research settings, and their free availability. The internationally known International Breast Cancer Intervention Study (IBIS) model was not used in this study because in IBIS the index case can only be female.

Including 307 Dutch MBC patients under the age of 80 years, to the best of our knowledge, the present study is the largest and the only nationwide study to evaluate the predictive accuracy of several different mutation carrier probability models. In addition, BOADICEA has not yet been validated in a population of MBC patients. The aim of this study was to evaluate the diagnostic accuracy of these models by investigating and comparing their discriminatory ability and calibration within a population of MBC patients. We were interested to know whether these models can accurately predict mutations in MBC individuals and thus increase diagnostic yield, opening the way to their use in the selection of MBC cases for DNA testing in a clinical setting.
2 | MATERIALS AND METHODS

2.1 | Families

All MBC patients who were diagnosed in the Netherlands between 1989 and 2009 (n = 1487) were identified via the Dutch National Cancer Registry. Affected males who had been referred for genetic testing of BRCA1 and BRCA2 to 1 of the 9 genetic cancer centres in the Netherlands were then used for this study (N = 364). The pedigrees and results of genetic testing were collected from the Amsterdam Medical Centre (AMC, n = 14), Erasmus Medical Centre (EMC, n = 37), Leiden University Medical Centre (LUMC, n = 40), Maastricht University Medical Centre (MUMC, n = 30), Dutch Cancer Institute (NKI, n = 28), Radboud University Medical Centre (RadboudUMC, n = 77), University Medical Centre Groningen (UMCG, n = 61), University Medical Centre Utrecht (UMCU, n = 44) and VU University Medical Centre (VUMC, n = 33). From these families, 57 patients were excluded from the study for the following reasons: disease or mutation status or pedigree unavailable (n = 23), the proband was diagnosed with Ductal carcinoma in situ (n = 1), probands were carriers of a class 2 or 3 variant of uncertain significance (VUS). According to the International Agency for Research on Cancer (IARC) classification they had a posterior probability of pathogenicity between 0.1% and 94.9%30 (n = 6). The age at diagnosis of breast cancer in the proband was above 80 years (cancer diagnoses that occur after 80 years of age are not included in BOADICEA because of a lack of data to constrain the model) (n = 18). Nine pedigrees were known in 2 different cancer genetic centres, so each was included only once.

A final total of 307 cases were included. The proband was always a male and affected with at least breast cancer. In total 364 of 1487 families (24%) had undergone a DNA test. Table S1, in the Supporting Information, shows how many probands were tested every year. Data quality control and imputation rules for missing data are described in Supporting Information. The collection of data was approved by local ethics committees.

2.2 | Mutation testing

BRCA1 and BRCA2 mutation analysis was performed at the various cancer genetics centres in the Netherlands. Diverse mutation screening methods such as denaturing gradient gel electrophoresis, high-resolution melting curve analysis, Sanger sequencing and/or multiplex ligation-dependent probe amplification were used, followed by confirmation of aberrant samples by Sanger sequencing. Variant classification was performed by the molecular clinical geneticists at the time of the genetic testing, according to internationally recognized criteria (https://enigmaconsortium.org/wp-content/uploads/2016/06/ENIGMA_Rules_2015-03-26.pdf, accessed April 2017 and the Breast cancer core database https://research.nhgri.nih.gov/bic/, accessed April 2017). VUS were re-evaluated for the present study and the 6 probands who were carriers of a VUS were excluded from the study (Clinvar database: [https://www.ncbi.nlm.nih.gov/clinvar/], accessed April 2017 and LOVD database: [http://databases.lovd.nl/shared/variants], accessed April 2017).30,31

2.3 | Risk prediction models

The BOADICEA model assumes that genetic susceptibility to breast cancer is due to BRCA1 and BRCA2 mutations but also takes a polygenic component into account.5,10,32 This algorithm allows predicted mutation probabilities and cancer risks in individuals to be estimated. Apart from first and second breast and ovarian cancer, it also includes prostate and pancreatic cancer in the calculations.33 BRCAPRO is a comparable model which, taking into account family history, calculates the likelihood of carrying a BRCA1 or BRCA2 gene mutation.34 In this study, we used BOADICEA version 3.0 and BRCAPRO 6.0 (CaGene6). The Myriad tables provide the combined probability of detecting a BRCA1 and BRCA2 mutation in counselees.29 In contrast to BOADICEA and BRCAPRO which both provide a continuous number for the probability of finding a mutation, probabilities in Myriad for MBC are stratified into specific groups, namely 6.9%, 15.9%, 17.4%, 28.3%, 33.3% and 36.6%.35 The probabilities in these tables are based on the observation of deleterious mutations in the counselees tested by Myriad Genetics Laboratories. We used the latest version of the tables, which was updated in February 2010 and is based on 162 914 tests.35 The probability that a mutation remained undetected due to limitations of the sequencing technology was taken into account in the analysis. During the first years of BRCA1/2 screening and up to 2007, a very restricted mutation screening took place. The average mutation screening sensitivity increased when modern sequencing technology became available. The mutation screening sensitivity was assumed to be 95% for all those screened at and after 2007. For the tests performed before 2007, we used mutation search sensitivities of 0.7 for BRCA1 and 0.8 for BRCA2.20

2.4 | Statistical evaluation

We evaluated the calibration and discrimination of the risk prediction models. Calibration tests whether BOADICEA, BRCAPRO and Myriad can accurately predict the total number of BRCA1 and BRCA2 mutation carriers in the sample set. The calibration of these models was tested in the whole cohort for different categories of predicted mutation carrier probabilities. To compute the number of mutations predicted under these models, we averaged the probabilities of detecting a BRCA1/2 mutation across all families in each category and then calculated the number of predicted mutation carriers (the predicted or expected number). Categories with carrier probability >20% were grouped together because the groups were small. These were compared with the actual number of mutations detected (the observed number) by calculating the observed/expected (predicted) ratio (O/E ratio). The exact 95% confidence intervals (CI) for the O/E were calculated under a Poisson assumption for the number of observed mutations.36,37 Discrimination is the ability of the model to distinguish between a mutation carrier and a non-carrier at the individual level. This was assessed using the Area Under the Receiver Operating Characteristic (ROC) Curve (AUC). Confidence intervals and tests for comparing AUCs were based on the DeLong et al38 method. Furthermore, we compared the sensitivity, specificity, NPV and PPV of the models at 10% and 20% carrier probability thresholds.
3 | RESULTS

Table 1 shows the characteristics of the 307 probands and families. Almost 19% of the patients were carrier of either a BRCA1 (2.9%) or a BRCA2 (16%) mutation. The average age of the onset of breast cancer among male carriers was 59.83 years.

3.1 | Calibration

The observed and predicted total number of mutations in each gene is shown in Table 2. The calibration of BOADICEA in terms of total number of mutations was better than the other models. Overall, 58 probands were carriers of a pathogenic mutation, whereas BOADICEA predicted 62 mutations (O/E: 0.94, 95% CI: [0.73-1.22]). BOADICEA predicted 5 BRCA1 and 57 BRCA2 mutation carriers compared with 9 and 49 observed, respectively (O/E ratio for BRCA1: 1.91, 95% CI: [0.99-3.66] and O/E ratio for BRCA2: 0.86, 95% CI: [0.65-1.14]). For BRCAPRO, the total number of predicted mutations was lower than observed (58 observed vs 48 predicted, O/E: 1.20, 95% CI: [0.93-1.56]). BRCAPRO predicted 8 BRCA1 and 40 BRCA2 mutation carriers among probands compared with 9 and 49 observed, respectively (O/E ratio for BRCA1:1.16, 95% CI: [0.61-2.24] and O/E ratio for BRCA2: 0.86, 95% CI: [0.65-1.14]).

### Table 1 Characteristics of the 307 probands and families

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Carriers number (% or mean per family)</th>
<th>Non-carriers number (% or mean per family)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probands</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrier of a BRCA1 or BRCA2 mutation</td>
<td>58/307 (18.9%) BRCA1: 9 (2.9%) BRCA2: 49 (16%)</td>
<td>249/307 (81%)</td>
</tr>
<tr>
<td>Unilateral breast cancer</td>
<td>58 (100%)</td>
<td>249 (100%)</td>
</tr>
<tr>
<td>Bilateral breast cancer</td>
<td>5 (8.6%)</td>
<td>8 (3.2%)</td>
</tr>
<tr>
<td>Breast cancer and prostate cancer</td>
<td>2 (3.4%)</td>
<td>14 (5.6%)</td>
</tr>
<tr>
<td>Average age of onset of breast cancer</td>
<td>59.83 y</td>
<td>60.09 y</td>
</tr>
<tr>
<td><strong>Families</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral breast cancer in family</td>
<td>202 (3.4%)</td>
<td>567 (2.28%)</td>
</tr>
<tr>
<td>Breast cancer and prostate cancer in family</td>
<td>24 (0.41)</td>
<td>30 (0.12)</td>
</tr>
<tr>
<td>Only prostate cancer</td>
<td>11 (0.19)</td>
<td>27 (0.11)</td>
</tr>
<tr>
<td>Breast cancer and ovarian cancer in family</td>
<td>0</td>
<td>2 (0.008)</td>
</tr>
<tr>
<td>Only ovarian cancer</td>
<td>11 (0.19)</td>
<td>13 (0.05)</td>
</tr>
</tbody>
</table>

### Table 2 Observed and expected number of mutations by predicted carrier probability

<table>
<thead>
<tr>
<th>Model</th>
<th>Carrier probability (%)a</th>
<th>Observed, n</th>
<th>Expected, n</th>
<th>O/Eb</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No mutation</td>
<td>BRCA1</td>
<td>BRCA2</td>
<td>Either</td>
<td>No mutation</td>
</tr>
<tr>
<td>BOADICEA</td>
<td>&lt;5</td>
<td>97</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>5-10</td>
<td>56</td>
<td>2</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>10-15</td>
<td>35</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>15-20</td>
<td>12</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>49</td>
<td>7</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>249</td>
<td>9</td>
<td>49</td>
<td>58</td>
</tr>
<tr>
<td>BRCAPRO</td>
<td>&lt;5</td>
<td>148</td>
<td>2</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>5-10</td>
<td>51</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>10-15</td>
<td>15</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>15-20</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>28</td>
<td>7</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>249</td>
<td>9</td>
<td>49</td>
<td>58</td>
</tr>
<tr>
<td>Myriad</td>
<td>&lt;5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5-10</td>
<td>193</td>
<td>3</td>
<td>23</td>
<td>26</td>
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<tr>
<td></td>
<td>10-15</td>
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<td>0</td>
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<tr>
<td></td>
<td>15-20</td>
<td>44</td>
<td>1</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>12</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>249</td>
<td>9</td>
<td>49</td>
<td>58</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available.

a Classes of carrier probability calculated with the respective model.
b Observed/expected (O/E) ratio, observed number of mutation carriers divided by number of mutation carriers expected according to the respective model.
c The 95% Confidence Interval (CI) for O/E does not include 1.
ratio for $BRCA_2$: 1.21, 95% CI: [0.92-1.60]). In none of the cases the difference between O/E ratios was significant. The Myriad tables provide a combined probability of detecting a $BRCA_1$ or $BRCA_2$ mutation and underestimated the total number of mutations (58 observed vs 34 predicted, O/E: 1.69, CI: [1.30-2.18]).

### 3.2 | Discrimination

ROCs are presented in Figure 1 for (A) BOADICEA $BRCA_1/2$, BRCPRO $BRCA_1/2$ and Myriad $BRCA_1/2$, (B) BOADICEA $BRCA_1$ and BRCPRO $BRCA_1$ (C) BOADICEA $BRCA_2$ and BRCPRO $BRCA_2$. Corresponding AUCs, or the likelihood that a mutation carrier will score higher than a non-carrier, are reported in Table 3. A value of 0.5 suggests that the test is no better than tossing a coin and a value of 1 indicates perfect discriminatory power. The AUC for BOADICEA was 0.776 (95% CI: [0.708-0.845]), for BRCPRO it was 0.798 (95% CI: [0.726-0.871]), and for Myriad it was 0.671 (95% CI: [0.599-0.743]), the latter being significantly lower than the AUCs for BOADICEA and BRCPRO ($P$-value $= .0072$ for comparison for AUCs of Myriad and BOADICEA, $P$-value $= .00029$ for comparison for AUCs of Myriad and BRCPRO). When predicting $BRCA_1$ or $BRCA_2$ mutations separately, BOADICEA and BRCPRO both showed better discrimination for $BRCA_1$ than for $BRCA_2$ (Table 3). Table 4 shows the performance of the different models at a carrier probability of 10% and 20% for BOADICEA and BRCPRO and the equivalent threshold score of 6.9 and 17.4 for Myriad. At a 10% threshold, BOADICEA showed the highest sensitivity (77.2%) and the lowest specificity (80.3%). At 10% threshold for $BRCA_1$, BOADICEA had a lower sensitivity compared to BRCPRO (33.3% vs 55.5%, respectively), however, specificities were comparable (98.7 vs 97.0). At 10% threshold for $BRCA_2$, sensitivity of BOADICEA was higher than sensitivity of BRCPRO (75.0% vs 72.9%) while its specificity was lower (61.2% vs 79.4%). Both models had a lower sensitivity and higher specificity for $BRCA_1$ compared to $BRCA_2$.

### 4 | DISCUSSION

Using a cohort consisting of 307 MBC cases assembled from 9 genetic counselling centres, this is the largest study to date to evaluate the performance of the 3 most commonly used mutation prediction models, BOADICEA, BRCPRO and Myriad, in the estimation of $BRCA_1$ and $BRCA_2$ mutation-carrier probabilities in MBC patients. We also provide the first validation of the use of BOADICEA in MBC patients. In contrast to previous studies, we not only studied discrimination but also examined calibration of the prediction models.

The reported prevalence of $BRCA_1/2$ mutations in MBC patients varies considerably between different populations and cancer genetic centres, ranging from 4% to 40% for $BRCA_2$ and up to 4% for $BRCA_1$ genes. Our study found that about 19% (58/307) of all MBC patients actually carry a $BRCA$ mutation. In the Netherlands all affected male individuals are currently offered $BRCA_1/2$ screening. As testing all patients might cause unnecessary additional distress in patients and relatives, a tool that can accurately determine the prior probability of MBC mutation carriers would therefore be of great clinical value. Moreover, testing all patients at the moment is cost-
inefficient, given limited healthcare resources, especially in non-western countries. However, we acknowledge that, regarding the price and availability of population-wide gene panel testing, we might soon be at the stage where it is actually cost-effective to screen all patients.

Every MBC patient in our study who was referred to a cancer genetics centre was offered a DNA test, regardless of family history or the prior probability of being a carrier. However, many of the originally identified MBC patients (n = 1487, diagnosed between 1989 and 2009) were not referred to cancer genetics centres, primarily because BRCA1/2 testing was only implemented in clinical practice in the late 1990’s. At that time some clinicians were either unaware of the possibility of BRCA1/2 testing of male patients or had a different pattern of referral criteria. It is also possible that in the early years, clinicians only referred patients with a strong family history or younger age at diagnosis. The average age for the 307 patients who were referred is significantly lower than those who were not referred (60.04 vs 68.06, P-value< .0009). Table S1 shows that the number of BRCA1/2 screenings has increased in recent years. It also shows that genetic tests were performed in some men several years after their diagnosis. Studies of the pathological features of BRCA1/2 MBC tumours showed that these tumours display distinct characteristics compared with BRCA1/2 female breast cancer tumours (eg, high histologic grade in BRCA2 MBC patients), which suggested greater biological aggressiveness. Although it is not directly proven for MBC caused by BRCA1/2 mutations, it might be the case that some patients in this specific group were not tested because they did not survive the disease. These factors partly explain why only 364 probands among the 1487 MBC patients actually received a DNA test, and the relatively high percentage of mutation carriers reported in the study (19%). Although this study is the largest study to date performed for prediction of mutation carrier probability in MBC patients, it is still a small cohort. The number of patients has limited the power of this study and as a result, in many cases, the differences are not significant.

### 4.1 | Calibration

In our cohort, BOADICEA showed the best calibration for the overall number of BRCA1 and BRCA2 mutations. When a cut-off of 10% and 20% prior probability was used, BRCAPRO showed a non-significant better performance (observed/predicted ratio BOADICEA: 0.81, 95% CI: [0.60-1.09] and 0.79, 95% CI: [0.57-1.09], vs BRCAPRO: 1.02, 95% CI: [0.75-1.38] and 0.94, 95% CI: [0.68-1.31], respectively).

### 4.2 | Discrimination

BOADICEA and BRCAPRO both showed good discrimination of mutation carriers vs non-carriers, whereas Myriad had a significantly lower AUC. Both BOADICEA and BRCAPRO showed better AUCs for BRCA1 than for BRCA2, these differences did not, however, reach statistical significance (P-value = .2187 for comparison of AUCs of BOADICEA, P-value = .3075 for comparison of AUCs of BRCAPRO). As BOADICEA and BRCAPRO were developed for female patients it seems likely that several factors included in these models result in better prediction of BRCA1 mutations. For example, BRCA1 mutations are associated with a higher ovarian cancer risk compared to BRCA2 mutations, and with an earlier age at diagnosis of breast cancer. As expected, the number of BRCA1 mutations observed in our cohort was much lower than the number of BRCA2 mutations (9 vs 49, respectively). This resulted in wide CIs for BRCA1 in both BOADICEA and BRCAPRO (Table 3). Nonetheless, both models showed good discrimination of BRCA1 and BRCA2 carriers and non-carriers, although discrimination of carriers of either mutation and of non-carriers is of limited utility in clinical practice because the overall carrier probability determines the decision to screen for mutations. Nevertheless, while probands are always tested simultaneously for BRCA1 and BRCA2 mutations in the Netherlands, the accurate discrimination of BRCA1 and BRCA2 carriers may be of considerable importance in countries with fewer financial resources.
In contrast to the Myriad prevalence data, BOADICEA and BRCAPRO both appear to be well calibrated and show a high discriminatory power to identify male BRCA1/2 mutation carriers. However, both models could still be improved. At the time of this study, estimates of BRCA1 and BRCA2 mutation frequencies based on a large Dutch series were unavailable and there were no specific penetrance estimates for cancers affecting sites other than the breast, so none of the models included incidence rates for Dutch population. We presume that incorporating data on Dutch incidences into the models would improve their accuracy in the present cohort.

Furthermore, the inclusion of other genetic and non-genetic risk factors known to be important in MBC such as radiation exposure, alcohol use, obesity, hormonal imbalances, disease and medical treatments leading to hyperestrogenism might also improve the accuracy of these models.

5 | CONCLUSION

In the largest cohort of MBC cases studied to date, we found that BOADICEA and BRCAPRO both showed good discriminatory ability for male BRCA1/2 carriers. In terms of total number of carriers, BOADICEA showed the best calibration, and BRCAPRO displayed a non-significant better fit when a mutation probability threshold of 10% or 20% was used. Myriad tables showed a significantly lower calibration and discrimination compared to the two other models.

Both BOADICEA and BRCAPRO are valuable tools when deciding whether to offer BRCA1 and BRCA2 DNA mutation screening to MBC patients and will be of considerable value in countries with limited healthcare resources that cannot offer testing to all MBC patients. However, both models could potentially be improved through the incorporation of population-specific parameters and risk factors for MBC.

BOADICEA is currently the first choice for calculation of mutation carrier probability in many countries and the developers are planning to include other breast cancer-related genes such as PALB2 (OMIM* 610355) and CHEK2 (OMIM* 604373), breast cancer-associated Single Nucleotide Polymorphism (SNPs), and environmental factors and risks in the algorithm. A model that incorporates additional MBC-related factors in a user-friendly tool will eventually be the preferred choice for the calculation of the mutation carrier probability in MBC patients.

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Conflict of interest

Nothing to declare.

REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.