


ORIGINAL ARTICLE

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

S. Moghadasi¹  | V. Grundeken¹ | L.A.M. Janssen¹ | N.H. Dijkstra² | M. Rodríguez-Girondo³ | W.A.G. van Zelst-Stams⁴ | J.C. Oosterwijk⁵ | M.G.E.M. Ausems⁶ | R.A. Oldenburg⁷ | M.A. Adank⁸ | E.W. Blom⁹ | M.W.G. Ruijs¹⁰ | T.A.M. van Os¹¹ | C.H.M. van Deurzen¹² | J.W.M. Martens¹³ | C.P. Schroder¹⁴ | J.T. Wijnen^{1,15} | M.P.G. Vreeswijk¹⁵ | C.J. van Asperen¹

¹Department of Clinical Genetics, Leiden University Medical Centre, Leiden, the Netherlands

²Dutch Breast Cancer Research Group, Amsterdam, the Netherlands

³Department of Medical Statistics and Bioinformatics, Leiden University Medical Centre, Leiden, the Netherlands

⁴Department of Human Genetics, Radboud University Medical Centre, Nijmegen, the Netherlands

⁵Department of Genetics, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

⁶Department of Genetics, University Medical Centre, Utrecht, the Netherlands

⁷Department of Clinical Genetics, Erasmus Medical Centre, Rotterdam, the Netherlands

⁸Department of Clinical Genetics, VU University Medical Centre, Amsterdam, the Netherlands

⁹Department Clinical Genetics, Maastricht University Medical Centre, Maastricht, the Netherlands

¹⁰Department of Clinical Genetics, the Netherlands Cancer Institute, Amsterdam, the Netherlands

¹¹Department of Clinical Genetics, Academic Medical Centre, Amsterdam, the Netherlands

¹²Department of Pathology, Erasmus Medical Centre, Rotterdam, the Netherlands

¹³Department of Medical Oncology, Erasmus Medical Centre, Rotterdam, the Netherlands

¹⁴Department of Medical Oncology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

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

¹⁵Department of Human Genetics, Leiden University Medical Centre, Leiden, the Netherlands

Correspondence

Prof Christi J. van Asperen, Department of Clinical Genetics, Leiden University Medical Centre, PO Box 9600, 2300 RC, Leiden, the Netherlands.

Email: Asperen@lumc.nl

Funding information

the Netherlands Organization for Scientific Research (NWO), Grant/Award number: 017.008.022; Leiden University Medical Centre, Grant/Award number: 30.925; Leids Universiteits Fonds, Grant/Award number: LUF 3274/7-11-13\K LUF 3274/7-11-13\K, NZ; Simonsfonds, Grant/Award number: 1074.

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 therapy¹ or PARP inhibitors.²

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.³ Male carriers may also be at increased risk for other types of cancer such as prostate, colon and pancreatic cancer.^{4,5} 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.⁶ 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 platinum¹ or PARP inhibitors,² 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.⁷ 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.⁸ 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.⁹

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.¹⁰⁻¹³

The performance of these models has generally been evaluated in mostly female probands with various ethnic backgrounds.¹⁴⁻²⁶ 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 al²⁷ 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 al²⁸ 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,²⁹ 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) model¹² 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 counsees.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 counsees 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.

TABLE 1 Characteristics of the 307 probands and families

	Characteristics	Carriers number (% or mean per family)	Non-carriers number (% or mean per family)
Probands	Carrier of a <i>BRCA1</i> or <i>BRCA2</i> mutation	58/307 (18.9%) <i>BRCA1</i> : 9 (2.9%) <i>BRCA2</i> : 49 (16%)	249/307 (81%)
	Unilateral breast cancer	58 (100%)	249 (100%)
	Bilateral breast cancer	5 (8.6%)	8 (3.2%)
	Breast cancer and prostate cancer	2 (3.4%)	14 (5.6%)
	Average age of onset of breast cancer	59.83 y	60.09 y
Families	Unilateral breast cancer in family including proband	202 (3.48)	567 (2.28)
	Bilateral breast cancer in family including proband	24 (0.41)	30 (0.12)
	Breast cancer and prostate cancer in family including proband	3 (0.05)	41 (0.16)
	Only prostate cancer	11 (0.19)	27 (0.11)
	Breast cancer and ovarian cancer in family	0	2 (0.008)
	Only ovarian cancer	11 (0.19)	13 (0.05)

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

TABLE 2 Observed and expected number of mutations by predicted carrier probability

Model	Carrier probability (%) ^a	Observed, <i>n</i>				Expected, <i>n</i>				O/E ^b	95% Confidence Interval
		No mutation	<i>BRCA1</i>	<i>BRCA2</i>	Either	No mutation	<i>BRCA1</i>	<i>BRCA2</i>	Either		
BOADICEA	<5	97	0	6	6	100.31	0.14	2.56	2.69	2.23	1.001-4.96 ^c
	5-10	56	2	6	8	59.25	0.23	4.53	4.75	1.68	0.84-3.36
	10-15	35	0	2	2	32.43	0.15	4.42	4.57	0.44	0.11-1.75
	15-20	12	0	5	5	14.12	0.14	2.74	2.88	1.74	0.72-4.17
	>20	49	7	30	37	39.25	4.07	42.68	46.75	0.79	0.57-1.09
	Total		249	9	49	58	245.36	4.72	56.91	61.64	0.94
BRCAPRO	<5	148	2	9	11	155.98	0.30	2.72	3.02	3.65	2.02-6.58 ^c
	5-10	51	0	5	5	52.02	0.37	3.61	3.98	1.26	0.52-3.02
	10-15	15	0	5	5	17.52	0.21	2.27	2.48	2.02	0.84-4.85
	15-20	7	0	2	2	7.45	0.15	1.40	1.55	1.29	0.32-5.17
	>20	28	7	28	35	25.86	6.69	30.45	37.14	0.94	0.68-1.31
	Total		249	9	49	58	258.83	7.72	40.44	48.17	1.20
Myriad	<5	0	0	0	0	0	NA	NA	0	NA	NA
	5-10	193	3	23	26	203.89	NA	NA	15.11	1.72	1.17-2.53 ^c
	10-15	0	0	0	0	0	NA	NA	0	NA	NA
	15-20	44	1	18	19	52.16	NA	NA	10.84	1.75	11.12-2.75 ^c
	>20	12	5	8	13	16.60	0	0	8.40	1.55	0.90-2.67
	Total		249	9	49	58	272.64	NA	NA	34.36	1.69

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.

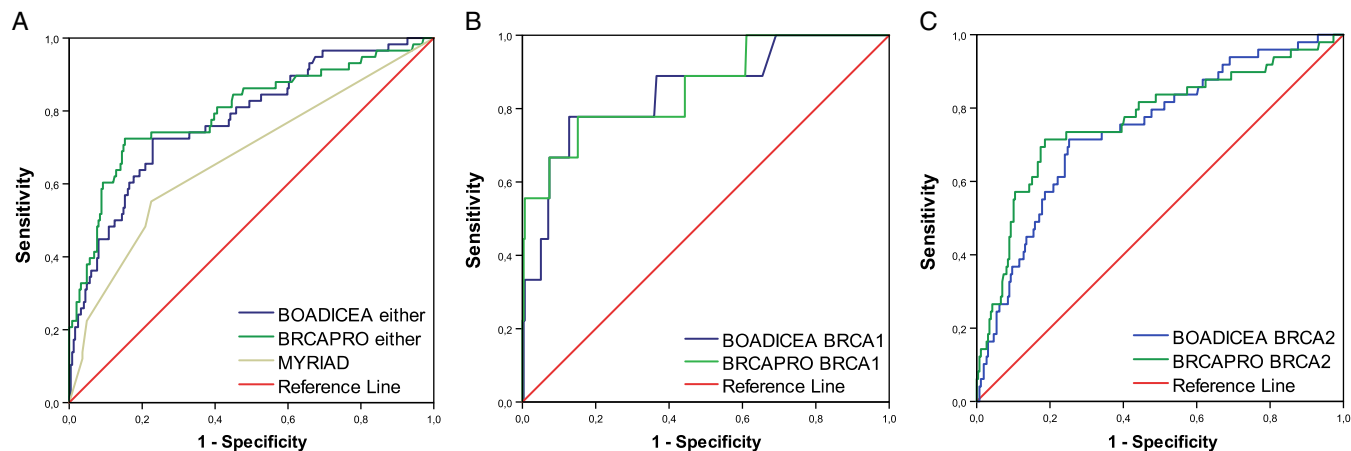


FIGURE 1 Receiver operating characteristic (ROC) curves. Receiver operator characteristic curves for (A) BOADICEA *BRCA1/2*, BRCAPRO *BRCA1/2* and Myriad *BRCA1/2*, (B) BOADICEA *BRCA1* and BRCAPRO *BRCA1* (C), BOADICEA *BRCA2* and BRCAPRO *BRCA2*, all at 10% cut-off

TABLE 3 Area under the ROC curve for each model

Model	ROC area (95% confidence interval)		
	Either <i>BRCA1</i> or <i>BRCA2</i>	<i>BRCA1</i>	<i>BRCA2</i>
BOADICEA	0.776 (0.708-0.845)	0.848 (0.700-0.996)	0.743 (0.667-0.819)
BRCAPRO	0.798 (0.726-0.871)	0.857 (0.708-0.999)	0.768 (0.687-0.849)
Myriad	0.671 (0.599-0.743)	NA	NA

Abbreviations: NA, not available; ROC curve, receiver operating characteristic curve.

ratio for *BRCA2*: 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 *BRCA1* or *BRCA2* 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 *BRCA1/2*, BRCAPRO *BRCA1/2* and Myriad *BRCA1/2*, (B) BOADICEA *BRCA1* and BRCAPRO *BRCA1*, and (C) BOADICEA *BRCA2* and BRCAPRO *BRCA2*. 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 BRCAPRO 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 BRCAPRO (P -value = .0072 for comparison for AUCs of Myriad and BOADICEA, P -value = .00029 for comparison for AUCs of Myriad and BRCAPRO). When predicting *BRCA1* or *BRCA2* mutations separately, BOADICEA and BRCAPRO both showed better discrimination for *BRCA1* than for *BRCA2* (Table 3). Table 4 shows the performance of the different models at a carrier probability of 10% and 20% for BOADICEA and BRCAPRO 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 (61.4%) for *BRCA1* and *BRCA2* combined. At a 20% threshold, BOADICEA again had the highest sensitivity (64.9%) and the lowest

specificity (80.3%). At 10% threshold for *BRCA1*, BOADICEA had a lower sensitivity compared to BRCAPRO (33.3% vs 55.5%, respectively), however, specificities were comparable (98.7 vs 97.0). At 10% threshold for *BRCA2*, sensitivity of BOADICEA was higher than sensitivity of BRCAPRO (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 *BRCA1* compared to *BRCA2*.

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, BRCAPRO and Myriad, in the estimation of *BRCA1* and *BRCA2* 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 *BRCA1/2* mutations in MBC patients varies considerably between different populations and cancer genetic centres, ranging from 4% to 40% for *BRCA2* and up to 4% for *BRCA1* genes.⁸ 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 *BRCA1/2* 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-

TABLE 4 Diagnostic performance of BOADICEA, BRCAPRO and Myriad at different threshold levels

Outcome	Cut-off	Model	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
BRCA1	10%	BOADICEA	33.3	98.7	42.9	98.0
		BRCAPRO	55.5	97.0	35.7	98.6
		Myriad	NA	NA	NA	NA
BRCA2	10%	BOADICEA	75.0	61.2	26.4	92.9
		BRCAPRO	72.9	79.4	39.7	94.0
		Myriad	NA	NA	NA	NA
Either BRCA1 or BRCA2	10%	BOADICEA	77.2	61.4	31.4	92.1
		BRCAPRO	73.7	79.9	45.7	93.0
		Myriad (6.9)	54.4	77.5	35.6	88.1
Either BRCA1 or BRCA2	20%	BOADICEA	64.9	80.3	43.0	90.9
		BRCAPRO	61.4	88.8	55.6	90.9
		Myriad (17.4)	22.8	95.2	52.0	84.3

Abbreviation: NA: not available.

Outcome calculated for total and 10% and 20% threshold and equivalent threshold score of 6.9 and 17.4 for Myriad, for BRCA1 or BRCA2 separately if available, or for both genes.

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.^{39,40} 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.⁴¹ 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.⁸

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 countries⁴² and the developers are planning to include other breast cancer-related genes such as *PALB2* (OMIM* 610355) and *CHEK2* (OMIM⁺ 604373),⁴³ 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.

ACKNOWLEDGEMENTS

We thank Medactie for help with editing of the article. We thank Petra J.M. van Hees for helping develop the database of MBC cases who underwent a *BRCA1/2* test and Anne Pagan for drawing part of the pedigrees in BRCAPRO and checking the drawn pedigrees in BOADICEA and BRCAPRO. This work is part of the research programme Mosaic, which is financed by the Netherlands Organization for Scientific Research (NWO) (Grant 017.008.022), the Van de Kampfonds from Leiden University Medical Centre (Grant 30.925), the Leids Universiteits Fonds (Grant LUF 3274/7-11-13\K, NZ) and the Simonsfonds (Grant 1074).

Conflict of interest

Nothing to declare.

REFERENCES

- Zhang J, Wang Z, Hu X, et al. Cisplatin and gemcitabine as the first line therapy in metastatic triple negative breast cancer. *Int J Cancer*. 2015;136(1):204-211.
- Lee JM, Ledermann JA, Kohn EC. PARP inhibitors for *BRCA1/2* mutation-associated and *BRCA*-like malignancies. *Ann Oncol*. 2014;25(1):32-40.
- Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male *BRCA1* and *BRCA2* mutation carriers. *J Natl Cancer Inst*. 2007;99(23):1811-1814.
- van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in *BRCA2* families: estimates for sites other than breast and ovary. *J Med Genet*. 2005;42:711-719.
- Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. *Br J Cancer*. 2008;98(8):1457-1466.
- NIH, National cancer institute. <http://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet>. Accessed by April 2017.
- National Institute for Health and Care Excellence (NICE). <http://www.nice.org.uk/>. Accessed by April 2017.
- Ottini L, Palli D, Rizzo S, et al. Male breast cancer. *Crit Rev Oncol Hematol*. 2010;73(2):141-155.
- Hamilton JG, Lobel M, Moyer A. Emotional distress following genetic testing for hereditary breast and ovarian cancer: a meta-analytic review. *Health Psychol*. 2009;28(4):510-518.
- Antoniou AC, Pharoah PP, Smith P, Easton DF. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. *Br J Cancer*. 2004;91:1580-1590.
- Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer*. 1994;73(3):643-651.
- Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med*. 2004;23(7):1111-1130.
- Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes *BRCA1* and *BRCA2*. *Am J Hum Genet*. 1998;62(1):145-158.
- Laitman Y, Simeonov M, Keinan-Boker L, Liphshitz I, Friedman E. Breast cancer risk prediction accuracy in Jewish Israeli high-risk women using the BOADICEA and IBIS risk models. *Genet Res (Camb)*. 2013;95(6):174-177.
- Varesco L, Viassolo V, Viel A, et al. 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. *Breast*. 2013;22(6):1130-1135.
- Fischer C, Kuchenbacker K, Engel C, et al. Evaluating the performance of the breast cancer genetic risk models BOADICEA, IBIS, BRCAPRO and Claus for predicting *BRCA1/2* mutation carrier probabilities: a study based on 7352 families from the German Hereditary Breast and Ovarian Cancer Consortium. *J Med Genet*. 2013;50(6):360-367.
- Kwong A, Wong CH, Suen DT, et al. Accuracy of *BRCA1/2* mutation prediction models for different ethnicities and genders: experience in a southern Chinese cohort. *World J Surg*. 2012;36(4):702-713.
- Schneegans SM, Rosenberger A, Engel U, et al. Validation of three *BRCA1/2* mutation-carrier probability models Myriad, BRCAPRO and BOADICEA in a population-based series of 183 German families. *Fam Cancer*. 2012;11(2):181-188.
- Panchal SM, Ennis M, Canon S, Bordeleau LJ. Selecting a *BRCA* risk assessment model for use in a familial cancer clinic. *BMC Med Genet*. 2008;9:116.
- Antoniou AC, Hardy R, Walker L, et al. Predicting the likelihood of carrying a *BRCA1* or *BRCA2* mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. *J Med Genet*. 2008;45(7):425-431.

21. Stahlbom AK, Johansson H, Liljegren A, von Wachenfeldt A, Arver B. Evaluation of the BOADICEA risk assessment model in women with a family history of breast cancer. *Fam Cancer*. 2012; 11(1):33-40.
22. Thirthagiri E, Lee SY, Kang P, et al. Evaluation of BRCA1 and BRCA2 mutations and risk-prediction models in a typical Asian country (Malaysia) with a relatively low incidence of breast cancer. *Breast Cancer Res*. 2008;10(4):R59.
23. Kurian AW, Gong GD, Chun NM, et al. Performance of BRCA1/2 mutation prediction models in Asian Americans. *J Clin Oncol*. 2008;26(29):4752-4758.
24. Huo D, Senie RT, Daly M, et al. Prediction of BRCA mutations using the BRCAPRO model in clinic-based African American, Hispanic, and other minority families in the United States. *J Clin Oncol*. 2009;27(8): 1184-1190.
25. Nanda R, Schumm LP, Cummings S, et al. Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. *JAMA*. 2005;294(15):1925-1933.
26. Parmigiani G, Chen S, Iversen ES Jr, et al. Validity of models for predicting BRCA1 and BRCA2 mutations. *Ann Intern Med*. 2007;147(7): 441-450.
27. Zanna I, Rizzolo P, Sera F, et al. The BRCAPRO 5.0 model is a useful tool in genetic counseling and clinical management of male breast cancer cases. *Eur J Hum Genet*. 2010;18(7):856-858.
28. Mitri ZI, Jackson M, Garby C, et al. BRCAPRO 6.0 model validation in male patients presenting for BRCA testing. *Oncologist*. 2015;20(6): 593-597.
29. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol*. 2002;20(6):1480-1490.
30. Plon SE, Eccles DM, Easton D, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. *Hum Mutat*. 2008;29(11): 1282-1291.
31. Lindor NM, Guidugli L, Wang X, et al. A review of a multifactorial probability-based model for classification of BRCA1 and BRCA2 variants of uncertain significance (VUS). *Hum Mutat*. 2012; 33(1):8-21.
32. Antoniou AC, Pharoah PD, McMullan G, et al. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. *Br J Cancer*. 2002;86:76-83.
33. University of Cambridge, Centre for Cancer Genetic Epidemiology July 2016. <http://ccge.medschl.cam.ac.uk/boadicea/>. Accessed by April 2017.
34. BRCAPRO. <http://bcf.dfci.harvard.edu/bayesmendel/brcapro.php>. Accessed by April 2017.
35. MYRIAD PRO. <https://www.myriadpro.com/hereditary-cancer-testing/hereditary-breast-and-ovarian-cancer-hboc-syndrome/prevalence-tables/>. Accessed by April 2017.
36. Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. *J Natl Cancer Inst*. 2001;93(5):358-366.
37. Rothman KJ, Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1998.
38. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845.
39. Silvestri V, Barrowdale D, Mulligan AM, et al. Male breast cancer in BRCA1 and BRCA2 mutation carriers: pathology data from the Consortium of Investigators of Modifiers of BRCA1/2. *Breast Cancer Res*. 2016;18(1):15.
40. Masci G, Caruso M, Caruso F, et al. Clinicopathological and immunohistochemical characteristics in male breast cancer: a retrospective case series. *Oncologist*. 2015;20(6):586-592.
41. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet*. 2003;72(5):1117-1130.
42. Lee AJ, Cunningham AP, Kuchenbaecker KB, et al. BOADICEA breast cancer risk prediction model: updates to cancer incidences, tumour pathology and web interface. *Br J Cancer*. 2014;110(2):535-545.
43. Lee AJ, Cunningham AP, Tischkowitz M, et al. Incorporating truncating variants in PALB2, CHEK2, and ATM into the BOADICEA breast cancer risk model. *Genet Med*. 2016;18(12):1190-1198.

SUPPORTING INFORMATION

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

How to cite this article: Moghadasi S, Grundeken V, Janssen LAM, et al. Performance of BRCA1/2 mutation prediction models in male breast cancer patients. *Clin Genet*. 2017;1-8. <https://doi.org/10.1111/cge.13065>