National Institute for Health and Care Excellence

Final

Ovarian cancer: identifying and managing familial and genetic risk

[D] Optimal methods of assessing the probability of having a pathogenic variant

NICE guideline NG241

Evidence reviews underpinning recommendation 1.3.3, bullet points 1 and 9 in table 1, bullet points 1, 2, 5 and 7 in table 2, and research recommendation 2 in the NICE guideline

March 2024

Final

These evidence reviews were developed by NICE

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ISBN: 978-1-4731-5824-5

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Methods of assessing the probability of having a pathogenic variant

Review question

What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

Introduction

Universal screening, in which every person at risk of ovarian cancer is offered testing for pathogenic variants associated with familial ovarian cancer, would be the most accurate means of finding all carriers. However, this method is associated with substantial upfront costs and would place considerable pressure on already stretched healthcare resources. Furthermore, universal screening can complicate the process of informed consent as it is assumed the individual has relatively low risk of being a carrier until they are diagnosed as being a carrier; this can be difficult to communicate or understand. Therefore, clinicians have used methods to risk stratify individuals into those at higher risk of being a carrier of a pathogenic variant associated with familial ovarian cancer. These are often based on taking a family history and looking for patterns of disease that would suggest a higher probability of being a carrier. Those at higher risk are then offered definitive testing for a pathogenic variant associated with familial ovarian cancer. Ideally, such a screening method would not miss any carriers when compared to universal screening yet would reduce the number of tests by only testing those at high risk of being carriers. Those tested would also be made aware of their increased risk and as such would be better informed of the potential outcome of their testing. The review explores which methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer are the most effective and how well they perform.

Summary of the protocol

See Table 1 for a summary of the Population, Index test, Reference standard, Target condition and Outcomes (PIRTO) characteristics of this review.

Table 1: Summary of the protocol (PIRT table)

Population	People with unknown risk of carrying a pathogenic variant

Index test	Familial risk assessment for pathogenic variants: for example:
	• *BRCA* risk assessment:
	  ○ BRCAPRO-LYTE
	  ○ BRCAPRO-LYTE-plus
	  ○ BRCAPRO-LYTE-simple
	  ○ International Breast Cancer Intervention Study Model
	  ○ Manchester scoring system
	  ○ Modified Manchester scoring system
	  ○ Ontario Family History Assessment Tool
	  ○ Pedigree Assessment Tool
	  ○ Referral Screening Tool
	• *BRCA*, *PALB2*, *ATM*, *CHEK2*, *BARD1*, *RAD51C* and *RAD51D* risk assessment:
	  ○ BOADICEA (CanRisk)

	• Clinical criteria based approach (for example, family history based criteria)
	  ○ Quest
	• Tools to predict Lynch Syndrome variants
	  ○ PREMM5
	• Clinical criteria for rare cancer susceptibility syndromes associated with ovarian cancer risk

Reference standard	• Germline pathogenic variant analysis
Target condition	Pathogenic variants in: • *BRCA1* or *BRCA2* • *PALB2*, *ATM*, *CHEK2*, *BARD1*, *RAD51C* and *RAD51D*
Outcomes	**Critical** Diagnostic accuracy in categorising those with/without pathogenic variants: • sensitivity • specificity • positive and negative likelihood ratios Calibration: • Predicted risk versus observed risk (including statistics of overall model fit) **Important** None

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Diagnostic evidence

Included studies

Overall, 57 studies were included for this review, typically cross-sectional diagnostic accuracy studies using data from prospective or retrospective cohorts.

The included studies reported the following *BRCA1/2* mutation carrier probability estimation methods: ARiCA, BOADICEA, BRCAPRO, BRCAPROLYTE, BRCAPROLYTE-Plus, BRCAPROLYTE-Simple, COS, DrABC, eCLAUS, FHAT, Finnish, HCSC, IBIS, IC model, KOHCal, LUMC, Manchester Scoring System [versions MSS1, MSS2 and MSS3], MYRIAD, MYRIAD II, NCCN criteria, PENN, PENN II, Tyrer-Cuzick and YALE.

One study used the Brief Family History Questionnaire and Extended Family History Questionnaire to estimate carrier probability for genetic mutations associated with Lynch Syndrome.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Index test	Reference standard	Outcomes
Ang 2022 Malaysia & Singapore Cross-sectional	N=2448 patients with breast cancer who underwent genetic testing Age, mean (SD), years: not reported	• PENNII • KOHCal • BOADICEA version 5.0 • ARiCA	• Germline pathogenic variant analysis	• Diagnostic accuracy
Antoniou 2008 UK Retrospective cohort	N=1934 families who underwent genetic testing Age, mean (SD), years: not reported	• BOADICEA • BRCAPRO • Manchester • Myriad • IBIS	• Germline pathogenic variant analysis	• Diagnostic accuracy
Antoniou 2006 Canada Prospective cohort	N=188 high-risk breast and/or ovarian families Age, mean (SD), years: not reported	• BOADICEA • BRCAPRO	• Germline pathogenic variant analysis	• Diagnostic accuracy
Antonucci 2017 Italy Retrospective cohort	N=517 subjects submitted to genetic counselling Age, mean (range), years: affected by breast cancer = 45 (22-77); affected by ovarian cancer = 43 (19-60)	• BRCAPRO 5.1 • BRCAPRO 6.0	• Germline pathogenic variant analysis	• Diagnostic accuracy
Barcenas 2006 USA Prospective cohort	N=472 families recruited at high-risk cancer genetic clinics Age, mean (SD), years: 50 (11)	• BOADICEA • BRCAPRO • Myriad II	• Germline pathogenic variant analysis	• Diagnostic accuracy
Berrino 2015 Italy	N=436 families eligible for genetic counselling and *BRCA* testing	• COS (European case-only study) updated for the Italian population	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
Cross-sectional	based on the number of cases and ages at diagnosis of breast and ovarian cancer Age, mean (SD), years: not reported	with new penetrance estimates of both BC and OC • BOADICEA • BRCAPRO 5.1 • BRCAPRO 6.0		
Berry 2002 USA Retrospective cohort	N=301 probands who underwent genetic testing; 216 (71%) were at high risk for carrying mutations on the basis of having three or more cases of having breast or ovarian cancer Age, mean (SD), years: not reported	• BRCAPRO	• Germline pathogenic variant analysis	• Diagnostic accuracy
Biswas 2013 USA Cross-sectional	N=2713 probands with family history information and genetic test results, 576 (21.2%) were *BRCA* mutation carriers Age, median (IQR), years: median 49 years (17)	• BRCAPRO - using the version in Bayes-Mendel 2.0-8 • BRCAPROLYTE - (simplified BRCAPRO by only collecting a limited family history) which evaluates BRCAPRO using age of the proband and ages of diagnosis for affected first- and second-degree relatives • BRCAPROLYTE-Plus - extends BRCAPROLYTE by imputing the ages of unaffected relatives • BRCAPROLYTE-Simple - simplifies BRCAPROLYTE by not collecting the family structure • FHAT - Family History Assessment Tool	• Germline pathogenic variant analysis	• Diagnostic accuracy
Biswas 2012 USA	N=796 families who underwent genetic testing	• BRCAPRO	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
Cross-sectional	Age, median (IQR), years: 46 (16)			
Bodmer 2006 The Netherlands Retrospective cohort	N=263 families with breast and/or ovarian cancer patients that were tested for *BRCA* mutations Age, mean (SD), years: not reported	• Frank (PENN) • Gilpin	• Germline pathogenic variant analysis	• Diagnostic accuracy
Capalbo 2006 Italy Prospective cohort	N=99 Italian probands with a family history of breast cancer Age, mean (SD), years: not reported	• BRCAPRO • Myriad • IC model	• Germline pathogenic variant analysis	• Diagnostic accuracy
Chew 2018 Singapore Cross-sectional	N=330 Singaporean probands from unrelated families; N=47 had either *BRCA1* or *BRCA2* mutation Age, mean (SD), years: not reported	Three versions of the Manchester Scoring System (MSS) were used: • MSS1 • MSS2 • MSS3	• Germline pathogenic variant analysis	• Diagnostic accuracy
Cropper 2017 USA Cross-sectional	N=1072 patients; N=99 had either *BRCA1* or *BRCA2* mutation Age, mean (SD), years: 51.1 (12.1)	NCCN (v 1.2014) clinical criteria for recommending BRCA testing: Analysis was done for patients meeting only 1 of the criteria versus those meeting 2 or more criteria.	• Germline pathogenic variant analysis	• Diagnostic accuracy
Daniels 2014 USA Cross-sectional	N=589 patients; N=180 had either *BRCA1* or *BRCA2* mutation Age, mean (SD), years: 55 (11) at ovarian cancer diagnosis	• BRCAPRO scores were calculated using CancerGene v5.1	• Germline pathogenic variant analysis	• Diagnostic accuracy
de la Hoya 2003 Spain	N=109 Spanish breast/ovarian families previously screened for germline mutations	• HCSC • LUMC • U-PENN • HUCH (Finnish)	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
Retrospective cohort	in both the *BRCA1* and *BRCA2* genes Age, mean (SD), years: not reported	• Frank (MYRIAD) • Counsellor		
Eoh 2017 South Korea Cross-sectional	N=232 patients with ovarian cancer; N=57 had a *BRCA1/2* mutation Age, median, years: 54 years at presentation	• BRCAPRO using CancerGene software, version 5.1 • MYRIAD using CancerGene software, version 5.1	• Germline pathogenic variant analysis	• Diagnostic accuracy
Euhus 2002 USA Retrospective cohort	N=148 pedigrees from families who had obtained *BRCA* gene mutation testing through several different university-based clinical cancer genetics programs. Age, mean (SD), years: not reported	• Risk counsellor [the risk counsellors were asked to estimate the probability of BRCA gene mutation for each pedigree by using a five-point scale ((1) ≤ 10%; (2) 11%–30%; (3) 31%–70%; (4) 71%–94%; and (5) ≥ 95%)] • BRCAPRO	• Germline pathogenic variant analysis	• Diagnostic accuracy
Evans 2004 UK Retrospective cohort	N=258 individuals from the North West of England with a family history of breast cancer Age, mean (SD), years: not reported	• BRCAPRO • Manchester • FRANK	• Germline pathogenic variant analysis	• Diagnostic accuracy
Evans 2009 UK Retrospective case series	2156 patients with breast (N=1918) or ovarian cancer (N=238). Pathology data were available for 1116 patients Age, median, years (for those with available pathology results): range between 32 and 56	• MSS1 • MSS2	• Germline pathogenic variant analysis	• Diagnostic accuracy
Evans 2017 UK Cross-sectional	N=231 women with epithelial ovarian cancer. N=17 had *BRCA1/2* mutation Age, mean (SD), years: not reported	• MSS2 • MSS3 • BOADICEA	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
Fasching 2007 Germany Prospective cohort	N=111 breast cancer affected patients from 103 kindreds with a family history of breast cancer Age, mean (range), years: 45.8 (44.4 - 47.2)	• Tyrer-Cuzick • MENDEL • BRCAPRO	• Germline pathogenic variant analysis	• Diagnostic accuracy
Fischer 2013 Gemany Cross-sectional	N=7352 index patients from families with a history of breast or ovarian cancer. N=1774 were *BRCA1/2* mutation carriers. Evaluation of BOADICEA-path was carried out in a subset of N=4927 pedigrees from the overall sample in which at least one family member had data on tumour markers. Age, median (IQR), years: age of onset of breast cancer 43.3 (35.9 to 49.6), age of onset of ovarian cancer 50.5 (43.1 to 59.5)	• BOADICEA • BRCAPRO • IBIS • eCLAUS • BOADICEA-Path (Antoniou 2012)	• Germline pathogenic variant analysis	• Diagnostic accuracy
Gerdes 2006 Denmark Cross-sectoinal	N=267 index patients from families with a history of breast or ovarian cancer. N=76 were *BRCA1/2* mutation carriers. N=110 index patients had ovarian cancer. Age, mean (SD), years: not reported	• Manchester Scoring System - 2006 version MSS1 • Frank 2/ Myriad model - version from spring 2005	• Germline pathogenic variant analysis	• Diagnostic accuracy
Hung 2019 Taiwan Cross-sectional	N=647 women, who underwent germline DNA sequencing of a cancer susceptibility gene panel. Age, mean (range), years: 50.2 (16-96)	• BOADICEA • BRCAPRO • Penn II • MYRIAD • Tyrer-Cuzick	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
Huo 2009 USA Retrospective cohort	N= 267 index patients from families with a history of breast or ovarian cancer. Age, mean (SD), years: not reported	• BRCAPRO	• Germline pathogenic variant analysis	• Diagnostic accuracy
James 2006 Australia Retrospective cohort	N=257 families who had completed *BRCA1/2* mutation screening Age, median (range), years: 52 (28-94)	• BRCAPRO • Manchester • FRANK • COUCH • FHAT	• Germline pathogenic variant analysis	• Diagnostic accuracy
Kang 2012 South Korea Retrospective cohort	N= 236 women at high risk of inherited breast cancer tested for *BRCA* mutations Age, mean (range), years: 42.2 (20-78)	• BRCAPRO - as implemented in CaGene 5.1 software • MYRIAD II	• Germline pathogenic variant analysis	• Diagnostic accuracy
Kang 2006 Australia Retrospective cohort	Pedigrees of N=380 families who had undergone *BRCA1/2* mutation analysis Age, mean (SD), years: not reported	• BRCAPRO • Manchester • MYRIAD • PENN	• Germline pathogenic variant analysis	• Diagnostic accuracy
Kast 2014 Germany Cross-sectional	N=9360 female index patients from unrelated families. N=1353 had pathogenic *BRCA1* variants; N=628 had had pathogenic *BRCA2* variants Age, mean, years: members with female breast cancer majority 40-49 years; members with male breast cancer majority <60	• Manchester Scoring System - 2004 version (MSS1) • Manchester Scoring System - 2009 version (MSS2) incorporating additional pathological parameters	• Germline pathogenic variant analysis	• Diagnostic accuracy
Kenan 2018 Israel Retrospective cohort	N=648 individuals who underwent oncogenetic counselling if they were genotyped for the predominant *BRCA* mutations in the Jewish population	• BOADICEA • PENN II • BRCAPRO • Myriad	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
	Age, mean (SD), years: 50.9 (11.4; range 19-85)			
Kim 2022 Canada Prospective cohort	N=169 women with non-serous, non-mucinous ovarian cancer. N=12 had Lynch Syndrome genetic mutations (*MLH1* N=2; *MSH6* N=7; *MSH2* N=1; *PMS2* N=2) Age, median (range), years: 53 (21 to 70)	• a 4-item self-reported brief Family History Questionnaire (bFHQ) • a 37-item extended Family History Questionnaire (eFHQ) administered by the research assistant	• Germline pathogenic variant analysis	• Diagnostic accuracy
Kurian 2008 USA and Canada Cross-sectional	N=200 East Asian probands matched to N=200 white probands Age, mean (SD), years: not reported	• BRCAPRO as implemented by CancerGene v4 software • MYRIAD II as implemented by CancerGene v4 software	• Germline pathogenic variant analysis	• Diagnostic accuracy
Kurian 2009 USA Prospective cohort	N=1365 patients diagnosed with invasive breast cancer < 65 years Age, mean (SD), years: African-American: <50 = 181, 50-54 = 217; Hispanic: <50 = 227, 50-54 = 198; Non-Hispanic white: <50 = 258, 50-54 = 284	• BRCAPRO • BOADICEA	• Germline pathogenic variant analysis	• Diagnostic accuracy
Kwong 2012 China (Hong Kong) Cross-sectional	N=310 probands with breast and ovarian cancers Age, mean (SD), years: African-American: <50 = 181, 50-54 = 217; Hispanic: <50 = 227, 50-54 = 198; Non-Hispanic white: <50 = 258, 50-54 = 284	• BRCAPRO as implemented in CaGene 4.3 • Myriad II as implemented in CaGene 4.3 • BOADICEA as implemented in CaGene 4.3	• Germline pathogenic variant analysis	• Diagnostic accuracy
Lindor 2007 USA	N=154 probands seen for genetic risk assessment	• LAMBDA • BRCAPRO • Couch 1.5 • MYRIAD II	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
Retrospective cohort	Age, years: most were in age groups <40 and 40-49	• PENN II		
Lindor 2010 USA Retrospective cohort	N=285 probands who had cancer risk assessment for mutations in *BRCA1* and *BRCA2* Age, mean (SD), years: age at breast cancer 45 (10.6), age at ovarian cancer 51.7 (12.7)	• PENN II	• Germline pathogenic variant analysis	• Diagnostic accuracy
Liu 2022 China Cohort (unclear if prospective)	N=731 patients in the validation sample; N=39 had *BRCA1* germline pathogenic variants (GPV); N=39 had *BRCA2* GPV; N=21 had GPV in other cancer predisposition genes Age, mean (SD), years: not reported	• Germline pathogenic variant risk prediction model called DNA-repair Associated Breast Cancer (DrABC) developed using a hierarchical neural network architecture • BRCAPRO version 2.1-7 • Myriad II • PENN II • BOADICEA v3 • NCCN guidelines (version 1.2020)	• Germline pathogenic variant analysis	• Diagnostic accuracy
Mazzola 2014 USA Cross-sectional	N=2038 families who underwent genetic testing Age, mean (SD), years: not reported	• BRCAPRO version 2.0-7 (in BayesMendel R package) • BRCAPRO version 2.0-8 (in BayesMendel R package)	• Germline pathogenic variant analysis	• Diagnostic accuracy
Mitri 2015 USA Retrospective cohort	N=146 men who had undergone genetic counselling and testing Age, mean (SD), years: 57 (14, range 18-87)	• BRCAPRO	• Germline pathogenic variant analysis	• Diagnostic accuracy
Moghadasi 2018	N=307 male breast cancer patients	• BRCAPRO • BOADICEA • MYRIAD	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
The Netherlands Retrospective cohort	Age, mean, years: age of onset of breast cancer carriers 59.8, non-carriers 60.1			
Oros 2006 Canada Retrospective cohort	N=224 probands from French Canadian families with at least three cases of breast cancer Age, mean (SD), years: not reported	• BRCAPRO • Manchester	• Germline pathogenic variant analysis	• Diagnostic accuracy
Panchal 2008 Canada Retrospective cohort	N=200 non-*BRCA* mutation and 100 *BRCA* mutation carriers Age, mean (SD), years: carriers 51 (12.7); non-carriers 52 (13.5)	• BRCAPRO • BOADICEA • Manchester • PENN II • MYRIAD II • IBIS	• Germline pathogenic variant analysis	• Diagnostic accuracy
Parmigiani 2007 USA Cross-sectional	N=3324 families who underwent genetic testing Age, mean (SD), years: not reported	• BRCAPRO • MYRIAD • FHAT • YALE • NCI • Finnish	• Germline pathogenic variant analysis	• Diagnostic accuracy
Rao 2009a China Prospective cohort	N=200 unrelated pedigrees who had 2 or more first or second degree relatives affected with invasive breast cancer and/or ovarian cancer Age, mean (SD), years: not reported	• BRCAPRO • COUCH • Sh-E	• Germline pathogenic variant analysis	• Diagnostic accuracy
Rao 2009b China Retrospective cohort	N=212 Han Chinese participants from families with more than three affected breast or ovarian cancer cases who had undergone *BRCA1/2* mutation analysis Age, median (95%CI), years: between 35.8 (32.1	• BRCAPRO • MYRIAD II	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
	- 39.5) and 48.7 (47.2 - 50.3)			
Roudgari 2008 UK Retrospective cohort	N=275 families with completed genetic testing for both *BRCA*1/2 mutation Age, years: age at cancer diagnosis <=50 n=180, >50 n=94	• BOADICE • Manchester • Tyrer-Cuzik • COS	• Germline pathogenic variant analysis	• Diagnostic accuracy
Schneegans 2012 Germany Retrospective cohort	N=183 unrelated families for which at least one affected member was tested for mutations in the *BRCA1* and *BRCA2* genes. Age, mean (SD), years: not reported	• BRCAPRO • BOADICEA	• Germline pathogenic variant analysis	• Diagnostic accuracy
Senda 2021 Japan Retrospective cohort	N=1995 unselected Japanese women with primary breast cancer Age, mean (SD), years: not reported	• Tyrer-Cuzick	• Germline pathogenic variant analysis	• Diagnostic accuracy
Simard 2007 Canada Prospective cohort	N=256 high risk families Age, years: mainly between 41 and 70	• Manchester	• Germline pathogenic variant analysis	• Diagnostic accuracy
Stahlbom 2012 Sweden Retrospective	N=652 women who consecutively attended the cancer genetic clinic for hereditary breast- and ovarian cancer but included n=263 with mutation screening results Age, mean (SD), years: not reported	• BOADICEA	• Germline pathogenic variant analysis	• Diagnostic accuracy
Teixeira 2017 Brazil Cross-sectional	N=115 patients but n=15 excluded for not meeting the inclusion criteria; analysed n=100	• BOADICEA • BRCAPRO • MYRIAD • Manchester	• Germline pathogenic variant analysis	• Diagnostic accuracy

Study	Population	Index test	Reference standard	Outcomes
	Age, median (range), years: 56.5 (34-81)			
Teller 2010 USA Retrospective cohort	N=520 families with at least one case of breast or ovarian cancer Age, mean (SD), years: not reported	• PAT • MYRIAD II • PENN II	• Germline pathogenic variant analysis	• Diagnostic accuracy
Terkelsen 2019 Denmark Prospective cohort	N=173 women diagnosed with breast cancer before 45 years of age Age, median (range), years: 37 (21-44)	• BOADICEA	• Germline pathogenic variant analysis	• Diagnostic accuracy
Thirthagiri 2008 Malaysia Prospective cohort	N=185 breast cancer patients with either early onset breast cancer (at age ≤ 40 years) or a personal and/or family history of breast or ovarian cancer but analysed n=145 Age, years: age at breast cancer diagnosis between 31 and 57	• MSS1 • BOADICEA	• Germline pathogenic variant analysis	• Diagnostic accuracy
Varesco 2013 Italy Retrospective cohort	N=918 index cases tested for *BRCA* mutations Age, mean (SD), years: not reported	• BOADICEA • BRCAPRO	• Germline pathogenic variant analysis	• Diagnostic accuracy
Vogel 2007 USA Retrospective cohort	N=78 Hispanic patients who underwent genetic testing and n=79 White controls Age, mean (SD), years: not reported	• BRCAPRO	• Germline pathogenic variant analysis	• Diagnostic accuracy
Zanna 2010 Italy Prospective cohort	N=102 male breast cancer sufferers Age, mean (SD), years: 63.6 (12)	• BRCAPRO • MYRIAD • IC model	• Germline pathogenic variant analysis	• Diagnostic accuracy

IQR: interquartile range; SD: standard deviation

See the full evidence tables in appendix D and summary ROC plots and forest plots in appendix E. For more information on cut-offs used to assess the performance of diagnostic tests or prediction models see Supplement 1 – Methods, Diagnostic and prediction model studies chapter.

Summary of the evidence

There was a large body of evidence that BOADICEA, BRCAPRO and Manchester Scoring System v1 show moderate discrimination between carriers and non-carriers of *BRCA1/2* mutations (AUC = 0.76 in all cases). This evidence was moderate to high quality.

A smaller body of moderate to high quality evidence suggests later versions of the Manchester Scoring System have improved its discrimination (AUC = 0.79 to 0.82; moderate to high quality evidence). The ARiCA, MYRIAD, MYRIAD II, PENN, PENNII, Finnish and FHAT models had slightly poorer discrimination (AUC range from 0.71 to 0.8) but still in the moderate range. This evidence was low to moderate quality.

There was evidence of heterogeneity in some of the pooled estimates of AUC (for example, for BOADICEA and BRCAPRO).

Sensitivity and specificity for discrimination between carriers and non-carriers of *BRCA1/2* mutations at different carrier probability thresholds (most commonly 10% and 20%) were reported and the models behaved as expected. At lower carrier probability thresholds sensitivity is high but specificity low. Increasing the carrier probability threshold decreases sensitivity but increases specificity. There was considerable heterogeneity between studies, however, at individual thresholds for many of the risk prediction models.

The calibration of the BOADICEA, BRCAPRO, COUCH, eCLAUS, IBIS, MYRIAD, MYRIAD II and PENN II *BRCA1/2* carrier probability models was examined graphically by plotting observed versus predicted carrier probabilities from the studies and through regression analyses where the study population was larger than 5. Visual inspection indicated that the models appeared reasonably well calibrated, although there was a suggestion that the models may tend to underestimate low carrier probabilities. The regression analyses showed that the BRCAPRO, COUCH, eCLAUS and IBIS tests tended to underestimate the number of expected cases at low probabilities and overestimate the number of expected cases at high probabilities of *BRCA1/2* mutation. The MYRIAD II test may show the opposite directional effect, with underestimation increasing at higher probabilities, but there was considerable uncertainty around the estimation of this trend effect. The BOADICEA test met the standard of adequate calibration (see also Appendix M).

Evidence from a single study suggested Brief and Extended Family History Questionnaires had moderate discrimination between carriers and non-carriers of Lynch Syndrome mutations.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Economic

No economic studies were identified which were applicable to this review question.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Diagnostic accuracy (sensitivity, specificity, positive and negative likelihood ratios) and calibration outcomes were chosen by the committee as critical outcomes because they measure the ability of a screening test to differentiate between those who carry a pathogenic variant associated with familial ovarian cancer from those who do not carry such pathogenic variant.

The quality of the evidence

The quality of the evidence from the included studies was assessed with modified GRADE and was very low to high quality with most of the evidence being of a moderate quality. This was predominately due to imprecision in the effect estimates and heterogeneity.

The evidence was mainly from prediction models for *BRCA* mutation carrier probability and there was very limited evidence for other mutations associated with familial ovarian cancer. Studies reporting carrier probability thresholds often used thresholds much higher than recommended in this guideline, possibly because they came from a time when genetic testing was more costly. The committee also noted that for the most part the plotted observed versus expected carrier probability data points were close enough to the line of best fit to enable them to use them for decision making. For these reasons, the committee based the recommendations on their knowledge and experience as well as the evidence.

Benefits and harms

Assessing the risk of having a pathogenic variant

There was evidence that there are several tools that the committee considered to be useful or moderately useful (sensitivity, specificity, likelihood ratios and area under the curve) in terms of their ability to estimate a person's risk of carrying *BRCA1* and *BRCA2* pathological variants. The committee noted that the calibration of some of these models was limited, but they were satisfied that this was outweighed by the discriminatory accuracies of the models as their main concern was to ensure that nobody at high probability of having a pathological variant is missed. The committee provided examples in their recommendation but did not

want to be too prescriptive because further carrier probability models could be developed and the existing ones refined with new versions. Furthermore, they agreed to include those examples in the recommendation where there was the largest body of evidence. The committee also discussed that they were not as comfortable including other prediction models (ARiCA, MYRIAD, MYRIAD II, PENN, PENNII, Finnish and FHAT) in the recommendation because, for example, of the small samples in the studies that some of the models were based on. Although this means that they were less certain about these tools they did not want to prohibit their use in specific clinical circumstances and to address this uncertainty they also made a research recommendation.

The committee acknowledged the limitations of the evidence noting that most came from tools that are restricted to *BRCA1* and *BRCA2* pathogenic variants whereas there are a number of other variants associated with an increased risk of ovarian cancer. There was also serious heterogeneity at the higher carrier probability thresholds of 10% or 20% for many of the models, however the results were more consistent at the 5% threshold which is closer to what the committee recommended elsewhere in the guideline. Because *BRCA1* and *BRCA2* tools were created to assess the risk of breast cancer, the committee highlighted that the carrier probability methods may not be as accurate in families with a history of only ovarian cancer rather than other forms of cancer. This would mean that the risks may be underestimated by the prediction models.

Information about the risk assessment

Based on experience the committee emphasised the importance of giving key information to people so that they are able to make an informed choice about genetic testing once their risk has been assessed. The committee discussed that the information about risk assessment needs to be explained to the person in relation to their family history so that they have an understanding about why their risk is being assessed. They noted that there is often a concern about how their family history may impact risk and who may be affected so the committee recommended that information should be provided about how risk is assessed and how they may obtain a comprehensive family history (if applicable) as well as which family members may be at risk. They also noted that navigation of clinical pathways can be complex so they highlighted that information about this and what the next steps are (depending on the outcomes of their risk assessment) should be provided so that the person is well prepared for the potential referrals that may be required and the specialist services that may be involved. Based on experience the committee decided that it is always important to give people information about any trials that may be appropriate.

Research recommendation

Given the uncertainties about other variants than *BRCA1* and *BRCA2*, and to address the gap in the evidence, the committee also made a research recommendation on optimal tools to assess mutation carrier probability for a wider range of ovarian cancer susceptibility genes, not limited to *BRCA1* and *BRCA2*.

Cost effectiveness and resource use

There was no existing economic evidence in this area.

The committee recognised that different tools for assessing risk may have varying completion and administration times. Also, the Manchester scoring system is more suitable for people affected with cancer, whilst CanRisk (BOADICEA) is generally more appropriate for unaffected people. It was further noted that certain tools may not be applicable to specific groups, such as families with only a single first-degree relative affected by ovarian cancer, in which case clinical judgment may be more relevant. Overall, the committee agreed that selecting a risk assessment tool should be based on the specific clinical circumstances.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.3 and bullet points 1 and 9 in Table 1 and bullet points 1,2,5 and 7 in Table 2, as well as research recommendation 2 (on optimal tools to assess mutation carrier probability) in the NICE guideline.

References – included studies

Effectiveness

Ang 2022

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Appendices

Appendix A Review protocol

Review protocol for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022337178
1.	Review title	Methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer
2.	Review question	What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?
3.	Objective	Several mutation probability assessment tools have been published and are widely but variably used in clinical practice. This review addresses the question of how best to assess the probability of a pathogenic variant being present in individuals and families with a history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE, MEDLINE in Process & MEDLINE EPub Ahead of Print

		Searches will be restricted by: • English language • Human Studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Familial ovarian cancer
6.	Population	Inclusion: People with unknown risk of carrying a pathogenic variant Exclusion: none

7.	Index test	Familial risk assessment for pathogenic variants: for example:
		• *BRCA* risk assessment:
		  ○ BRCAPRO-LYTE
		  ○ BRCAPRO-LYTE-plus
		  ○ BRCAPRO-LYTE-simple
		  ○ International Breast Cancer Intervention Study Model
		  ○ Manchester scoring system
		  ○ Modified Manchester scoring system
		  ○ Ontario Family History Assessment Tool
		  ○ Pedigree Assessment Tool
		  ○ Referral Screening Tool
		• *BRCA*, *PALB2*, *ATM*, *CHEK2*, *BARD1*, *RAD51C* and *RAD51D* risk assessment:
		  ○ BOADICEA (CanRisk)
		• Clinical criteria based approach (for example, family history based criteria)
		  ○ Quest
		• Tools to predict Lynch Syndrome variants

		○ PREMM5 Clinical criteria for rare cancer susceptibility syndromes associated with ovarian cancer risk
8.	Reference standard	• Germline pathogenic variant analysis
9.	Types of study to be included	• Cross-sectional diagnostic accuracy studies or systematic reviews of such studies. • Diagnostic prediction model studies • Test and treat studies – if they report diagnostic accuracy data.
10.	Other exclusion criteria	**Inclusion criteria**: • Full text papers **Exclusion criteria**: • Conference abstracts • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/study quality. • Non-English language articles
11.	Context	Not applicable (no changes to scope question and no existing guidance will be updated by this review)
12.	Primary outcomes (critical outcomes)	Diagnostic accuracy in categorising those with/without pathogenic variants: • sensitivity • specificity • positive and negative likelihood ratios Calibration: • Predicted risk versus observed risk (including statistics of overall model fit)
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI-Reviewer and de-duplicated.

		Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following checklists: • QUADAS-2 for diagnostic accuracy studies • PROBAST tool for prediction model studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.

16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where appropriate, meta-analysis of diagnostic test accuracy will be performed using the metandi and midas applications in STATA and Cochrane Review Manager.
		
		Likelihood ratios or sensitivity and specificity with 95% CIs will be used as the outcomes for diagnostic test usefulness. Diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies.
		
		Decision making thresholds (for binary accuracy data)
		• Sensitivity:
		  ○ Useful test: 0.9
		  ○ Not a useful test 0.6
		• Specificity:
		  ○ Useful test: 0.7
		  ○ Not a useful test 0.5
		
		Decision making thresholds (for likelihood ratios [LR])
		• For positive likelihood ratios:
		  ○ Useful test LR ≥ 5.0
		  ○ Not a useful test 1 < LR < 2.0
		
		• For negative likelihood ratios:
		  ○ Useful test LR ≤ 0.2
		  ○ Not a useful test 0.5 < LR ≤ 1.0
		
		<u>Validity</u>
		The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/

17.	Analysis of sub-groups	Evidence will be stratified by: • Setting: at home, primary, secondary and tertiary care

		• Patients with cancer versus without
		• Low vs High prevalence populations: for example the general population vs high risk setting (such as people with family history)
		
		Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
		
		• Groups identified in the equality considerations section of the scope
		  ○ socioeconomic and geographical factors
		  ○ age
		  ○ ethnicity
		  ○ disabilities
		  ○ people for whom English is not their first language or who have other communication needs.
		  ○ trans people (particularly trans men)
		  ○ non-binary people
		  ○ Type of pathogenic variant
		  ○ Women who have had a BSO
		  ○ Population based studies sub groups
		
		Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.

18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative

		☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	August 2022		
22.	Anticipated completion date	13 March 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑

		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	**5a Named contact** National Institute for Health and Care Excellence (NICE) **5b Named contact e-mail** foc@nice.org.uk **5c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	Senior Systematic Reviewer. Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE) Systematic Reviewer. Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)		
26.	Funding sources/sponsor	This systematic review is being completed by NICE		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022337178
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE
32.	Keywords	Pathogenic variants, risk assessment, diagnostic accuracy
33.	Details of existing review of same topic by same authors	
34.	Current review status	☐ Ongoing ☐ Completed but not published ☒ Completed and published ☐ Completed, published and being updated

		☐ Discontinued
35.	Additional information	
36.	Details of final publication	www.nice.org.uk

GRADE: Grading of Recommendations Assessment, Development and Evaluation; NICE: National Institute for Health and Care Excellence

Appendix B Literature search strategies

Literature search strategies for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

Database: Ovid MEDLINE ALL

Date of last search: 24/01/2023

#	Searches
1	exp Ovarian Neoplasms/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
3	or/1-2
4	exp Breast Neoplasms/
5	exp "Neoplasms, Ductal, Lobular, and Medullary"/
6	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
7	or/4-6
8	3 or 7
9	exp Genetic Predisposition to Disease/
10	Pedigree/
11	exp Neoplastic Syndromes, Hereditary/
12	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
13	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
14	HNPCC.tw,kf.
15	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
16	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
17	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
18	gardner* syndrome*.tw,kf.
19	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
20	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
21	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
22	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
23	risk factors/
24	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
25	((carrier* or gene*) adj3 mutat*).tw,kf.
26	exp Genes, Tumor Suppressor/
27	exp Tumor Suppressor Proteins/
28	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
29	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
30	exp Fanconi Anemia Complementation Group Proteins/
31	(Fanconi An?emia adj3 protein*).tw,kf.
32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.
33	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
34	Rad51 Recombinase/
35	Ataxia Telangiectasia Mutated Proteins/

#	Searches
36	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
37	Checkpoint Kinase 2/
38	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
39	Carcinoma, Small Cell/ge [Genetics]
40	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
41	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
42	exp Sertoli-Leydig Cell Tumor/
43	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
44	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
45	Epithelial Cell Adhesion Molecule/
46	Epithelial cell adhesion molecule*.tw,kf.
47	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
48	or/9-47
49	8 and 48
50	exp Risk Assessment/
51	(risk adj3 (tool* or assess* or interval* or analys?s or estimat* or predict* or factor* or model* or scor* or stratif* or test* or evaluat*)).ti,ab,kf.
52	((assess* or probability or predict* or scor*) adj3 (tool* or model* or system* or test* or threshold*)).ti,ab,kf.
53	(clinical adj3 (criteri* or assess* or classif*)).ti,ab,kf.
54	exp Genetic Testing/
55	(genetic adj3 (test* or screen* or predict*)).ti,ab,kf.
56	Diagnostic Tests, Routine/
57	BRCAPRO*.ti,ab,kf.
58	("Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm" or BOADICEA).ti,ab,kf.
59	(CANRISK or "cancer risk adj1 tool").ti,ab,kf.
60	(International Breast Cancer Intervention Study or IBIS or Tyrer-Cuzick).ti,ab,kf.
61	(manchester scor* or MSS).ti,ab,kf.
62	(Ontario Family History Assessment Tool or Ontario FHAT).ti,ab,kf.
63	(((pedigree or family history or referral) adj2 (tool* or checklist* or question*)) or B-RST).ti,ab,kf.
64	(PREMM* or "prediction model for gene mutation*").ti,ab,kf.
65	or/50-64
66	49 and 65
67	letter/
68	editorial/
69	news/
70	exp historical article/
71	Anecdotes as Topic/
72	comment/
73	case reports/
74	(letter or comment*).ti.
75	animals/ not humans/
76	exp Animals, Laboratory/
77	exp Animal Experimentation/
78	exp Models, Animal/
79	exp Rodentia/
80	(rat or rats or mouse or mice or rodent*).ti.
81	or/67-80
82	66 not 81
83	limit 82 to English language
84	exp "sensitivity and specificity"/

#	Searches
85	(sensitivity or specificity).ti,ab.
86	((pre test or pretest or post test) adj probability).ti,ab.
87	(predictive value* or PPV or NPV).ti,ab.
88	likelihood ratio*.ti,ab.
89	likelihood function/
90	((area under adj4 curve) or AUC).ti,ab.
91	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
92	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
93	gold standard.ab.
94	exp Diagnostic errors/
95	(false positiv* or false negativ*).tw.
96	or/84-95
97	83 and 96
98	Meta-Analysis/
99	Meta-Analysis as Topic/
100	(meta analy* or metanaly* or metaanaly*).ti,ab.
101	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
102	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
103	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
104	(search* adj4 literature).ab.
105	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
106	cochrane.jw.
107	or/98-106
108	83 and 107
109	97 or 108

Database: Ovid Embase

Date of last search: 24/01/2023

#	Searches
1	exp ovary tumor/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
3	or/1-2
4	exp breast tumor/
5	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
6	or/4-5
7	3 or 6
8	exp genetic predisposition/
9	pedigree/
10	exp hereditary tumor syndrome/
11	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
12	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
13	HNPCC.tw,kf.
14	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
15	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
16	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
17	gardner* syndrome*.tw,kf.
18	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.

#	Searches
19	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
20	(("hereditary breast and ovarian cancer") or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
21	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
22	risk factor/
23	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
24	((carrier* or gene*) adj3 mutat*).tw,kf.
25	tumor suppressor gene/
26	exp tumor suppressor protein/
27	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
28	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
29	Fanconi anemia protein/
30	(Fanconi An?emia adj3 protein*).tw,kf.
31	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.
32	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
33	Rad51 protein/
34	ATM protein/
35	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
36	checkpoint kinase 2/
37	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
38	small cell carcinoma/
39	genetics/
40	38 and 39
41	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
42	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
43	androblastoma/ or Sertoli cell tumor/ or Leydig cell tumor/
44	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
45	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
46	epithelial cell adhesion molecule/
47	Epithelial cell adhesion molecule*.tw,kf.
48	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
49	or/8-37,40-48
50	7 and 49
51	exp risk assessment/
52	(risk adj3 (tool* or assess* or interval* or analys?s or estimat* or predict* or factor* or model* or scor* or stratif* or test* or evaluat*)).ti,ab,kf.
53	((assess* or probability or predict* or scor*) adj3 (tool* or model* or system* or test* or threshold*)).ti,ab,kf.
54	(clinical adj3 (criteri* or assess* or classif*)).ti,ab,kf.
55	exp genetic screening/
56	(genetic adj3 (test* or screen* or predict*)).ti,ab,kf.
57	exp diagnostic test/
58	BRCAPRO*.ti,ab,kf.
59	("Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm" or BOADICEA).ti,ab,kf.
60	(CANRISK or "cancer risk adj1 tool").ti,ab,kf.
61	(International Breast Cancer Intervention Study or IBIS or Tyrer-Cuzick).ti,ab,kf.
62	(manchester scor* or MSS).ti,ab,kf.
63	(Ontario Family History Assessment Tool or Ontario FHAT).ti,ab,kf.

#	Searches
64	(((pedigree or family history or referral) adj2 (tool* or checklist* or question*)) or B-RST).ti,ab,kf.
65	(PREMM* or "prediction model for gene mutation*").ti,ab,kf.
66	or/51-65
67	50 and 66
68	letter.pt. or letter/
69	note.pt.
70	editorial.pt.
71	case report/ or case study/
72	(letter or comment*).ti.
73	animal/ not human/
74	nonhuman/
75	exp Animal Experiment/
76	exp Experimental Animal/
77	animal model/
78	exp Rodent/
79	(rat or rats or mouse or mice or rodent*).ti.
80	or/68-79
81	67 not 80
82	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
83	81 not 82
84	limit 83 to English language
85	exp "sensitivity and specificity"/
86	(sensitivity or specificity).ti,ab.
87	((pre test or pretest or post test) adj probability).ti,ab.
88	(predictive value* or PPV or NPV).ti,ab.
89	likelihood ratio*.ti,ab.
90	((area under adj4 curve) or AUC).ti,ab.
91	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
92	diagnostic accuracy/
93	diagnostic test accuracy study/
94	gold standard.ab.
95	exp diagnostic error/
96	(false positiv* or false negativ*).ti,ab.
97	differential diagnosis/
98	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
99	or/85-98
100	84 and 99
101	systematic review/
102	meta-analysis/
103	(meta analy* or metanaly* or metaanaly*).ti,ab.
104	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
105	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
106	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
107	(search* adj4 literature).ab.
108	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
109	((pool* or combined) adj2 (data or trials or studies or results)).ab.
110	cochrane.jw.
111	or/101-110
112	84 and 111
113	100 or 112

Database: Cochrane Database of Systematic Reviews, Issue 1 of 12, January 2023 & Cochrane Central Register of Controlled Trials, Issue 1 of 12, January 2023

Date of last search: 26/01/2023

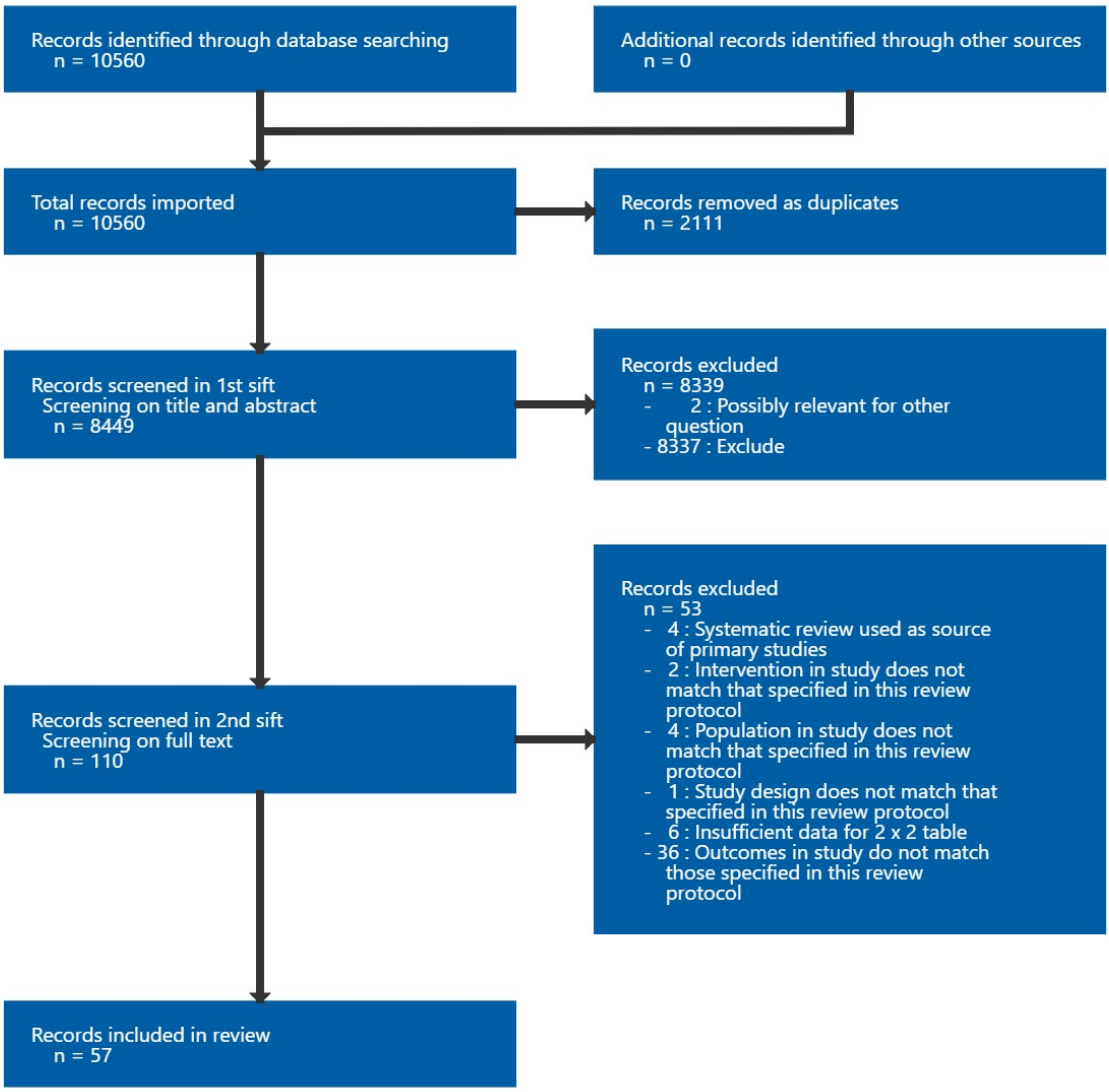
#	Searches
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2	(ovar* NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Breast Neoplasms] explode all trees
#5	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#6	((breast* or mammary) NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)):ti,ab,kw
#7	{OR #4-#6}
#8	#3 OR #7
#9	MeSH descriptor: [Genetic Predisposition to Disease] explode all trees
#10	MeSH descriptor: [Pedigree] this term only
#11	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees
#12	((hereditary or inherit* or familial) NEAR/3 (nonpolyposis or "non polyposis") NEAR/3 (colon or colorectal or bowel) NEAR/3 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#13	((lynch or "Muir Torre") NEAR/2 (syndrome* or cancer*)):ti,ab,kw
#14	HNPCC:ti,ab,kw
#15	(peutz* or intestin* NEXT polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* NEAR/1 lentigino*)):ti,ab,kw
#16	((hamartoma* or "polyps and spots" or cowden*) NEAR/2 (syndrome* or polyp*)):ti,ab,kw
#17	((hereditary or inherit* or familial or adenomato* or attenuated) NEAR/3 polyp* NEAR/3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)):ti,ab,kw
#18	gardner* NEXT syndrome*:ti,ab,kw
#19	(MUTYH or MYH or FAP or AFAP or APC):ti,ab,kw
#20	((familial or inherit* or heredit* or predispos* or pre NEXT dispos* or susceptib* or ancestr* or genealog* or descent) NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#21	("hereditary breast and ovarian cancer" or HBOC or "Li Fraumeni syndrome" or SBLA or LFS):ti,ab,kw
#22	(famil* NEAR/2 histor* NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#23	MeSH descriptor: [Risk Factors] this term only
#24	((risk* or probabil*) NEAR/3 (high* or increas* or factor* or rais*) NEAR/3 (mutat* or malignan* or gene* or variant*)):ti,ab,kw
#25	((carrier* or gene*) NEAR/3 mutat*):ti,ab,kw
#26	MeSH descriptor: [Genes, Tumor Suppressor] explode all trees
#27	MeSH descriptor: [Tumor Suppressor Proteins] explode all trees
#28	((tumor* or tumour* or cancer* or metastasis or metastases or growth*) NEAR/2 (suppress* NEAR/1 (gene* or protein*))):ti,ab,kw
#29	(anti NEXT oncogene* or antioncogene* or onco NEXT suppressor* or oncosuppressor*):ti,ab,kw
#30	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#31	(("Fanconi Anemia" or "fanconi anaemia") NEAR/3 protein*):ti,ab,kw
#32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2):ti,ab,kw
#33	("breast cancer gene 1" or "breast cancer gene 2"):ti,ab,kw
#34	MeSH descriptor: [Rad51 Recombinase] this term only
#35	MeSH descriptor: [Ataxia Telangiectasia Mutated Proteins] this term only
#36	(("Ataxia telangiectasia" NEAR/1 mutated NEAR/1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1):ti,ab,kw
#37	MeSH descriptor: [Checkpoint Kinase 2] this term only
#38	(((checkpoint or "check point" or "serine threonine") NEAR/2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2):ti,ab,kw
#39	MeSH descriptor: [Carcinoma, Small Cell] this term only and with qualifier(s): [genetics - GE]

#	Searches
#40	("small cell" NEAR/2 (cancer* or carcinoma*) NEAR/2 gene*):ti,ab,kw
#41	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or "SNF2 beta"):ti,ab,kw
#42	MeSH descriptor: [Sertoli-Leydig Cell Tumor] explode all trees
#43	(((Sertoli or leydig) NEAR/3 (tumor* or tumour* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or androblastoma* or andreoblastoma* or SLCT or gynandroblastoma*):ti,ab,kw
#44	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or "K12H48 LIKE"):ti,ab,kw
#45	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only
#46	Epithelial cell adhesion NEXT molecule*:ti,ab,kw
#47	(EPCAM* or "EP CAM" or ESA or KSA or M4S1 or "MK 1" or DIAR5 or EGP* or Ly74 or gp40 or CD326 or GA733* or GA 733 or KS14 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or "MOC 31" or "Ber Ep4" or TACSTD1):ti,ab,kw
#48	{OR #9-#47}
#49	#8 AND #48
#50	MeSH descriptor: [Risk Assessment] explode all trees
#51	(risk NEAR/3 (tool* or assess* or interval* or analysis or analyses or estimat* or predict* or factor* or model* or scor* or stratif* or test* or evaluat*)):ti,ab,kw
#52	((assess* or probability or predict* or scor*) NEAR/3 (tool* or model* or system* or test* or threshold*)):ti,ab,kw
#53	(clinical NEAR/3 (criteri* or assess* or classif*)):ti,ab,kw
#54	MeSH descriptor: [Genetic Testing] explode all trees
#55	(genetic NEAR/3 (test* or screen* or predict*)):ti,ab,kw
#56	MeSH descriptor: [Diagnostic Tests, Routine] this term only
#57	BRCAPRO*:ti,ab,kw
#58	("Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm" or BOADICEA):ti,ab,kw
#59	(CANRISK or "cancer risk" NEAR/1 tool):ti,ab,kw
#60	("International Breast Cancer Intervention Study" or IBIS or Tyrer-Cuzick):ti,ab,kw
#61	(manchester NEXT scor* or MSS):ti,ab,kw
#62	("Ontario Family History Assessment Tool" or "Ontario FHAT"):ti,ab,kw
#63	(((pedigree or "family history" or referral) NEAR/2 (tool* or checklist* or question*)) or B-RST):ti,ab,kw
#64	(PREMM* or "prediction model for gene" NEXT mutation*):ti,ab,kw
#65	{OR #50-#64}
#66	#49 AND #65
#67	conference:pt or (clinicaltrials or trialsearch):so
#68	#66 NOT #67

Appendix C Diagnostic evidence study selection

Study selection for: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

Ang, 2022

Bibliographic Reference	Ang, Boon Hong; Ho, Weang Kee; Wijaya, Eldarina; Kwan, Pui Yoke; Ng, Pei Sze; Yoon, Sook Yee; Hasan, Siti Norhidayu; Lim, Joanna M C; Hassan, Tiara; Tai, Mei-Chee; Allen, Jamie; Lee, Andrew; Taib, Nur Aishah Mohd; Yip, Cheng Har; Hartman, Mikael; Lim, Swee Ho; Tan, Ern Yu; Tan, Benita K T; Tan, Su-Ming; Tan, Veronique K M; Ho, Peh Joo; Khng, Alexis J; Dunning, Alison M; Li, Jingmei; Easton, Douglas F; Antoniou, Antonis C; Teo, Soo Hwang; Predicting the Likelihood of Carrying a BRCA1 or BRCA2 Mutation in Asian Patients With Breast Cancer.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2022; vol. 40 (no. 14); 1542-1551

Study details

Country/ies where study was carried out	Malaysia and Singapore
Study type	Cross sectional
Study dates	Not reported
Inclusion criteria	Women diagnosed clinically with breast cancer (invasive and noninvasive) who were recruited in the Malaysian Breast Cancer Genetic (MyBrCa) study and the Singapore Breast Cancer Cohort (SGBCC) study. Cases were recruited from two hospitals in Malaysia and six hospitals in Singapore.
Exclusion criteria	Not reported
Patient characteristics	Validation sample was N=2448 patients with breast cancer (N=95 *BRCA* carriers). **Gender:** not reported **Age (years, mean (SD)):** not reported

	Ethnicity: Chinese (75.4%), Malay and Indian (% not reported) **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	1. PENNII 2. KOHCal 3. BOADICEA version 5.0 4. ARiCA
Reference standard(s)	Germline DNA was sequenced in two batches, using targeted sequencing panels. Carriers of pathogenic variants in non-*BRCA* genes were treated as noncarriers.
Duration of follow-up	Not applicable
Sources of funding	Wellcome Trust (Grant No.: v203477/Z/16/Z). The Malaysian Breast Cancer Genetic Study was established using funds from the Malaysian Ministry of Science, and the Malaysian Ministry of Higher Education High Impact Research Grant (Grant No.: UM.C/HIR/MOHE/06), and additional funding was received from Yayasan Sime Darby, Yayasan PETRONAS, Estee Lauder Group of Companies, Khind Starfish Foundation, and other donors of Cancer Research Malaysia. The Singapore Breast Cancer Cohort was supported by the National Research Foundation Singapore (Grant No.: NRF-NRFF2017-02), NUS start-up Grant, National University Cancer Institute Singapore (NCIS) Centre Grant (Grant No.: NMRC/CG/NCIS/2010, NMRC/CG/012/2013, CGAug16M005), Breast Cancer Prevention Programme (BCPP), Asian Breast Cancer Research Fund, and the NMRC Clinician Scientist Award (SI Category; Grant No.: NMRC/CSA-SI/0015/2017) and the Breast Cancer Screening and Prevention Programme Grant (Grant No.: NUHSRO/2020/121/BCSPP/LOA). A.C.A. is supported by Cancer Research UK (Grant No.: C12292/A20861, PPRPGM-Nov20\100002).
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Antoniou, 2008

Bibliographic Reference	Antoniou, A C; Hardy, R; Walker, L; Evans, D G; Shenton, A; Eeles, R; Shanley, S; Pichert, G; Izatt, L; Rose, S; Douglas, F; Eccles, D; Morrison, P J; Scott, J; Zimmern, R L; Easton, D F; Pharoah, P D P; 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.; Journal of medical genetics; 2008; vol. 45 (no. 7); 425-31

Study details

Country/ies where study was carried out	UK

Study type	Retrospective cohort study
Study dates	Not reported
Inclusion criteria	• families with unknown mutation status when genetic testing was initiated • at least one family member (index case) was screened for *BRCA1* and/or *BRCA2* mutations using a primary mutation search, and information on the mutation-testing methods used was available.
Exclusion criteria	• Families if the age information on the index tested individual was not available • Ashkenazi Jewish origin
Patient characteristics	N=1934 families who underwent genetic testing **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA • BRCAPRO • Manchester • Myriad • IBIS
Reference standard(s)	• Germline pathogenic variant analysis

Duration of follow-up	na
Sources of funding	This study was supported by a grant from the UK Department of Health. PDPP is Cancer Research UK Senior Clinical Research Fellow. DFE is a Cancer Research UK principal research fellow. ACA is funded by CR-UK.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Date of birth and/or age data were completely missing for approximately 57% of all the individuals submitted. Families were excluded from the analyses if the age information on the index tested individual was not available and had to be inferred.)*

Antoniou, 2006

Bibliographic Reference	Antoniou, Antonis C; Durocher, Francine; Smith, Paula; Simard, Jacques; Easton, Douglas F; INHERIT BRCAs program, members; BRCA1 and BRCA2 mutation predictions using the BOADICEA and BRCAPRO models and penetrance estimation in high-risk French-Canadian families.; Breast cancer research : BCR; 2006; vol. 8 (no. 1); r3

Study details

Country/ies where study was carried out	Canada
Study type	Prospective cohort study
Study dates	Between 1996 and 2003
Inclusion criteria	High-risk French-Canadian breast and/or ovarian families Participants were required to meet one or more of the following criteria: • 4 first or second degree relatives diagnosed with breast and/or ovarian cancer at any age • 3 first degree relatives diagnosed at any age • family known to carry a deleterious gene (these individuals excluded from model comparisons) • over 18 years of age • mentally competent
Exclusion criteria	Not reported
Patient characteristics	N=188 families **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported

	Socioeconomic and geographical factors: not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA • BRCAPRO
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This work was supported by the Canadian Institutes of Health Research (CIHR) for the INHERIT BRCAs research program, Fonds de la Recherche en Santé du Québec (FRSQ)/Réseau de Médecine Génétique Appliquée (RMGA) and the Canadian Breast Cancer Research Alliance. ACA is funded by Cancer Research UK; FD is a recipient of a Research Career Award in the Health Sciences by IRSC/Rx&D HRF; PS was funded by the INHERIT BRCAs program; JS is Chair holder of the Canada Research Chair in Oncogenetics; and DFE is a Principal Research Fellow of Cancer Research UK.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Antonucci, 2017

Bibliographic Reference	Antonucci, Ivana; Provenzano, Martina; Sorino, Luca; Balsamo, Michela; Aceto, Gitana Maria; Battista, Pasquale; Euhus, David; Cianchetti, Ettore; Ballerini, Patrizia; Natoli, Clara; Palka, Giandomenico; Stuppia, Liborio; Comparison between CaGene 5.1 and 6.0 for BRCA1/2 mutation prediction: a retrospective study of 150 BRCA1/2 genetic tests in 517 families with breast/ovarian cancer.; Journal of human genetics; 2017; vol. 62 (no. 3); 379-387

Study details

Country/ies where study was carried out	Italy
Study type	Retrospective cohort study
Study dates	Between 2000 and 2013
Inclusion criteria	Patients selected for molecular analysis if: • 'BRCAPRO' positive after risk evaluation with CaGene 5.1 or 6.0 (CP ⩾10%) (55 patients) • or entering in the high CP risk category based on pedigree analysis, although being BRCAPRO negative for both CaGene 5.1 and 6.0 (95 patients).
Exclusion criteria	Not reported
Patient characteristics	N=517 subjects submitted to genetic counselling but n=150 (29%) were selected for molecular analysis

	Gender: 10/150 males **Age (years, mean (range)):** affected by breast cancer = 45 (22-77); affected by ovarian cancer = 43 (19-60) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO 5.1 • BRCAPRO 6.0
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Barcenas, 2006

Bibliographic Reference	Barcenas, Carlos H; Hosain, G M Monawar; Arun, Banu; Zong, Jihong; Zhou, Xiaojun; Chen, Jianfang; Cortada, Jill M; Mills, Gordon B; Tomlinson, Gail E; Miller, Alexander R; Strong, Louise C; Amos, Christopher I; Assessing BRCA carrier probabilities in extended families.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2006; vol. 24 (no. 3); 354-60

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	Between 1996 and 2003
Inclusion criteria	• Pedigrees of families recruited between 1996 and 2003 at high-risk cancer genetic clinics affiliated with the Texas Cancer Genetics Consortium
Exclusion criteria	Not reported

Patient characteristics	Pedigree data from N=472 families **Gender:** males = 14/472 **Age (years, mean (SD)):** 50 (11) **Ethnicity:** Ashkenazi Jewish descent = 97/472 **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA • BRCAPRO • Myriad II
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Berrino, 2015

Bibliographic Reference	Berrino, Jacopo; Berrino, Franco; Francisci, Silvia; Peissel, Bernard; Azzollini, Jacopo; Pensotti, Valeria; Radice, Paolo; Pasanisi, Patrizia; Manoukian, Siranoush; Estimate of the penetrance of BRCA mutation and the COS software for the assessment of BRCA mutation probability.; Familial cancer; 2015; vol. 14 (no. 1); 117-28

Study details

Country/ies where study was carried out	Italy
Study type	Cross sectional study (for model validation)
Study dates	Families were recruited between 2004 and 2008
Inclusion criteria	Families eligible for genetic counselling and *BRCA* testing based on the number of cases and ages at diagnosis of breast and ovarian cancer.

Exclusion criteria	Families with variants of uncertain significance were excluded from the study.
Patient characteristics	Pedigree and mutation status data from N=436 families **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	4 carrier prediction models: • COS (European case-only study) updated for the Italian population with new penetrance estimates of both BC and OC • BOADICEA • BRCAPRO 5.1 • BRCAPRO 6.0
Reference standard(s)	*BRCA* gene mutation testing was performed either by denaturing high performance liquid chromatography (DHPLC) or by direct sequencing or by a combination of both methods examining all coding exons and corresponding splice sites of both genes. People who tested negative at these analyses were investigated for the occurrence of large genomic rearrangements by multiple ligation-dependant probe amplification (MLPA), using commercially available kits (MRC-Holland).

	BRCA1 or *BRCA2* positive was defined as: • variants generating a premature stop codon • base pair changes, confirmed splicing mutations and genomic deletions leading to the loss of the translation start point • confirmed splicing mutations and genomic deletions leading to the in-frame loss of exonic region coding for functional protein domains • variants at the nearly invariant GT and AT dinucleotides at the 5' and 3' intron ends, which are predicted to affect mRNA splicing • missense mutations and small in-frame deletions classified as pathogenic by multifactorial probability based models • missense mutations affecting the highly conserved cysteine residues of the RING-finger domain of the BRCA1 proteind *BRCA* mutation negative was defined as: • none of the above genetic alterations • no variants of uncertain significance
Duration of follow-up	Not applicable.
Sources of funding	The 6th Framework Program of the European Community and the Fondazione IRCCS Istituto Nazionale dei Tumori.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Berry, 2002

Bibliographic Reference	Berry, Donald A; Iversen, Edwin S Jr; Gudbjartsson, Daniel F; Hiller, Elaine H; Garber, Judy E; Peshkin, Beth N; Lerman, Caryn; Watson, Patrice; Lynch, Henry T; Hilsenbeck, Susan G; Rubinstein, Wendy S; Hughes, Kevin S; Parmigiani, Giovanni; BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2002; vol. 20 (no. 11); 2701-12

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	Between 1995 and 1998
Inclusion criteria	The criteria used to refer individuals to the cancer genetic counselling services is unclear. However, every family was included for which at least one member had been tested, regardless of family history.

Exclusion criteria	• A family was excluded if the proband had not completed testing of both genes
Patient characteristics	N=301 probands who underwent genetic testing; 216 (71%) were at high risk for carrying mutations on the basis of having three or more cases of having breast or ovarian cancer **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** Ashkenazi Jewish = 42% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(All individuals referred to a cancer genetic counselling service appeared eligible for inclusion. Referral criteria are unclear. Every family for which at least one member had been tested were included, regardless of family history.)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Biswas, 2013

Bibliographic Reference	Biswas, Swati; Atienza, Philamer; Chipman, Jonathan; Hughes, Kevin; Barrera, Angelica M Gutierrez; Amos, Christopher I; Arun, Banu; Parmigiani, Giovanni; Simplifying clinical use of the genetic risk prediction model BRCAPRO.; Breast cancer research and treatment; 2013; vol. 139 (no. 2); 571-9

Study details

Country/ies where study was carried out	USA
Study type	Cross-sectional study
Study dates	Not reported, but data collected before 2007
Inclusion criteria	Probands with family history information and genetic test results. Used the data from Parmigiani 2007 (3 population based samples of participants in research studies and 8 samples from genetic counselling clinics) as well as additional more up to date data from MD Anderson Cancer Center.
Exclusion criteria	Not reported
Patient characteristics	Data from 2713 probands, 576 (21.2%) are *BRCA* mutation carriers **Gender:** males tested 3.2% **Age (years, mean (SD)):** median age 49 years (IQR 17 years) **Ethnicity:** Ashkenazi Jewish descent 27.4% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO - using the version in BayesMendel 2.0-8 • BRCAPROLYTE - (simplified BRCAPRO by only collecting a limited family history) which evaluates BRCAPRO using age of the proband and ages of diagnosis for affected first- and second-degree relatives • BRCAPROLYTE-Plus - extends BRCAPROLYTE by imputing the ages of unaffected relatives • BRCAPROLYTE-Simple - simplifies BRCAPROLYTE by not collecting the family structure • FHAT - Family History Assessment Tool

Reference standard(s)	• Germline pathogenic variant analysis but techniques used are not reported
Duration of follow-up	Not applicable
Sources of funding	Susan G Komen grant KG081303, National Cancer Institute grants 1R03CA173834-01 and 2P30CA006516-47 and the Dana Farber Cancer Institute
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Families were obtained from the Cancer Genetics Network Carrier Probability Validation project and who had already been selected based on family history information and genetic test results)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(The data used are mostly from high-risk families)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(No details of techniques used for germline pathogenic variant analysis – techniques would pre-date 2007.)*

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(No details of techniques used for germline pathogenic variant analysis – techniques would pre-date 2007.)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Biswas, 2012

Bibliographic Reference	Biswas, Swati; Tankhiwale, Neelam; Blackford, Amanda; Barrera, Angelica M Gutierrez; Ready, Kaylene; Lu, Karen; Amos, Christopher I; Parmigiani, Giovanni; Arun, Banu; Assessing the added value of breast tumor markers in genetic risk prediction model BRCAPRO.; Breast cancer research and treatment; 2012; vol. 133 (no. 1); 347-55

Study details

Country/ies where study was carried out	USA
Study type	Cross-sectional study
Study dates	Families included in the model validation sample had their data collected before 2009
Inclusion criteria	Not reported - data collected at MD Anderson Cancer Center.
Exclusion criteria	Families without intact data were excluded from the validation set. For example, if any family member was known to be affected but his/her affection age was missing, that family was excluded from the validation sample.
Patient characteristics	N=796 families who underwent genetic testing **Gender:** Males tested 1.1% **Age (years, mean (SD)):** median age of probands 46 years (IQR 16 years)

	Ethnicity: Ashkenazi Jewish = 10% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	4 models were tested - using different versions of BayesMendel, the parent package of BRCAPRO and by including or omitting tumour marker information from the family history. Only the last model is included in our analysis as it uses all the marker information and the more up-to-date version of BRCAPRO. • Model 1.4-3, named after the version number of BayesMendel, the parent package of BRCAPRO. It was previously validated, but it could include relatives only up to the second degree, and is examined as a baseline; the remaining models account for any degree/type of relative: • ‘‘No ER/PR’’ with no marker information • ‘‘ER/PR’’, with ER and PR only, • ‘‘ER/PR, Her-2’’ with ER, PR, and Her-2/neu. Model (4) is available in version 2.0-6 of BayesMendel; Models 2 & 3 were also derived from version 2.0-6 of BayesMendel but omitted some or all of the tumour marker information from the family history.
Reference standard(s)	Not reported
Duration of follow-up	Not applicable
Sources of funding	Susan G Komen for the Cure Grant KG081303, an Intramural Seed Grant from the University of North Texas Health Science Center, and the Program in Human and Computational Genomics at MDACC.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Family data obtained from a high risk cancer centre)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Looks like data used are mostly from high-risk families)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Genetic testing techniques not reported)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(Genetic testing techniques not reported)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Bodmer, 2006

Bibliographic Reference	Bodmer, D; Ligtenberg, M J L; van der Hout, A H; Gloudemans, S; Ansink, K; Oosterwijk, J C; Hoogerbrugge, N; Optimal selection for BRCA1 and BRCA2 mutation testing using a combination of 'easy to apply' probability models.; British journal of cancer; 2006; vol. 95 (no. 6); 757-62

Study details

Country/ies where study was carried out	The Netherlands
Study type	Retrospective cohort study
Study dates	Between 1999 and 2001
Inclusion criteria	• Selection for genetic testing based on expert opinion of clinical geneticist
Exclusion criteria	Not reported
Patient characteristics	N=263 families with breast and/or ovarian cancer patients that were tested for *BRCA* mutations **Gender:** not reported **Age (years, mean (SD)): not reported** **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• Frank • Gilpin
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported

Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Capalbo, 2006

Bibliographic Reference	Capalbo, C; Ricevuto, E; Vestri, A; Ristori, E; Sidoni, T; Buffone, O; Adamo, B; Cortesi, E; Marchetti, P; Scambia, G; Tomao, S; Rinaldi, C; Zani, M; Ferraro, S; Frati, L; Screpanti, I; Gulino, A; Giannini, G; BRCA1 and BRCA2 genetic testing in Italian breast and/or ovarian cancer families: mutation spectrum and prevalence and analysis of mutation prediction models.; Annals of oncology : official journal of the European Society for Medical Oncology; 2006; vol. 17suppl7; vii34-40

Study details

Country/ies where study was carried out	Italy
Study type	Prospective cohort study
Study dates	Between 2002 and 2005
Inclusion criteria	• 3 or more breast cancer cases diagnosed at any age or two first degree relatives affected before 50 • early onset breast cancer (>35 years) • breast and ovarian cancer in the same individual or one breast cancer case and at least one ovarian, or one breast and one ovarian diagnosed before 50 in first degree relatives • 2 or more ovarian cancer cases • male breast cancer
Exclusion criteria	Not reported
Patient characteristics	N=99 Italian probands with a family history of breast cancer **Gender:** not reported **Age (years, mean (SD)):** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • Myriad • IC model

Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This work was partially supported by grants from Associazione Italiana per la Ricerca sul Cancro, Ministry of Health, the National Research Council (CNR), the Ministry of University and Research, the Pasteur Institute, Cenci-Bolognetti Foundation.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Chew, 2018

Bibliographic Reference	Chew, Winston; Moorakonda, Rajesh Babu; Courtney, Eliza; Soh, Hazel; Li, Shao Tzu; Chen, Yanni; Shaw, Tarryn; Allen, John Carson; Evans, Dafydd Gareth R; Ngeow, Joanne; Evaluation of the relative effectiveness of the 2017 updated

Manchester scoring system for predicting BRCA1/2 mutations in a Southeast Asian country.; Journal of medical genetics; 2018; vol. 55 (no. 5); 344-350

Study details

Country/ies where study was carried out	Singapore
Study type	Cross-sectional study
Study dates	2014 to 2017
Inclusion criteria	Consecutive index patients from unrelated families, who had undergone clinical primary germline mutation testing for *BRCA1/2* mutations at the Cancer Genetics Service at the National Cancer Centre Singapore.
Exclusion criteria	Patients from families with a known BRCA1/2 mutation prior to genetic testing were excluded.
Patient characteristics	N=330 Singaporean probands from unrelated families; N=47 had either *BRCA1* or *BRCA2* mutation **Gender:** not reported (1 male breast cancer index patient) **Age (years, mean (SD)):** not reported **Ethnicity:** Chinese 69.7%, Indian 5.5%, Malay 9.4%, others 15.5% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	Three versions of the Manchester Scoring System (MSS) were used: • MSS1 the original model

	• MSS2 the first iteration which added scores based on breast histopathological markers, such as grade, morphology and receptor status of the index patient • MSS3 the second iteration with changes including: adding scores for adopted patients (family history unknown), increasing the downward adjustment for HER2 receptor status and increasing the weightage for TNBC and high-grade serous ovarian cancer
Reference standard(s)	Patients were tested using next-generation sequencing (NGS) panels that included full gene sequencing as well as coverage for large deletion/duplications in *BRCA1/2*. The NGS panels used were either organ specific (for example, breast cancer panel) or pan-cancer panel, determined by a combination of family history factors and/or patient preferences.
Duration of follow-up	Not applicable
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Cropper, 2017

Bibliographic Reference	Cropper, Caiqian; Woodson, Ashley; Arun, Banu; Barcenas, Carlos; Litton, Jennifer; Noblin, Sarah; Liu, Diane; Park, Minjeong; Daniels, Molly; Evaluating the NCCN Clinical Criteria for Recommending BRCA1 and BRCA2 Genetic Testing in Patients With Breast Cancer.; Journal of the National Comprehensive Cancer Network : JNCCN; 2017; vol. 15 (no. 6); 797-803

Study details

Country/ies where study was carried out	USA
Study type	Cross-sectional (retrospective chart review).
Study dates	2013 to 2014
Inclusion criteria	People seen for genetic counselling with a personal history of either invasive breast cancer or ductal carcinoma in situ and complete 3-generation pedigrees available for review. All had undergone clinical genetic testing that included *BRCA1/2*.
Exclusion criteria	Participants who underwent *BRCA1/2* testing without having met any NCCN criteria for hereditary breast or ovarian cancer genetic testing.
Patient characteristics	N=1072 patients; N=99 had either *BRCA1* or *BRCA2* mutation **Gender:** 7.6% male **Age (years, mean (SD)):** 51.1 years (12.1) **Ethnicity:** Ashkenazi Jewish 5.6% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported

	Non-binary people: not reported
Index test(s)	NCCN (v 1.2014) clinical criteria for recommending BRCA testing: • Breast cancer (BC) at age ≤45 y • BC at age ≤50 y with 2nd breast primary at any age • BC at age ≤50 y with ≥1 close blood relative with breast cancer at any age • BC at age ≤50 y with unknown or limited family history • BC at age ≤60 y with triple-negative HR status • BC at any age with ≥1 close blood relatives with breast cancer at age ≤ 50 years • BC at any age with ≥2 close blood relatives with breast cancer at any age • BC at any age with ≥1 close blood relatives with epithelial ovarian cancer • BC at any age with ≥2 close blood relatives with pancreatic or high-grade prostate cancer • BC at any age with a close male relative with breast cancer • personal history of both breast and epithelial ovarian cancer • personal history of male breast cancer • BC at any age as an individual of ethnicity with higher mutation frequency (eg, Ashkenazi Jewish) Analysis was done for patients meeting only 1 of the criteria versus those meeting 2 or more criteria.
Reference standard(s)	All patients had undergone clinical genetic testing that included BRCA1 and BRCA2 and other high penetrance genes as indicated based on personal/family history. Techniques not reported.
Duration of follow-up	Not applicable.
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Relatively high risk group as they had to meet NCCN referral for testing criteria)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Testing methods not reported)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(Testing methods not reported)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Daniels, 2014

Bibliographic Reference	Daniels, M.S.; Babb, S.A.; King, R.H.; Urbauer, D.L.; Batte, B.A.L.; Brandt, A.C.; Amos, C.I.; Buchanan, A.H.; Mutch, D.G.; Lu, K.H.; Underestimation of risk of a BRCA1 or BRCA2 mutation in women with high-grade serous ovarian cancer by BRCAPRO: A multi-institution study; Journal of Clinical Oncology; 2014; vol. 32 (no. 12); 1249-1255

Study details

Country/ies where study was carried out	USA
Study type	Cross sectional (retrospective chart review)
Study dates	1996 to 2011

Inclusion criteria	Women who had been diagnosed with invasive epithelial ovarian cancer (including fallopian tube or primary peritoneal cancer), had been referred for genetic counselling (where complete pedigrees including all first- and second-degree relatives with and without cancer were collected as standard), and had undergone *BRCA1/BRCA2* genetic testing were included. Women were identified from the records of 3 participating centres: MD Anderson Cancer Center, Washington University and Duke University.
Exclusion criteria	Not reported
Patient characteristics	N=589 patients; N=180 had either *BRCA1* or *BRCA2* mutation; N=413 had OC with high grade serous component **Gender:** 7.6% male **Age (years, mean (SD)):** 55 years (11) at OC diagnosis **Ethnicity:** Ashkenazi Jewish 10% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO scores were calculated using CancerGene v5.1
Reference standard(s)	• BRCA1/BRCA2 genetic testing - methods not reported
Duration of follow-up	Not applicable
Sources of funding	Financial support: Karen H. Lu (one of the authors)
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Mutation testing methods not reported)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(Mutation testing methods not reported)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

de la Hoya, 2003

Bibliographic Reference	de la Hoya, M; Diez, O; Perez-Segura, P; Godino, J; Fernandez, J M; Sanz, J; Alonso, C; Baiget, M; Diaz-Rubio, E; Caldes, T; Pre-test prediction models of BRCA1 or BRCA2 mutation in breast/ovarian families attending familial cancer clinics.; Journal of medical genetics; 2003; vol. 40 (no. 7); 503-10

Study details

Country/ies where study was carried out	Spain
Study type	Retrospective cohort study
Study dates	Not reported

Inclusion criteria	• Pedigrees selected for complete *BRCA* gene sequencing on the basis of cancer family history information suggestive of an inherited breast and ovarian cancer predisposition (all pedigrees included at least three or more first or second degree relatives affected with breast or ovarian cancer in the same lineage). Pedigrees were constructed on the basis of an index case considered to have the highest probability of being a deleterious mutation carrier (generally the youngest affected subject available in each family).
Exclusion criteria	not reported
Patient characteristics	N=109 Spanish breast/ovarian families previously screened for germline mutations in both the *BRCA1* and *BRCA2* genes. **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• HCSE • LUMC • U-PENN • HUCH • Frank • Counsellor
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na

Sources of funding	This work was supported by Fondo de Investigación Sanitaria (FIS) grant number 01/3040, 01/0024-02, 01/0024-03. Javier Godino is a fellow of FIS (99/1906).
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Test threshold is unclear, looks like 10%)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Eoh, 2017

Bibliographic Reference	Eoh, Kyung Jin; Park, Ji Soo; Park, Hyung Seok; Lee, Seung-Tae; Han, Jeongwoo; Lee, Jung-Yun; Kim, Sang Wun; Kim, Sunghoon; Kim, Young Tae; Nam, Eun Ji; BRCA1 and BRCA2 mutation predictions using the BRCAPRO and Myriad models in Korean ovarian cancer patients.; Gynecologic oncology; 2017; vol. 145 (no. 1); 137-141

Study details

Country/ies where study was carried out	South Korea
Study type	Cross sectional (retrospective case review)
Study dates	2010 to 2016
Inclusion criteria	Patients with ovarian cancer referred to the Department of Obstetrics and Gynecology at the Severance Hospital of Yonsei University for genetic counselling and who underwent genetic testing between November 2010 and August 2016
Exclusion criteria	Not reported.
Patient characteristics	N=232 patients with ovarian cancer; N=57 had a *BRCA1/2* mutation **Gender:** not reported **Age (years, median):** 54 years at presentation **Ethnicity:** Korean 99.1% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO using CancerGene software, version 5.1 • MYRIAD using CancerGene software, version 5.1
Reference standard(s)	Genetic testing for *BRCA1/2* mutations: all small base pair variations were identified using Sanger sequencing on a 3730 DNA Analyzer with the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems,Foster City, CA, USA). Sequencing data were aligned against appropriate reference sequences and analyzed using the Sequencher 5.3 software (Gene Codes Corp., Ann Arbor, MI, USA).

Duration of follow-up	Not applicable
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Euhus, 2002

Bibliographic Reference	Euhus, David M; Smith, Kristin C; Robinson, Linda; Stucky, Amy; Olopade, Olufunmilayo I; Cummings, Shelly; Garber, Judy E; Chittenden, Anu; Mills, Gordon B; Rieger, Paula; Esserman, Laura; Crawford, Beth; Hughes, Kevin S; Roche, Connie A; Ganz, Patricia A; Seldon, Joyce; Fabian, Carol J; Klemp, Jennifer; Tomlinson, Gail; Pretest prediction of BRCA1 or BRCA2

mutation by risk counselors and the computer model BRCAPRO.; Journal of the National Cancer Institute; 2002; vol. 94 (no. 11); 844-51

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	Not reported
Inclusion criteria	• Pedigrees from families who had obtained *BRCA* gene mutation testing
Exclusion criteria	• pedigrees for any families that had not undergone complete *BRCA1* and *BRCA2* gene sequencing, regardless of whether a mutation had been identified • pedigrees from families in which the proband was not affected by either breast or ovarian cancer • pedigrees from families with mutations of uncertain clinical significance • families that were ascertained through a mutation screening research project rather than through a clinical counselling setting • pedigrees that were exact duplicates of pedigrees submitted by another institution
Patient characteristics	N=148 pedigrees from families who had obtained *BRCA* gene mutation testing through several different university-based clinical cancer genetics programs. **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** with Ashkenazi Jewish ancestry = 15/148 **Socioeconomic and geographical factors:** not reported

	Disabilities: not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• Risk counsellor [the risk counsellors were asked to estimate the probability of BRCA gene mutation for each pedigree by using a five-point scale ((1) ≤ 10%; (2) 11%–30%; (3) 31%–70%; (4) 71%–94%; and (5) ≥ 95%)] • BRCAPRO
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Pedigrees were obtained from a highly pre-screened selection of women attending a cancer genetics clinic who had already been selected for complete BRCA gene sequencing on the basis of family history information suggestive of an inherited breast and ovarian cancer predisposition.)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Evans, 2004

Bibliographic Reference	Evans, D G R; Eccles, D M; Rahman, N; Young, K; Bulman, M; Amir, E; Shenton, A; Howell, A; Lalloo, F; A new scoring system for the chances of identifying a BRCA1/2 mutation outperforms existing models including BRCAPRO.; Journal of medical genetics; 2004; vol. 41 (no. 6); 474-80

Study details

Country/ies where study was carried out	UK
Study type	Retrospective cohort study
Study dates	Not reported
Inclusion criteria	• affected individuals with breast and/or ovarian cancer, with a family history of breast or ovarian cancer, were ascertained from attendees at cancer genetics clinics in the Manchester region of North West England • informed consent for mutation screening of *BRCA1* and *BRCA2*

	• samples were initially prioritised using a clinician's assessment of the likelihood of identifying a mutation: minimal requirement was two close relatives (usually first degree relatives of each other) with breast cancer at 50 years of age, but combinations of male and female breast cancer and breast and ovarian cancer were particularly prioritised for mutation analysis. Exceptions to this were two research projects where population based cases of breast cancer at, 31 years of age and sporadic breast cancer at 35 years of age were screened for mutations in both genes.
Exclusion criteria	Not reported
Patient characteristics	N=258 individuals from the North West of England with a family history of breast cancer **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • Manchester • FRANK
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Evans, 2009

Bibliographic Reference	Evans, D G R; Lalloo, F; Cramer, A; Jones, E A; Knox, F; Amir, E; Howell, A; Addition of pathology and biomarker information significantly improves the performance of the Manchester scoring system for BRCA1 and BRCA2 testing.; Journal of medical genetics; 2009; vol. 46 (no. 12); 811-7

Study details

Country/ies where study was carried out	UK
Study type	Retrospective case series
Study dates	Between 1960 and 1990
Inclusion criteria	Patients with breast cancer (diagnosed between 1960 and 1990) who were also fully tested for *BRCA1/2* and had pathology data, identified from the records of a regional medical genetics service.
Exclusion criteria	Not reported
Patient characteristics	2156 patients with breast (N=1918) or ovarian cancer (N=238). Pathology data were available for 1116 patients **Gender:** not reported **Age (years, median):** for those with available pathology results range between 32 and 56 **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• Manchester (adjusted for pathology and receptor status) - MSS1 • Manchester (unadjusted for pathology and receptor status) - MSS2
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na

Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Pathology data were available for less than half of the included patients)*

Evans, 2017

Bibliographic Reference	Evans, D Gareth; Harkness, Elaine F; Plaskocinska, Inga; Wallace, Andrew J; Clancy, Tara; Woodward, Emma R; Howell, Tony A; Tischkowitz, Marc; Lalloo, Fiona; Pathology update to the Manchester Scoring System based on testing in over 4000 families.; Journal of medical genetics; 2017; vol. 54 (no. 10); 674-681

Study details

Country/ies where study was carried out	UK
Study type	Cross sectional study
Study dates	Validation data gathered between 2013 and 2015
Inclusion criteria	The Manchester Scoring System v 3 (MSS3) was developed using empirical data gathered from the Manchester mutation-screening programme. These were index cases from unrelated families affected by breast or ovarian cancer. The MSS3 validation sample was a population based series from Cambridge of women (> 18 years) diagnosed with high-grade serous or endometrioid ovarian cancer within the last 12 months, but at any age and irrespective of family history (GTEOC study).
Exclusion criteria	Not reported
Patient characteristics	N=231 women with epithelial ovarian cancer. N=17 had *BRCA1/2* mutation **Gender:** 100% female **Age (years, mean (SD)):** not reported **Ethnicity:** not reported (the Jewish population is excluded from the Manchester score) **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• Manchester Scoring System v2 (MSS2) • Manchester Scoring System v3 (MSS3) - adding additional points for high-grade serous ovarian cancer and adding grade score to those with triple-negative breast cancer, while reducing the score for those with HER2+ breast cancer

	• BOADICEA
Reference standard(s)	Mutation testing: until 2013, testing involved Sanger sequencing of all coding exons and intron/exon boundaries as well as Multiplex Ligation dependent Probe Amplification (MLPA) to test for large rearrangements. Since 2013, testing has involved next-generation sequencing analysis of the coding sequences of both genes plus MLPA.
Duration of follow-up	Not applicable
Sources of funding	National Institute for Health Research (NIHR) and the Genesis Prevention Appeal
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Fasching, 2007

Bibliographic Reference	Fasching, Peter A; Bani, Mayada R; Nestle-Kramling, Carolin; Goecke, Tim O; Niederacher, Dieter; Beckmann, Matthias W; Lux, Michael P; Evaluation of mathematical models for breast cancer risk assessment in routine clinical use.; European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP); 2007; vol. 16 (no. 3); 216-24

Study details

Country/ies where study was carried out	Germany
Study type	Prospective cohort study
Study dates	Between 1994 and 2001
Inclusion criteria	• 2 first degree female relatives with a history of invasive breast or ovarian cancer, with one of them at least 50 years old at the onset of disease • 1 first-degree female relative with a history of invasive breast or ovarian cancer younger than 30 years old at the onset of disease • 1 first degree male relative with a history of invasive breast cancer
Exclusion criteria	Not reported
Patient characteristics	N=111 breast cancer affected patients from 103 kindreds with a family history of breast cancer **Gender:** not reported **Age (years, mean (range)):** 45.8 (44.4 - 47.2) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported

	People with communication needs (for example, not English 1st language): not reported **Non-binary people:** not reported
Index test(s)	• Tyrer-Cuzick • MENDEL • BRCAPRO
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Test threshold is unclear, looks like 10%)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Fischer, 2013

Bibliographic Reference	Fischer, Christine; Kuchenbacker, Karoline; Engel, Christoph; Zachariae, Silke; Rhiem, Kerstin; Meindl, Alfons; Rahner, Nils; Dikow, Nicola; Plendl, Hansjorg; Debatin, Irmgard; Grimm, Tiemo; Gadzicki, Dorothea; Flottmann, Ricarda; Horvath, Judit; Schrock, Evelin; Stock, Friedrich; Schafer, Dieter; Schwaab, Ira; Kartsonaki, Christiana; Mavaddat, Nasim; Schlegelberger, Brigitte; Antoniou, Antonis C; Schmutzler, Rita; German Consortium for Hereditary Breast and Ovarian, Cancer; 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.; Journal of medical genetics; 2013; vol. 50 (no. 6); 360-7

Study details

Country/ies where study was carried out	Germany
Study type	Cross sectional (retrospective case review)
Study dates	1997 to 2011
Inclusion criteria	A family was eligible if at least one of the following criteria was fulfilled: 1. ≥3 female family members diagnosed with breast cancer 2. ≥2 women diagnosed with breast cancer, one of whom is diagnosed at ≤50 years of age 3. families with ≥1 female diagnosed breast cancer and one diagnosed with ovarian cancer (or in the same woman) 4. ≥1 woman with breast cancer diagnosed before 36 years 5. ≥1 female family member diagnosed with bilateral breast cancer (first cancer diagnosed before 51 years) 6. ≥1 female family member diagnosed with ovarian cancer before 41 years 7. ≥2 female family members diagnosed with ovarian cancer 8. ≥1 male and ≥1 female diagnosed with breast cancer
Exclusion criteria	Not reported

Patient characteristics	N=7352 index patients from families with a history of breast or ovarian cancer. N=1774 were *BRCA1/2* mutation carriers. Evaluation of BOADICEA-path was carried out in a subset of N=4927 pedigrees from the overall sample in which at least one family member had data on tumour markers. **Gender:** male 1.2% of index patients **Age (years, median(IQR)):** age of onset of BC 43.3 (35.9 to 49.6), age of onset of OC 50.5 (43.1 to 59.5) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA • BRCAPRO • IBIS • eCLAUS • BOADICEA-Path (Antoniou 2012)
Reference standard(s)	Mutation testing: High performance liquid chromatography (dHPLC) of PCR products encompassing all coding exons of the *BRCA1* and *BRCA2* genes and subsequent sequencing of conspicuous amplicons or direct sequencing of all *BRCA* amplicons was performed. Sequences of both genes were evaluated based on the NCBI (National Center for Biotechnology Information) cDNA reference sequences U14680.1 (*BRCA1* gene) and U43746.1 (*BRCA2* gene). In case of negative sequencing results, analysis for deletions or duplications of the *BRCA1* gene was carried out by multiplex ligation-dependent probe amplification.
Duration of follow-up	Not applicable
Sources of funding	Deutsche Krebshilfe, grant number 109076 and 109030. Statistical analysis was supported by CR-UK grant: C12292/A11174.

Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Gerdes, 2006

Bibliographic Reference	Gerdes, A-M; Cruger, D G; Thomassen, M; Kruse, T A; Evaluation of two different models to predict BRCA1 and BRCA2 mutations in a cohort of Danish hereditary breast and/or ovarian cancer families.; Clinical genetics; 2006; vol. 69 (no. 2); 171-8

Study details

Country/ies where study was carried out	Denmark
Study type	Cross sectional study (retrospective case review)
Study dates	1993 to 2005

Inclusion criteria	Families who had *BRCA1/2* mutation analysis at either of 2 clinical genetics departments from 1993 to 2005 in southwestern Denmark.
Exclusion criteria	Not reported
Patient characteristics	N=267 index patients from families with a history of breast or ovarian cancer. N=76 were *BRCA1/2* mutation carriers. N=110 index patients had ovarian cancer. **Gender:** male 5.6% of index patients **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• Manchester Scoring System - 2006 version MSS1 • Frank 2/ Myriad model - version from spring 2005
Reference standard(s)	Mutation analysis: the entire coding region and splice sites were screened in *BRCA1* and *BRCA2*. Exon 11 of *BRCA1* and exons 10 and 11 of *BRCA2* were PCR amplified and screened with the protein truncation test. The rest of the coding exons were PCR amplified with one PCR product covering each exon and examined with denaturing high-performance liquid chromatography (DHPLC). Large genomic rearrangements were examined by the Multiplex Ligation-dependent Probe Amplification system (MLPA.
Duration of follow-up	Not applicable
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear (*Wide criteria for testing were used mainly because no national or international guidelines existed back in 1993 when some of the samples were collected)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Families with high-risk family history)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Hung, 2019

Bibliographic Reference	Hung, Fei-Hung; Wang, Yong Alison; Jian, Jhih-Wei; Peng, Hung-Pin; Hsieh, Ling-Ling; Hung, Chen-Fang; Yang, Max M; Yang, An-Suei; Evaluating BRCA mutation risk predictive models in a Chinese cohort in Taiwan.; Scientific reports; 2019; vol. 9 (no. 1); 10229

Study details

Country/ies where study was carried out	Taiwan
Study type	Cross-sectional diagnostic accuracy study
Study dates	July 2015 to April 2017
Inclusion criteria	Family history of ovarian or breast cancer at any age (2 or more individuals on the same lineage of the family), personal history of ovarian or breast cancer with age of diagnosis less than or equal to 40, bilateral breast cancer, triple negative breast cancer, or both ovarian and breast cancer in the same individual.
Exclusion criteria	Known mutation status in any cancer susceptibility genes and male probands
Patient characteristics	N=647 women, who underwent germline DNA sequencing of a cancer susceptibility gene panel. Age (mean, range): 50.2 (16-96) Personal history of BC/OC: 503 (77.7%) Family history of BC/OC: 385 (59.5%) In those with BC/OC, age on onset <40: 265 (52.7%) In those with BC/OC, ovarian cancer: 10 (2.0%)
Index test(s)	5 models
Reference standard(s)	Germline pathogenic variant analysis via exonal and exon-flanking region sequencing on a next generation sequencing platform
Duration of follow-up	na
Sources of funding	Health and welfare surcharge of tobacco products in Taiwan (Ministry of Health and Welfare), the Ministry of Science and Technology and the Taiwan Protein Project
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Huo, 2009

Bibliographic Reference	Huo, Dezheng; Senie, Ruby T; Daly, Mary; Buys, Saundra S; Cummings, Shelly; Ogutha, Jacqueline; Hope, Kisha; Olopade, Olufunmilayo I; Prediction of BRCA Mutations Using the BRCAPRO Model in Clinic-Based African American, Hispanic, and Other Minority Families in the United States.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2009; vol. 27 (no. 8); 1184-90

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort
Study dates	1993 to 1996

Inclusion criteria	Self-reported African American, Hispanic, Asian-American, and Native American families. A family was eligible if at least one member had been tested for *BRCA1* and *BRCA2* mutations. For families with two or more members tested, the first family member enrolled at the respective institutions was designated as the proband. Families were identified via 2 sources: the Breast Cancer Family Registry a consortium established by the National Cancer Institute in 1995 or the Cancer Risk Clinic at the University of Chicago.
Exclusion criteria	Families with Ashkenazi Jewish ancestry were excluded from the analysis.
Patient characteristics	N=267 index patients from families with a history of breast or ovarian cancer. N=76 were *BRCA1/2* mutation carriers. N=110 index patients had ovarian cancer. **Gender:** male 5.6% of index patients **Age (years, mean (SD)):** not reported **Ethnicity:** African American 104/267, Hispanic 13-/267, Asian American 37/267, Other 21/267 **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO - implemented using the BayesMendel 1.3-2 package in R
Reference standard(s)	Full sequencing analysis was done for probands, and single-site testing for the family-specific mutation was done for relatives of mutation-positive probands. For participants from the BCFR Philadelphia site, polymerase chain reaction fragments that covered the *BRCA1* and *BRCA2* genes were analyzed by using the enzyme mutation detection assay or heteroduplex analysis. Candidate mutations were confirmed by using direct sequencing. Test results were considered positive if the mutation was protein truncating (ie, nonsense, frame-shifting insertions or deletions, splice site mutations) or a known deleterious missense mutation according to the Breast Cancer Information Core. Variants of unknown significance were considered negative.
Duration of follow-up	Not applicable.

Sources of funding	Supported by National Cancer Institute Grant No. CA-RO1 89085-01A, by the Falk Medical Research Trust, and by the Entertainment Industry National Women's Cancer Research Alliance.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

James, 2006

Bibliographic Reference	James, Paul A; Doherty, Rebecca; Harris, Marion; Mukesh, Bickol N; Milner, Alvin; Young, Mary-Anne; Scott, Clare; Optimal selection of individuals for BRCA mutation testing: a comparison of available methods.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2006; vol. 24 (no. 4); 707-15

Study details

Country/ies where study was carried out	Australia
Study type	Retrospective cohort study
Study dates	Between 1997 and 2003
Inclusion criteria	• at least 2 first or second degree relatives with breast or ovarian cancer • at least 1 additional high risk feature (an individual diagnosed with BC before 40, or OC before 50; bilateral breast or breast and ovarian cancer; male breast cancer; or Ashkenazi Jewish decent)
Exclusion criteria	Not reported
Patient characteristics	N=257 families who had completed *BRCA1/2* mutation screening **Gender:** female = 97% **Age (years, median (range)):** 52 (28-94) **Ethnicity:** Ashkenazi ancestry = 15% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • Manchester • FRANK • COUCH • FHAT

Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kang, 2012

Bibliographic Reference	Kang, Eunyoung; Park, Sue K; Yang, Jae Jeong; Park, Boyoung; Lee, Min Hyuk; Lee, Jong Won; Suh, Young Jin; Lee, Jeong Eon; Kim, Hyun-Ah; Oh, Se Jeong; Kim, Sung-Won; Korean Breast Cancer, Society; Accuracy of BRCA1/2 mutation prediction models in Korean breast cancer patients.; Breast cancer research and treatment; 2012; vol. 134 (no. 3); 1189-97

Study details

Country/ies where study was carried out	South Korea
Study type	Cross sectional (retrospective case review)
Study dates	2003 to 2010
Inclusion criteria	Individuals were considered to have a high risk of inheriting breast cancer, who underwent *BRCA* mutation testing at Seoul National University Bundang Hospital. Probands were the first in their family to be tested for *BRCA1/2*.
Exclusion criteria	Not reported
Patient characteristics	N=236 index patients from unrelated families who had completed *BRCA1/2* mutation tests **Gender:** all female **Age (years, mean (range)):** 42.2 (20-78) at diagnosis of breast cancer **Ethnicity:** South Korean **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	1. BRCAPRO - as implemented in CaGene 5.1 software 2. MYRIAD II
Reference standard(s)	Confirmation-sensitive gel electrophoresis (CSGE) or direct full sequencing (DFS) alone was performed. Complete genetic screening was carried out using both DFS and multiple ligation-dependent probe amplification (MLPA) to screen genomic rearrangements for *BRCA1* and *BRCA2*.

Duration of follow-up	Not applicable
Sources of funding	A grant from the National R&D Program for Cancer Control, Ministry for Health, Welfare and Family affairs, Republic of Korea (1020350).

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kang, 2006

Bibliographic Reference	Kang, H H; Williams, R; Leary, J; kConFab, Investigators; Ringland, C; Kirk, J; Ward, R; Evaluation of models to predict BRCA germline mutations.; British journal of cancer; 2006; vol. 95 (no. 7); 914-20

Study details

Country/ies where study was carried out	Australia
Study type	Retrospective cohort study
Study dates	Between 1998 and2004
Inclusion criteria	• at least 1affected family member had a life time risk of breast cancer of 1: 4 or greater as defined by the Australian National Breast Cancer (NBCC) guidelines (NBCC GeneticsWorking Group, 2000). This included individuals with at least two first- or second-degree relatives on one side of the family diagnosed with breast or ovarian cancer, together with additional features on the same side of the family. These features included an additional relative with breast or ovarian cancer; breast cancer diagnosed before the age of 40 years, ovarian cancer before 50 years, bilateral breast cancer, breast and ovarian cancer in the same woman, Jewish ancestry or breast cancer in a male relative
Exclusion criteria	• families in which no affected individuals were available for *BRCA1/2* testing • families of Ashkenazi Jewish ancestry
Patient characteristics	Pedigrees of 380 families who had undergone *BRCA1/2* mutation analysis in the period 1998-2004. **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported

Index test(s)	• BRCAPRO • Manchester • MYRIAD • PENN
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	kConFaB has been funded by the Kathleen Cuningham Foundation, National Breast Cancer Foundation, National Health and Medical Research Council (NHMRC), Cancer Council of Victoria, Cancer Council of South Australia, Queensland Cancer Fund, Cancer Council of New South Wales, Cancer Foundation of Western Australian and Cancer Council of Tasmania. This work is supported by National Health and Medical Research Council.
Outcomes	See Appendix L

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Pedigrees were obtained from those attending cancer clinics and who had undergone BRCA1/2 mutation analysis)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear *(Specific issues associated with the models: The Myriad*

Section	Question	Answer
		tables only allowed inclusion of a maximum of three members of the family, including the patient. Breast cancers diagnosed above 50 years were ignored, whereas for those diagnosed before 50 years there was no stratification according to the age at diagnosis. Further deficiencies included the equal weighting given to male and female breast cancers and the inability to input bilateral breast cancer or other tumours associated with BRCA1/2 mutation. Both the Penn model and BRCAPRO required computer access. In the case of BRCAPRO, the time taken to enter family trees was a major impediment to routine use. BRCAPRO only incorporates first- and second-degree relatives and therefore cousins of the proband who are affected with cancer will not be used to generate a probability score unless the counsellor changes the proband. This scenario was in part responsible for the low k

Section	Question	Answer
		scores associated with the use of BRCAPRO. The Penn model restricted questions to three generations, and did not include ovarian cancer only families or mother–daughter ovarian–breast cancer inheritance patterns.)
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kast, 2014

Bibliographic Reference	Kast, Karin; Schmutzler, Rita K; Rhiem, Kerstin; Kiechle, Marion; Fischer, Christine; Niederacher, Dieter; Arnold, Norbert; Grimm, Tiemo; Speiser, Dorothee; Schlegelberger, Brigitte; Varga, Dominic; Horvath, Judit; Beer, Marit; Briest, Susanne; Meindl, Alfons; Engel, Christoph; Validation of the Manchester scoring system for predicting BRCA1/2 mutations in 9,390 families suspected of having hereditary breast and ovarian cancer.; International journal of cancer; 2014; vol. 135 (no. 10); 2352-61

Study details

Country/ies where study was carried out	Germany
Study type	Cross sectional study

Study dates	Not reported
Inclusion criteria	Families on the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) registry. Inclusion criteria for families were: 1. Three or more women with breast cancer. No breast cancer before the age of 51 years. No male breast cancer, no ovarian cancer. 2. Two or more women with breast cancer, at least one of whom before the age of 51 years. No male breast cancer, no ovarian cancer. 3. One single woman with unilateral breast cancer before the age of 36 years. No male breast cancer, no ovarian cancer. 4. One single woman with bilateral breast cancer (first diagnosis before the age of 51 years). No other female breast cancers, no male breast cancer, no ovarian cancer. 5. One or more women with breast and ovarian cancer (same woman or different women). No male breast cancer. 6. One or more cases of male breast cancer.
Exclusion criteria	Families which were included through a known pathogenic mutation rather than by clinical criteria were excluded.
Patient characteristics	N=9360 female index patients from unrelated families. N=1353 had pathogenic *BRCA1* variants; N=628 had had pathogenic *BRCA2* variants **Gender:** not reported **Age (years, mean (SD)):** members with female breast cancer majority 40-49 years; members with male breast cancer majority <60 **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported

Index test(s)	• Manchester Scoring System - 2004 version (MSS1) • Manchester Scoring System - 2009 version (MSS2) incorporating additional pathological parameters
Reference standard(s)	One female member of each family (index patient), who had breast cancer, was tested for deleterious mutations in *BRCA1* and *BRCA2*. Mutation analysis of all coding exons of *BRCA1* and *BRCA2* was performed by direct sequencing or a pre-screening step followed by direct sequencing of suspect fragments. The following pre-screening methods were used: Single-Strand Conformation Polymorphism (SSCP), Protein Truncation Test (PTT), Denaturing High-Performance Liquid Chromatography (DHPLC), and High Resolution Melting(HRM). If no deleterious sequence alterations were found in these steps, an additional screening for large genomic alterations was performed using multiplex ligation-dependant probe amplification.
Duration of follow-up	Not applicable
Sources of funding	Deutsche Krebshilfe Grant number:109076
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kenan, 2018

Bibliographic Reference	Kenan, E.S.; Friger, M.; Shochat-Bigon, D.; Schayek, H.; Bernstein-Molho, R.; Friedman, E.; Accuracy of risk prediction models for breast cancer and BRCA1/BRCA2 mutation carrier probabilities in Israel; Anticancer Research; 2018; vol. 38 (no. 8); 4557-4563

Study details

Country/ies where study was carried out	Israel
Study type	Retrospective cohort study
Study dates	Between 2000 and 2005
Inclusion criteria	• All individuals (males and females) who underwent oncogenetic counselling, if they were genotyped for the predominant *BRCA* mutations in the Jewish population
Exclusion criteria	Not reported
Patient characteristics	N=648 individuals who underwent oncogenetic counselling if they were genotyped for the predominant *BRCA* mutations in the Jewish population. **Gender:** not reported **Age (years, mean (SD)):** 50.9 (11.4; range 19-85) **Ethnicity:** Ashkenazi Jewish origin = 61.8%, non-Ashkenazi Jewish origin = 27.3%, mixed Ashkenazi-non-Ashkenazi Jewish origin = 7.9%, non-Jewish origin = 2.5%, mixed Jewish/non-Jewish origin =0.5% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported

	People with communication needs (for example, not English 1st language): not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA • PENN II • BRCAPRO • Myriad
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This work was partially funded by a Grant from the Maccabi HMO to Eitan Friedman; This work was carried out in partial fulfilment of the duties for a Master's Degree by Efrat Schwartz Kenan at the Department of Public Health' Ben-Gurion University of the Negev, Beer Sheba.
Outcomes	See Appendix L

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear (*Participants who underwent oncogenetic counselling and were genotyped for the predominant BRCA mutations in the Jewish population.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(61.8% of the study population were Ashkenazi Jewish origin)*

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kim, 2022

Bibliographic Reference	Kim, Soyoun Rachel; Tone, Alicia; Kim, Raymond; Cesari, Matthew; Clarke, Blaise; Hart, Tae; Aronson, Melyssa; Holter, Spring; Lytwyn, Alice; Maganti, Manjula; Oldfield, Leslie; Gallinger, Steven; Bernardini, Marcus Q; Oza, Amit M; Djordjevic, Bojana; Lerner-Ellis, Jordan; Van de Laar, Emily; Vicus, Danielle; Pugh, Trevor J; Pollett, Aaron; Ferguson, Sarah Elizabeth; Eiriksson, Lua; Brief family history questionnaire to screen for Lynch syndrome in women with newly diagnosed non-serous, non-mucinous ovarian cancers.; International journal of gynecological cancer : official journal of the International Gynecological Cancer Society; 2022

Study details

Country/ies where study was carried out	Canada
Study type	Prospective cohort study
Study dates	2015-2019
Inclusion criteria	<70 years of age with newly diagnosed non-serous, non-mucinous epithelial ovarian cancer of all stages.
Exclusion criteria	Not reported

Patient characteristics	N=169 women with non-serous, non-mucinous ovarian cancer. N=12 had Lynch Syndrome genetic mutations (*MLH1* N=2; *MSH6* N=7; *MSH2* N=1; *PMS2* N=2) **Gender:** female 100% **Age (years, median (range)):** 53 (21 to 70) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• a 4-item self-reported brief Family History Questionnaire (bFHQ) • a 37-item extended Family History Questionnaire (eFHQ) administered by the research assistant
Reference standard(s)	Genetic diagnosis of Lynch Syndrome: participants underwent germline testing using a Next Generation Sequencing mismatch repair panel. Those with pathogenic or likely pathogenic variants in mismatch repair genes were considered to have Lynch syndrome, while those with a variant of unknown significance were considered to have a negative germline result.
Duration of follow-up	Not applicable
Sources of funding	Canadian Cancer Society (Grant#: 704038) and Juravinski Cancer Centre Foundation Grant (Grant #: T-159)
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kurian, 2008

Bibliographic Reference	Kurian, Allison W; Gong, Gail D; Chun, Nicolette M; Mills, Meredith A; Staton, Ashley D; Kingham, Kerry E; Crawford, Beth B; Lee, Robin; Chan, Salina; Donlon, Susan S; Ridge, Yolanda; Panabaker, Karen; West, Dee W; Whittemore, Alice S; Ford, James M; Performance of BRCA1/2 mutation prediction models in Asian Americans.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2008; vol. 26 (no. 29); 4752-8

Study details

Country/ies where study was carried out	USA and Canada
Study type	Cross sectional (retrospective case review)
Study dates	1995 to 2007

Inclusion criteria	Patients tested for *BRCA1/2* mutations because of personal history of early-onset breast or ovarian cancer, and/or a family history of one or more relatives with breast and/or ovarian cancer. Referrals for testing were made according to NCCN (v 1.2007) guidelines. Only probands who were the first member of their families to be tested for *BRCA1/2* mutations were included. The analysis used a sample of probands with East Asian ancestry (defined as having four grandparents of Chinese, Filipino, Japanese, Korean, Hawaiian/Pacific Islander, Taiwanese, Thai, or Vietnamese origin) and a matched group of white probands (defined as all four grandparents of white race).
Exclusion criteria	Fewer than four grandparents were Asian (for the East Asian subgroup), testing results or pedigree were absent, the pedigree duplicated that of another proband, or no white proband was available for matching. White individuals reporting Ashkenazi Jewish or Hispanic ancestry were excluded.
Patient characteristics	N=200 East Asian probands matched to N=200 white probands. **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity (in East Asian group):** Chinese ancestry (44.5%), Japanese (24%), Filipina (16.5%), Korean (2.5%), Vietnamese (2%), and mixed or other Asian ethnicity (10.5%) **Ethnicity (in White group):** 100% White (excluding Ashkenazi Jewish or Hispanic ancestry). **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO as implemented by CancerGene v4 software • MYRIAD II as implemented by CancerGene v4 software

Reference standard(s)	Full sequencing of *BRCA1* and *BRCA2* was performed by Myriad Genetics Laboratories (Salt Lake City, UT) in most participants; those tested after August 2002 also underwent evaluation for five common genetic rearrangements, which was then added to full sequencing by Myriad Genetic Laboratories.
Duration of follow-up	Not applicable
Sources of funding	Allison W. Kurian, James M. Ford
Outcomes	See Appendix L

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kurian, 2009

Bibliographic Reference	Kurian, Allison W; Gong, Gail D; John, Esther M; Miron, Alexander; Felberg, Anna; Phipps, Amanda I; West, Dee W; Whittemore, Alice S; Performance of prediction models for BRCA mutation carriage in three racial/ethnic groups: findings from the Northern California Breast Cancer Family Registry.; Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology; 2009; vol. 18 (no. 4); 1084-91

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	Between January 1995 and April 2003
Inclusion criteria	Category A inclusion criteria (patients whose cancers were likely to be hereditary): • breast cancer diagnosis before age 35 • bilateral breast cancer, with first diagnosis before age 50 • prior ovarian or childhood cancer • at least one first-degree relative with breast or ovarian cancer Category B inclusion criteria (patients whose cancers were less likely to be hereditary): • all other patients aged < 65 at diagnosis
Exclusion criteria	Not reported
Patient characteristics	N=1365 patients diagnosed with invasive breast cancer < 65 years. Divided into two groups according to likelihood that cancer was genetic. **Gender:** not reported **Age (years, mean (SD)):** African-American: <50 = 181, 50-54 = 217; Hispanic: <50 = 227, 50-54 = 198; Non-Hispanic white: <50 = 258, 50-54 = 284 **Ethnicity:** African-American = 398; Hispanic = 425; Non-Hispanic white = 542 **Socioeconomic and geographical factors:** not reported

	Disabilities: not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • BOADICEA
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Financial support: National Cancer Institute, National Institutes of Health, under RFA CA-95-003 through a cooperative agreement with the Northern California Cancer Center (U01 CA69417), and NIH grants CA69417 and CA94069.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Test threshold is unclear, looks like 10%)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Kwong, 2012

Bibliographic Reference	Kwong, Ava; Wong, Connie H N; Suen, Dacita T K; Co, Michael; Kurian, Allison W; West, Dee W; Ford, James M; Accuracy of BRCA1/2 mutation prediction models for different ethnicities and genders: experience in a southern Chinese cohort.; World journal of surgery; 2012; vol. 36 (no. 4); 702-13

Study details

Country/ies where study was carried out	China (Hong Kong)
Study type	Cross sectional study
Study dates	2007- before 2012
Inclusion criteria	Participants were identified from the database at The Hong Kong Hereditary and High Risk Breast Cancer Family Registry. The Registry collects data from high-risk breast/ovarian cancer probands and families referred for genetic counselling based on age of onset, family history suggestive of hereditary predisposition, bilateral breast cancer status, and male breast cancer patients.
Exclusion criteria	Not reported
Patient characteristics	N=310 probands **Gender:** 285 female, 25 male

	Age (years, mean (SD)): African-American: <50 = 181, 50-54 = 217; Hispanic: <50 = 227, 50-54 = 198; Non-Hispanic white: <50 = 258, 50-54 = 284 **Ethnicity:** Chinese ancestry 100% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO as implemented in CaGene 4.3 • Myriad II as implemented in CaGene 4.3 • BOADICEA as implemented in CaGene 4.3
Reference standard(s)	Mutation testing methods not reported
Duration of follow-up	Not applicable
Sources of funding	Dr. Ellen Li Charitable Foundation and Kuok Foundation
Outcomes	See Appendix L

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Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Participants were recruited through a hereditary and high risk breast cancer family registry)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(All probands were of Chinese ancestry, 98% were breast cancer patients)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Testing methods not reported)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(Testing methods not reported)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Not clear if patients received the same reference standard)*

Lindor, 2007

Bibliographic Reference	Lindor, N.M.; Lindor, R.A.; Apicella, C.; Dowty, J.G.; Ashley, A.; Hunt, K.; Mincey, B.A.; Wilson, M.; Smith, M.C.; Hopper, J.L.; Predicting BRCA1 and BRCA2 gene mutation carriers: Comparison of LAMBDA, BRCAPRO, Myriad II, and modified Couch models; Familial Cancer; 2007; vol. 6 (no. 4); 473-482

Study details

Country/ies where study was carried out	USA
Study type	Retrospective Cohort Study
Study dates	Between 1996 and 2005
Inclusion criteria	• Individuals who underwent clinical genetic testing for mutations in *BRCA1* and *BRCA2* (criteria for eligibility were unclear)
Exclusion criteria	• Families having only variants of unknown significance
Patient characteristics	N=154 probands seen for genetic risk assessment in a multidisciplinary tertiary care group practice between 1996 and 2005 **Gender:** women = 277 (97.2%) **Age (years):** most were in age groups <40 and 40-49 **Ethnicity:** Ashkenazi Jewish = 27 (9.5%) **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• LAMBDA • BRCAPRO • Couch 1.5 • MYRIAD II • PENN II

Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Test threshold is unclear)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Lindor, 2010

Bibliographic Reference	Lindor, Noralane M; Johnson, Kiley J; Harvey, Hayden; Shane Pankratz, V; Domchek, Susan M; Hunt, Katherine; Wilson, Marcia; Cathie Smith, M; Couch, Fergus; Predicting BRCA1 and BRCA2 gene mutation carriers: comparison of PENN II model to previous study.; Familial cancer; 2010; vol. 9 (no. 4); 495-502

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	Between 1996 and 2005
Inclusion criteria	• probands (defined as the initial consultants in the families) from 322 independent families who had cancer risk assessment at the Mayo Clinic and subsequently and had clinical genetic testing for mutations in *BRCA1* and *BRCA2* at Myriad Genetics Laboratories, Inc, Salt Lake City Utah that included complete sequencing of both genes and, since 8/2003, testing for a five-site rearrangement-panel in *BRCA1*
Exclusion criteria	• families who had DNA variants of unknown significance • with missing data
Patient characteristics	N=285 probands (defined as the initial consultants in the families) from 322 independent families who had cancer risk assessment at the Mayo Clinic and subsequently had clinical genetic testing for mutations in *BRCA1* and *BRCA2* **Gender:** 277/285 women **Age (years, mean (SD)):** age at breast cancer 45 (10.6), age at ovarian cancer 51.7 (12.7) **Ethnicity:** Ashkenazi Jewish = 9.5% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• PENN II

Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Threshold for PENN II is unclear)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear *(Threshold for PENN II is unclear)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Liu, 2022

Bibliographic Reference	Liu, Jiaqi; Zhao, Hengqiang; Zheng, Yu; Dong, Lin; Zhao, Sen; Huang, Yukuan; Huang, Shengkai; Qian, Tianyi; Zou, Jiali; Liu, Shu; Li, Jun; Yan, Zihui; Li, Yalun; Zhang, Shuo; Huang, Xin; Wang, Wenyan; Li, Yiqun; Wang, Jie; Ming, Yue; Li, Xiaoxin;

Xing, Zeyu; Qin, Ling; Zhao, Zhengye; Jia, Ziqi; Li, Jiaxin; Liu, Gang; Zhang, Menglu; Feng, Kexin; Wu, Jiang; Zhang, Jianguo; Yang, Yongxin; Wu, Zhihong; Liu, Zhihua; Ying, Jianming; Wang, Xin; Su, Jianzhong; Wang, Xiang; Wu, Nan; DrABC: deep learning accurately predicts germline pathogenic mutation status in breast cancer patients based on phenotype data.; Genome medicine; 2022; vol. 14 (no. 1); 21

Study details

Country/ies where study was carried out	China
Study type	Cohort study (unclear whether prospective)
Study dates	2017 to 2019
Inclusion criteria	Female patients with breast cancer. The model was developed using a sample from the Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College. The model was validated using a sample from 6 other hospitals.
Exclusion criteria	Patients with missing data
Patient characteristics	N=731 patients in the validation sample; N=39 had *BRCA1* germline pathogenic variants (GPV); N=39 had *BRCA2* GPV; N=21 had GPV in other cancer predisposition genes. **Gender:** 100% women **Age (years, mean (SD)):** not reported **Ethnicity:** 100% Chinese **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported

	Non-binary people: not reported
Index test(s)	• Germline pathogenic variant risk prediction model called DNA-repair Associated Breast Cancer (DrABC) developed using a hierarchical neural network architecture • BRCAPRO version 2.1-7 • Myriad II • PENN II • BOADICEA v3 • NCCN guidelines (version 1.2020)
Reference standard(s)	Genomic DNA was extracted from peripheral blood or saliva. Germline pathogenic variants in patients from each centre were analysed by their local diagnostic laboratory, which generated a clinical genetic test report for each participant. Each laboratory provided results by the enrichment of the coding regions and consensus splice sites of 50 cancer predisposition genes in the DNA repair pathway using a targeted panel followed by sequencing.
Duration of follow-up	Not applicable
Sources of funding	National Natural Science Foundation of China (81802669 to J.L., 81501852 and 82072391 to N.W., 61871294 to J.S., 81472046 and 81772299 to Z.W.), the CAMS Innovation Fund for Medical Sciences (2020-I2M-C&T-B-068 to J.L., 2020-I2M-C&T-A-015 to Y.M., 2021-I2M1-051 to N.W., and 2021-I2M-1-052 to Z.W.), the Beijing Hope Run Special Fund (LC2020B05 to J.L.), Beijing Natural Science Foundation (JQ20032 to N.W.), Tsinghua University-Peking Union Medical College Hospital Initiative Scientific Research Program (to N.W.), the PUMC Youth Fund & the Fundamental Research Funds for the Central Universities (No.3332019052 to Y. M.), Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (No. 2019PT320025), Science Foundation of Zhejiang Province (LR19C060001 to J.S), and the Fundamental Research Funds for Wenzhou Institute of University of Chinese Academy of Sciences (WIBEZD2017009-05 to J.S.)
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Mazzola, 2014

Bibliographic Reference	Mazzola, Emanuele; Chipman, Jonathan; Cheng, Su-Chun; Parmigiani, Giovanni; Recent BRCAPRO upgrades significantly improve calibration.; Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology; 2014; vol. 23 (no. 8); 1689-95

Study details

Country/ies where study was carried out	USA
Study type	Cross-sectional
Study dates	Not reported (pre 2007)
Inclusion criteria	Pedigrees at high-risk for *BRCA* mutation collected in 8 genetic counselling clinics (the CGN validation study - see Parmigiani 2007).
Exclusion criteria	Pedigrees that generated errors when run through the BRCAPRO R-package software.
Patient characteristics	N=2038 families who underwent genetic testing

	Gender: not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO version 2.0-7 (in BayesMendel R package) • BRCAPRO version 2.0-8 (in BayesMendel R package)
Reference standard(s)	Testing for germline pathogenic variants - methods reported in Parmigiani 2007 - these varied between centres and the authors that their methods may have missed certain mutations like large deletions or intronic mutations.
Duration of follow-up	Not applicable
Sources of funding	NIH/NCI awards 5R21CA177233-02 and 5P30CA006516-49
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Limited information reported)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear

Section	Question	Answer
		(Limited information reported)
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Methods predate 2007 - authors admit that certain mutations, such as large deletions or intronic mutations may have been missed.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(Methods predate 2007 - authors admit that certain mutations, such as large deletions or intronic mutations may have been missed.)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Mitri, 2015

Bibliographic Reference	Mitri, Zahi I; Jackson, Michelle; Garby, Carolyn; Song, Juhee; Giordano, Sharon H; Hortobagyi, Gabriel N; Singletary, Claire N; Hashmi, S Shahrukh; Arun, Banu K; Litton, Jennifer K; BRCAPRO 6.0 Model Validation in Male Patients Presenting for BRCA Testing.; The oncologist; 2015; vol. 20 (no. 6); 593-7

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort
Study dates	Between February 1997 and September 2011
Inclusion criteria	• men who had undergone genetic counselling and testing
Exclusion criteria	not reported
Patient characteristics	N=146 men who had undergone genetic counselling and testing **Gender:** men **Age (years, mean (SD)):** 57 (14, range 18-87) **Ethnicity:** not Ashkenazi Jewish = 27% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO
Reference standard(s)	• Germline pathogenic variant analysis
Sources of funding	The present study was supported by Litton funding from the Woolf-Toomim Fund and Institutional database and data analyses funding from National Cancer Institute Cancer Center Support Grant P30CA016672.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Male population only)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Moghadasi, 2018

Bibliographic Reference	Moghadasi, S; Grundeken, V; Janssen, L A M; Dijkstra, N H; Rodriguez-Girondo, M; van Zelst-Stams, W A G; Oosterwijk, J C; Ausems, M G E M; Oldenburg, R A; Adank, M A; Blom, E W; Ruijs, M W G; van Os, T A M; van Deurzen, C H M; Martens, J W M; Schroder, C P; Wijnen, J T; Vreeswijk, M P G; van Asperen, C J; Performance of BRCA1/2 mutation prediction models in male breast cancer patients.; Clinical genetics; 2018; vol. 93 (no. 1); 52-59

Study details

Country/ies where study was carried out	the Netherlands

Study type	Retrospective cohort study
Study dates	Between 1989 and 2009
Inclusion criteria	• All male breast cancer patients who were diagnosed in the Netherlands between 1989 and 2009 and were identified via the Dutch National Cancer Registry
Exclusion criteria	• disease or mutation status or pedigree unavailable • the proband was diagnosed with Ductal carcinoma in situ • probands were carriers of a class 2 or 3 variant of uncertain significance • according to the International Agency for Research on Cancer (IARC) classification they had a posterior probability of pathogenicity between 0.1% and 94.9% • age at diagnosis of breast cancer in the proband was above 80 years
Patient characteristics	N=307 male breast cancer patients **Gender:** male only **Age (years, mean (SD)):** age of onset of breast cancer carriers 59.8, non-carriers 60.1 **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • BOADICEA • MYRIAD

Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	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).
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Male population only)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Oros, 2006

Bibliographic Reference	Oros, K K; Ghadirian, P; Maugard, C M; Perret, C; Paredes, Y; Mes-Masson, A-M; Foulkes, W D; Provencher, D; Tonin, P N; Application of BRCA1 and BRCA2 mutation carrier prediction models in breast and/or ovarian cancer families of French Canadian descent.; Clinical genetics; 2006; vol. 70 (no. 4); 320-9

Study details

Country/ies where study was carried out	Canada
Study type	Retrospective cohort study
Study dates	Not reported
Inclusion criteria	• family with at least 3 cases of female breast cancer diagnosed before the age of 65 years, epithelial ovarian cancer, or male breast cancer The index case was a first second or third degree relative of the affected individual. The family member most likely to harbour a *BRCA1/2* mutation
Exclusion criteria	Not reported
Patient characteristics	N=224 probands from French Canadian families with at least three cases of breast cancer **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported

	People with communication needs (for example, not English 1st language): not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • Manchester
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This work was supported by grants from joint initiative from the Cancer Research Society, Inc., and CIHR to P. N. T. and by the grant from the Re´seau Cancer: Axe Cancer Banque de Tissus de Donne´es pour les Cancers du Sein et de l'Ovaire du
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Panchal, 2008

Bibliographic Reference	Panchal, Seema M; Ennis, Marguerite; Canon, Sandra; Bordeleau, Louise J; Selecting a BRCA risk assessment model for use in a familial cancer clinic.; BMC medical genetics; 2008; vol. 9; 116

Study details

Country/ies where study was carried out	Canada
Study type	Retrospective case control study
Study dates	Between 1995 and 2006
Inclusion criteria	• Underwent genetic testing tested between 1995 and 2006
Exclusion criteria	• probands who had a known relative with a *BRCA1* or *BRCA2* mutation
Patient characteristics	N=200 non-*BRCA* mutation and 100 *BRCA* mutation carriers **Gender:** carriers women 92%; non-carriers women 98% **Age (years, mean (SD)):** carriers 51 (12.7); non-carriers 52 (13.5) **Ethnicity:** Ashkenazi Jewish descent carriers 39%; non-carriers 40% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported

Index test(s)	• BRCAPRO • BOADICEA • Manchester • PENN II • MYRIAD II • IBIS
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	No source of funding was used for this study.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Parmigiani, 2007

Bibliographic Reference	Parmigiani, Giovanni; Chen, Sining; Iversen, Edwin S Jr; Friebel, Tara M; Finkelstein, Dianne M; Anton-Culver, Hoda; Ziogas, Argyrios; Weber, Barbara L; Eisen, Andrea; Malone, Kathleen E; Daling, Janet R; Hsu, Li; Ostrander, Elaine A; Peterson, Leif E; Schildkraut, Joellen M; Isaacs, Claudine; Corio, Camille; Leondaridis, Leoni; Tomlinson, Gail; Amos, Christopher I; Strong, Louise C; Berry, Donald A; Weitzel, Jeffrey N; Sand, Sharon; Dutson, Debra; Kerber, Rich; Peshkin, Beth N; Euhus, David M; Validity of models for predicting BRCA1 and BRCA2 mutations.; Annals of internal medicine; 2007; vol. 147 (no. 7); 441-50

Study details

Country/ies where study was carried out	USA
Study type	Cross sectional multicentre analysis
Study dates	Not reported
Inclusion criteria	• unclear (3 population based samples of participants in research studies and 8 samples from genetic counselling clinics)
Exclusion criteria	not reported
Patient characteristics	N=3324 families who underwent genetic testing **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported

	People with communication needs (for example, not English 1st language): not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • MYRIAD • FHAT • YALE • NCI • Finnish
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Grant Support: In part by the NCI Cancer Genetics Network. Work of the Cancer Genetics Network Statistical Coordinating Center was supported by National Cancer Institute grant CA78284. Work of Drs. Parmigiani and Chen and Ms. Friebel was also supported in part by National Cancer Institute grants P50CA88843, P50CA62924-05, and 5P30 CA06973-39, R01CA105090-01A1; National Institutes of Health grant HL 99-024; and the Hecht Fund. Work of investigators at the Fred Hutchinson Cancer Research Center was supported in part by National Institutes of Health grants R01 CA 36397, R01 CA 63705, and K05 CA-90754. The work of Dr. Weitzel and Ms. Sand was supported in part by California Cancer Research Program of the University of California (grant no. 99-86874) and in part by a General Clinical Research Center grant from National Institutes of Health (M01 RR00043) awarded to the City of Hope National Medical Center. Data from Georgetown University were provided by the Familial Cancer Registry Shared Resource of Lombardi Comprehensive Cancer Center, which is supported in part by the National Institutes of Health (grant P30-CA-51008).
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(3 population based samples of participants in research*

Section	Question	Answer
		studies and 8 samples from genetic counselling clinics)
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Rao, 2009a

Bibliographic Reference	Rao, Nan-Yan; Hu, Zhen; Li, Wen-Feng; Huang, Juan; Ma, Zhong-Liang; Zhang, Bin; Su, Feng-Xi; Zhou, Jie; Di, Gen-Hong; Shen, Kun-Wei; Wu, Jiong; Lu, Jin-Song; Luo, Jian-Min; Yuan, Wen-Tao; Shen, Zhen-Zhou; Huang, Wei; Shao, Zhi-Ming; Models for predicting BRCA1 and BRCA2 mutations in Han Chinese familial breast and/or ovarian cancer patients.; Breast cancer research and treatment; 2009; vol. 113 (no. 3); 467-77

Study details

Country/ies where study was carried out	China
Study type	Prospective cohort study
Study dates	Between 2005 and 2007

Inclusion criteria	• unrelated pedigrees who had 2 or more first or second degree relatives affected with invasive breast cancer and/or ovarian cancer (the youngest living available affected case (the proband) was selected)
Exclusion criteria	• women who only had an early onset age • bilateral breast cancer cases without family history
Patient characteristics	N=200 unrelated pedigrees who had 2 or more first or second degree relatives affected with invasive breast cancer and/or ovarian cancer **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • COUCH • Sh-E
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na

Sources of funding	This research was supported in part by the grants from the National Basic Research Program of China (2006CB910501), National Natural Science Foundation of China (30371580, 30572109;to ZM. S.); Shanghai Science and Technology Committee (03J14019, 06DJ14004, 06DZ19504; to ZM. S.).
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Han Chinese population)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Rao, 2009b

Bibliographic Reference	Rao, Nan-Yan; Hu, Zhen; Yu, Jin-Ming; Li, Wen-Feng; Zhang, Bin; Su, Feng-Xi; Wu, Jiong; Shen, Zhen-Zhou; Huang, Wei; Shao, Zhi-Ming; Evaluating the performance of models for predicting the BRCA germline mutations in Han Chinese familial breast cancer patients.; Breast cancer research and treatment; 2009; vol. 116 (no. 3); 563-70

Study details

Country/ies where study was carried out	China
Study type	Retrospective cohort study
Study dates	Not reported
Inclusion criteria	• unclear (reported in an earlier study); reported that the patient cohort was part of the China multi-hospital based screening program
Exclusion criteria	• unclear (reported in an earlier study)
Patient characteristics	N=212 Han Chinese participants from families with more than three affected breast or ovarian cancer cases who had undergone *BRCA1/2* mutation analysis **Gender:** 3/212 men **Age (years, mean (CI95%):** between 35.8 (32.1 - 39.5) and 48.7 (47.2 - 50.3) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • MYRIAD II

Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This research was supported in part by the grants from the National Basic Research Program of China (2006CB910501), National Natural Science Foundation of China (30371580, 30572109; to ZM. S.); Shanghai Science and Technology Committee (03J14019, 06DJ14004, 06DZ19504; to ZM. S.)
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Roudgari, 2008

Bibliographic Reference	Roudgari, Hassan; Miedzybrodzka, Zosia H; Haites, Neva E; Probability estimation models for prediction of BRCA1 and BRCA2 mutation carriers: COS compares favourably with other models.; Familial cancer; 2008; vol. 7 (no. 3); 199-212

Study details

Country/ies where study was carried out	UK
Study type	Retrospective cohort study
Inclusion criteria	• families with completed genetic testing for both *BRCA1* and *BRCA2* genes First degree relatives of an affected individual (or second degree via intervening male relative) in a family with four or more families affected with either breast or ovarian cancer • or one first degree relative (or second degree via intervening male relative) with both breast and ovarian cancer
Exclusion criteria	not reported
Patient characteristics	N=275 Scottish families with completed genetic testing for both *BRCA1* and *BRCA2* mutation **Gender:** not reported **Age (years):** age at cancer diagnosis <=50 n=180, >50 n=94 **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA • Manchester • Tyrer-Cuzick • COS

Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	The Iranian Ministry of Health and Higher Education and EU financial support
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Family history information was only complete for 17% of the combined dataset)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Schneegans, 2012

Bibliographic Reference	Schneegans, S M; Rosenberger, A; Engel, U; Sander, M; Emons, G; Shoukier, M; Validation of three BRCA1/2 mutation-carrier probability models Myriad, BRCAPRO and BOADICEA in a population-based series of 183 German families.; Familial cancer; 2012; vol. 11 (no. 2); 181-8

Study details

Country/ies where study was carried out	Germany
Study type	Retrospective cohort study
Study dates	Between 1999 and 2009
Inclusion criteria	• all patients that attended interdisciplinary breast cancer consultancy in the Breast Cancer Center at the University Medical Center of Goettingen between 1999 and 2009 • underwent *BRCA1* and *BRCA2* mutation testing
Exclusion criteria	Not reported
Patient characteristics	N=183 unrelated families for which at least one affected member (the so called index-patient) was tested for mutations in the *BRCA1* and *BRCA2* genes. **Gender:** men and women **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BRCAPRO • BOADICEA

Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Senda, 2021

Bibliographic Reference	Senda, Noriko; Kawaguchi-Sakita, Nobuko; Kawashima, Masahiro; Inagaki-Kawata, Yukiko; Yoshida, Kenichi; Takada, Masahiro; Kataoka, Masako; Torii, Masae; Nishimura, Tomomi; Kawaguchi, Kosuke; Suzuki, Eiji; Kataoka, Yuki; Matsumoto, Yoshiaki; Yoshibayashi, Hiroshi; Yamagami, Kazuhiko; Tsuyuki, Shigeru; Takahara, Sachiko; Yamauchi, Akira; Shinkura, Nobuhiko; Kato, Hironori; Moriguchi, Yoshio; Okamura, Ryuji; Kan, Norimichi; Suwa, Hirofumi; Sakata, Shingo; Mashima, Susumu; Yotsumoto, Fumiaki; Tachibana, Tsuyoshi; Tanaka, Mitsuru; Togashi, Kaori; Haga, Hironori; Yamada, Takahiro;

Kosugi, Shinji; Inamoto, Takashi; Sugimoto, Masahiro; Ogawa, Seishi; Toi, Masakazu; Optimization of prediction methods for risk assessment of pathogenic germline variants in the Japanese population.; Cancer science; 2021; vol. 112 (no. 8); 3338-3348

Study details

Country/ies where study was carried out	Japan
Study type	Retrospective cohort study
Study dates	Between September 2011 and October 2016
Inclusion criteria	• unselected Japanese women with primary breast cancer registered at Kyoto Breast Cancer Research Network institutions, including Kyoto University Hospital and 15 affiliated hospitals
Exclusion criteria	Not reported
Patient characteristics	N=1995 unselected Japanese women with primary breast cancer registered at Kyoto Breast Cancer Research Network institutions, including Kyoto University Hospital and 15 affiliated hospitals **Gender:** women **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported

Index test(s)	• Tyrer-Cuzick
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Simard, 2007

Bibliographic Reference	Simard, Jacques; Dumont, Martine; Moisan, Anne-Marie; Gaborieau, Valerie; Malouin, Helene; Durocher, Francine; Chiquette, Jocelyne; Plante, Marie; Avard, Denise; Bessette, Paul; Brousseau, Claire; Dorval, Michel; Godard, Beatrice; Houde, Louis; INHERIT, BRCAs; Joly, Yann; Lajoie, Marie-Andree; Leblanc, Gilles; Lepine, Jean; Lesperance, Bernard; Vezina, Helene; Parboosingh, Jillian; Pichette, Roxane; Provencher, Louise; Rheaume, Josee; Sinnett, Daniel; Samson, Carolle; Simard, Jean-Claude; Tranchant, Martine; Voyer, Patricia; Easton, Douglas; Tavtigian, Sean V; Knoppers, Bartha-Maria; Laframboise,

Rachel; Bridge, Peter; Goldgar, David; Evaluation of BRCA1 and BRCA2 mutation prevalence, risk prediction models and a multistep testing approach in French-Canadian families with high risk of breast and ovarian cancer.; Journal of medical genetics; 2007; vol. 44 (no. 2); 107-21

Study details

Country/ies where study was carried out	Canada
Study type	Prospective cohort study
Study dates	started in 1996
Inclusion criteria	Participants were required to meet one or more of the following criteria: • 4 first or second degree relatives diagnosed with breast and/or ovarian cancer at any age • 3 first degree relatives diagnosed at any age • family known to carry a deleterious gene (these individuals excluded from model comparisons) • over 18 years of age • mentally competent
Exclusion criteria	not reported
Patient characteristics	N=982 but n=191 high risk families ascertained from regional familial cancer clinics throughout the province of Quebec with at least one DNA sample tested were included in the analysis as they were screened for mutations **Gender:** women = 849/982 **Age (years):** mainly between 41 - 70 **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported

	Disabilities: not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• Manchester
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This work was supported by the Canadian Institutes of Health Research (CIHR) and their Institute of Cancer and Institute of Gender and Health for the INHERIT BRCAs research programme, Fonds de la Recherche en Sante´ du Que´bec (FRSQ)/Re´seau de Me´decine Ge´ne´tique Applique´e (RMGA), the Canadian Breast Cancer Research Alliance and the CURE foundation. JS is chairholder of the Canada Research Chair in Oncogenetics.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low

Section	Question	Answer
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Stahlbom, 2012

Bibliographic Reference	Stahlbom, Anne Kinhult; Johansson, Hemming; Liljegren, Annelie; von Wachenfeldt, Anna; Arver, Brita; Evaluation of the BOADICEA risk assessment model in women with a family history of breast cancer.; Familial cancer; 2012; vol. 11 (no. 1); 33-40

Study details

Country/ies where study was carried out	Sweden
Study type	Retrospective cohort study
Study dates	Between January 2002 and June 2006
Inclusion criteria	• women (index persons) who consecutively attended the cancer genetic clinic for hereditary breast- and ovarian cancer at any of three hospitals in Stockholm • at least 17% life time risk for breast cancer using Claus tables • fulfilled age criteria for being eligible for annual breast imaging (mammography ± ultrasound) • age <=60 years
Exclusion criteria	• individuals with an identified mutation other than in BRCA1 or *BRCA2*
Patient characteristics	N=652 women (index persons) who consecutively attended the cancer genetic clinic for hereditary breast- and ovarian cancer at any of three hospitals in Stockholm but included n=263 with mutation screening results. **Gender:** women

	Age (years, mean (SD)): not reported **Ethnicity:** not Scandinavians = 254/263, Iranian 5/263, Iraqi = 1/263, Ashkenazi Jewish = 3/263 **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This study was supported by grant from the Swedish Cancer Society.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Teixeira, 2017

Bibliographic Reference	Teixeira, Natalia; Maistro, Simone; Del Pilar Estevez Diz, Maria; Mourits, Marian J; Oosterwijk, Jan C; Folgueira, Maria Aparecida Koike; de Bock, Geertruida H; Predictability of BRCA1/2 mutation status in patients with ovarian cancer: How to select women for genetic testing in middle-income countries.; Maturitas; 2017; vol. 105; 113-118

Study details

Country/ies where study was carried out	Brazil
Study type	Cross-sectional study
Study dates	Between 2012 and 2015
Inclusion criteria	• patients undergoing treatment or follow-up for invasive epithelial ovarian cancer at the Instituto do Cancer do Estado de São Paulo (ICESP) between October 2012 and February 2015
Exclusion criteria	Patients with: • borderline ovarian tumours

	• benign lesions • metastatic disease from another primary site • primary ovarian tumours diagnosed before January 2009 • those without a pathology report confirming epithelial ovarian cancer
Patient characteristics	N=115 patients but n=15 excluded for not meeting the inclusion criteria; analysed n=100 **Gender:** all women **Age (years, median (range)):** 56.5 (34-81) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA • BRCAPRO • MYRIAD • Manchester
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This work was supported, in part, by a grant from Diagnósticos da América (DASA), and by a grant from Núcleo de Apoio a Pesquisa, Biobanco USP, Rede Acadêmica de Pesquisa em Câncer. These funding sources had no involvement in study design; data collection, analysis or interpretation; writing of the manuscript; nor in the decision to submit the article for publication.

Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(115 out of 463 (25%) invited patients agreed to participate)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Teller, 2010

Bibliographic Reference	Teller, P; Hoskins, K F; Zwaagstra, A; Stanislaw, C; Iyengar, R; Green, V L; Gabram, S G A; Validation of the pedigree assessment tool (PAT) in families with BRCA1 and BRCA2 mutations.; Annals of surgical oncology; 2010; vol. 17 (no. 1); 240-6

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	not reported
Inclusion criteria	• complete cancer information spanning at least 3 generations • information on ethnic background of family • at least one case of breast or ovarian cancer in the family • *BRCA1* or *BRCA2* test results available on at least one individual in the family affected with breast or ovarian cancer
Exclusion criteria	• multiple subjects representing the same family were excluded from the study so that each family was only represented once in the data set
Patient characteristics	N=520 families with at least one case of breast or ovarian cancer **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** Caucasian = 68%, Ashkenazi Jewish = 13%, African American = 2%, Hispanic & Asian = 1% **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• PAT

	• MYRIAD II • PENN II
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Study supported by the AVON Foundation
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Terkelsen, 2019

Bibliographic Reference	Terkelsen, Thorkild; Christensen, Lise-Lotte; Fenton, Deirdre Cronin; Jensen, Uffe Birk; Sunde, Lone; Thomassen, Mads; Skytte, Anne-Bine; Population frequencies of pathogenic alleles of BRCA1 and BRCA2: analysis of 173 Danish breast cancer pedigrees using the BOADICEA model.; Familial cancer; 2019; vol. 18 (no. 4); 381-388

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective cohort study
Study dates	Between January 2013 to May 2018
Inclusion criteria	All women from the program with early-onset breast cancer, which was defined as breast cancer before the age of 45 years: • female breast cancer before 45 years of age (2013 or later) • no previous genetic testing of *BRCA1* or *BRCA2* • no targeted test for a known pathogenic variant in *BRCA1* or *BRCA2* • no previous history of BC and/or ovarian cancer Referral for genetic work-up* *Families eligible for genetic work-up and counselling according to the Danish national guidelines (2018): BC<40, ovarian cancer (any age), ER- HER2- BC<60, bilateral BC (any age), male BC (any age), two 1st degree BC<50, or three 1st degree BC (any age)
Exclusion criteria	Not reported
Patient characteristics	N=173 women diagnosed with breast cancer before 45 years of age **Gender:** women **Age (years, median (range)):** 37 (21-44)

	Ethnicity: not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	The study was funded by a cancer research grant administered by Aarhus University Hospital, Denmark. The funder had no role in study design, data collection and analysis, decision to publish, or the preparation of the manuscript

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Test threshold is unclear, looks like 10%)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Thirthagiri, 2008

Bibliographic Reference	Thirthagiri, E; Lee, S Y; Kang, P; Lee, D S; Toh, G T; Selamat, S; Yoon, S-Y; Taib, N A Mohd; Thong, M K; Yip, C H; Teo, S H; 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 research : BCR; 2008; vol. 10 (no. 4); r59

Study details

Country/ies where study was carried out	Malaysia
Study type	Prospective cohort
Study dates	Between January 2003 and December 2007.
Inclusion criteria	All breast cancer patients had: • early-onset breast cancer (≤ 40 years) and 1 or more additional cases of breast cancer in first- or second-degree relatives • breast cancer (≥ 40 years) and two or more additional cases of breast cancer in first- or second-degree relatives • bilateral breast cancer or a personal or family history of ovarian cancer

	Additionally, approximately 50% of patients with only early-onset breast cancer (≥ 40 years) with no significant family history or breast cancer (≤ 40 years) and one additional case of breast cancer in a first- or second-degree relative were also included in the analysis
Exclusion criteria	• individuals with deleterious *BRCA2* mutations • those who had a single case of breast cancer and no family history of breast, ovarian, pancreatic or prostate cancer in first-, second- or third-degree relatives
Patient characteristics	N=185 breast cancer patients with either early onset breast cancer (at age ≤ 40 years) or a personal and/or family history of breast or ovarian cancer but analysed n=145 **Gender:** women **Age (years, mean (SD)):** not reported **Ethnicity:** Malay families = 44, Chinese families = 118, Indian families = 22, others = 3 **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• Manchester • BOADICEA
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na

Sources of funding	This study was funded by research grants from the Malaysian Ministry of Science, Technology and Innovation, University Malaya Research Grants and Cancer Research Initiatives Foundation.
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Varesco, 2013

Bibliographic Reference	Varesco, L; Viassolo, V; Viel, A; Gismondi, V; Radice, P; Montagna, M; Alducci, E; Della Puppa, L; Oliani, C; Tommasi, S; Caligo, M A; Vivanet, C; Zuradelli, M; Mandich, P; Tibiletti, M G; Cavalli, P; Lucci Cordisco, E; Turchetti, D; Boggiani, D; Bracci, R; Bruzzi, P; Bonelli, L; 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 (Edinburgh, Scotland); 2013; vol. 22 (no. 6); 1130-5

Study details

Country/ies where study was carried out	Italy
Study type	Retrospective cohort study
Study dates	Between 2006 and 2008
Inclusion criteria	• all consecutive Italian index cases initiating a complete BRCA1 and BRCA2 genetic testing (that is, family mutation status was unknown) between 01/01/2006 and 31/12/2008
Exclusion criteria	• index cases not of Italian ancestry • unavailability of test results or incomplete testing • inadequate pedigree information • lack of written informed consent to the use of clinical and genetic data for research purposes
Patient characteristics	N=918 consecutive index cases tested for *BRCA* mutations in the 15 participating cancer genetics clinic **Gender:** 886/918 females **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported
Index test(s)	• BOADICEA • BRCAPRO

Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This study was supported by Italian Ministry of Health, Programma Straordinario Oncologia 2006 “Alleanza contro il Cancro”, project “Italian Network Tumori EredoeFamigliari (INTEF): tools for clinical practice and research” and project “Introducing new laboratory tests in clinical practice and oncological networks: methodological and organizational problems”, and by Italian Association for Research on Cancer (AIRC) (Project IG 5706 2008).
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Vogel, 2007

Bibliographic Reference	Vogel, Kristen J; Atchley, Deann P; Erlichman, Julie; Broglio, Kristine R; Ready, Kaylene J; Valero, Vicente; Amos, Christopher I; Hortobagyi, Gabriel N; Lu, Karen H; Arun, Banu; BRCA1 and BRCA2 genetic testing in Hispanic patients:

mutation prevalence and evaluation of the BRCAPRO risk assessment model.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2007; vol. 25 (no. 29); 4635-41

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study
Study dates	Between February 1997 and July 2006
Inclusion criteria	• Hispanic individuals who underwent genetic testing • White controls who underwent genetic testing
Exclusion criteria	• If the age/age at death of an unaffected individual was unknown, that individual was excluded
Patient characteristics	N=78 Hispanic patients who underwent genetic testing evaluated between February 1997 and July 2006 and 79 White controls **Gender:** not reported **Age (years, mean (SD)):** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported **Non-binary people:** not reported

Index test(s)	• BRCAPRO
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	Not reported
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Test threshold is unclear)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Zanna, 2010

Bibliographic Reference	Zanna, Ines; Rizzolo, Piera; Sera, Francesco; Falchetti, Mario; Aretini, Paolo; Giannini, Giuseppe; Masala, Giovanna; Gulino, Alberto; Palli, Domenico; Ottini, Laura; The BRCAPRO 5.0 model is a useful tool in genetic counseling and clinical management of male breast cancer cases.; European journal of human genetics: EJHG; 2010; vol. 18 (no. 7); 856-8

Study details

Country/ies where study was carried out	Italy
Study type	Prospective cohort study
Study dates	Between 1991 and 2007
Inclusion criteria	• male breast cancer diagnosed between 1991-2007 • resident in Eastern Tuscany
Exclusion criteria	not reported
Patient characteristics	N=102 Italian male breast cancer sufferers recruited between 1991 - 2007 **Gender:** men **Age (years, mean (SD)):** 63.6 (12.0) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example, not English 1st language):** not reported

	Non-binary people: not reported
Index test(s)	• BRCAPRO • MYRIAD • IC model
Reference standard(s)	• Germline pathogenic variant analysis
Duration of follow-up	na
Sources of funding	This study was supported by Regione Toscana in the frame of the High-Risk Cancer Family Project and by a grant from Associazione Italiana per la Ricerca sul Cancro (AIRC)
Outcomes	See Appendix L

Critical appraisal - NGA Critical appraisal - QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Male breast cancer sufferers only)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low

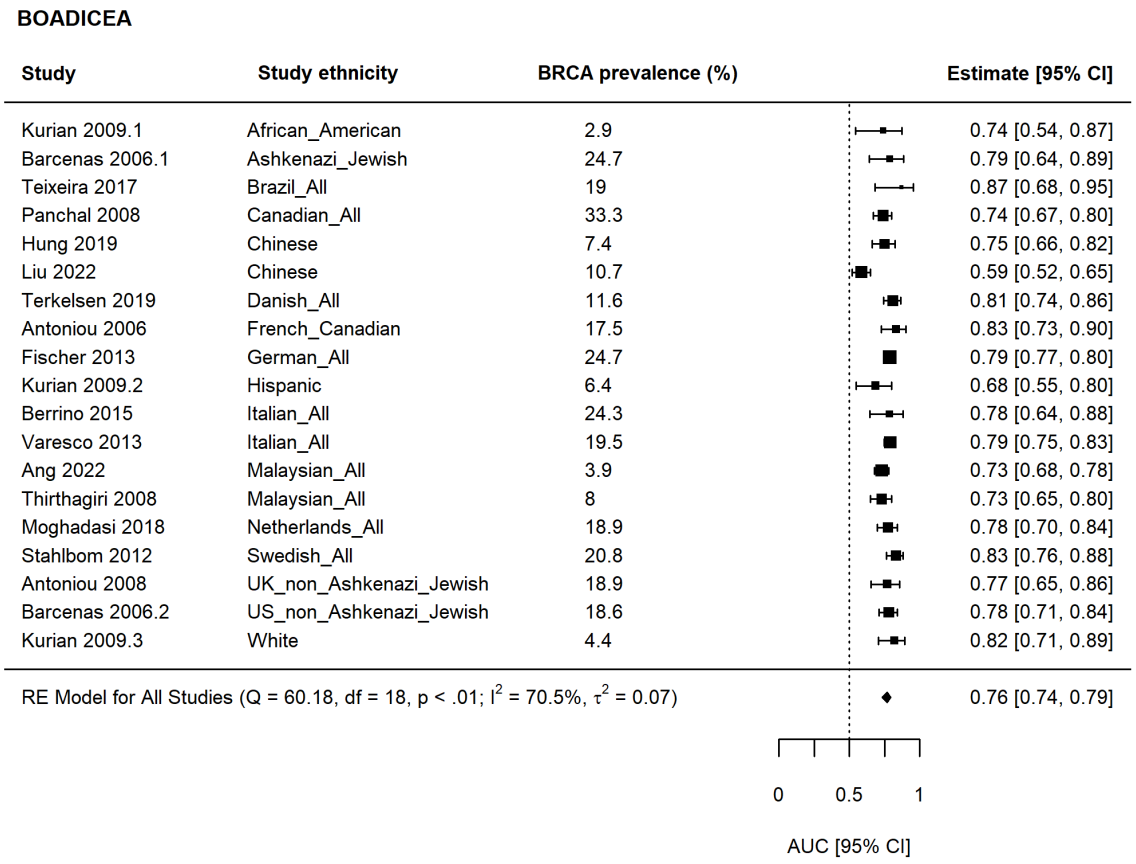
Section	Question	Answer
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Appendix E Forest plots and SROC plots

Forest plots for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

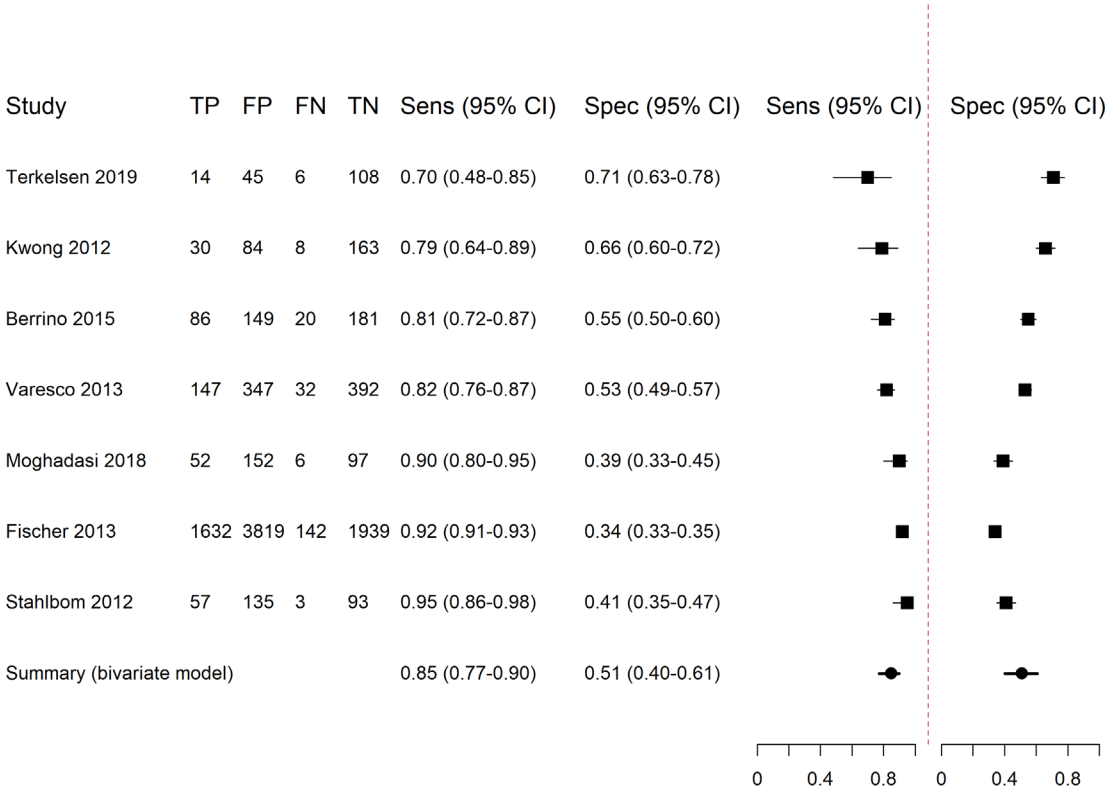
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: AUC of BOADICEA for identification of pathogenic BRCA1/2 variants



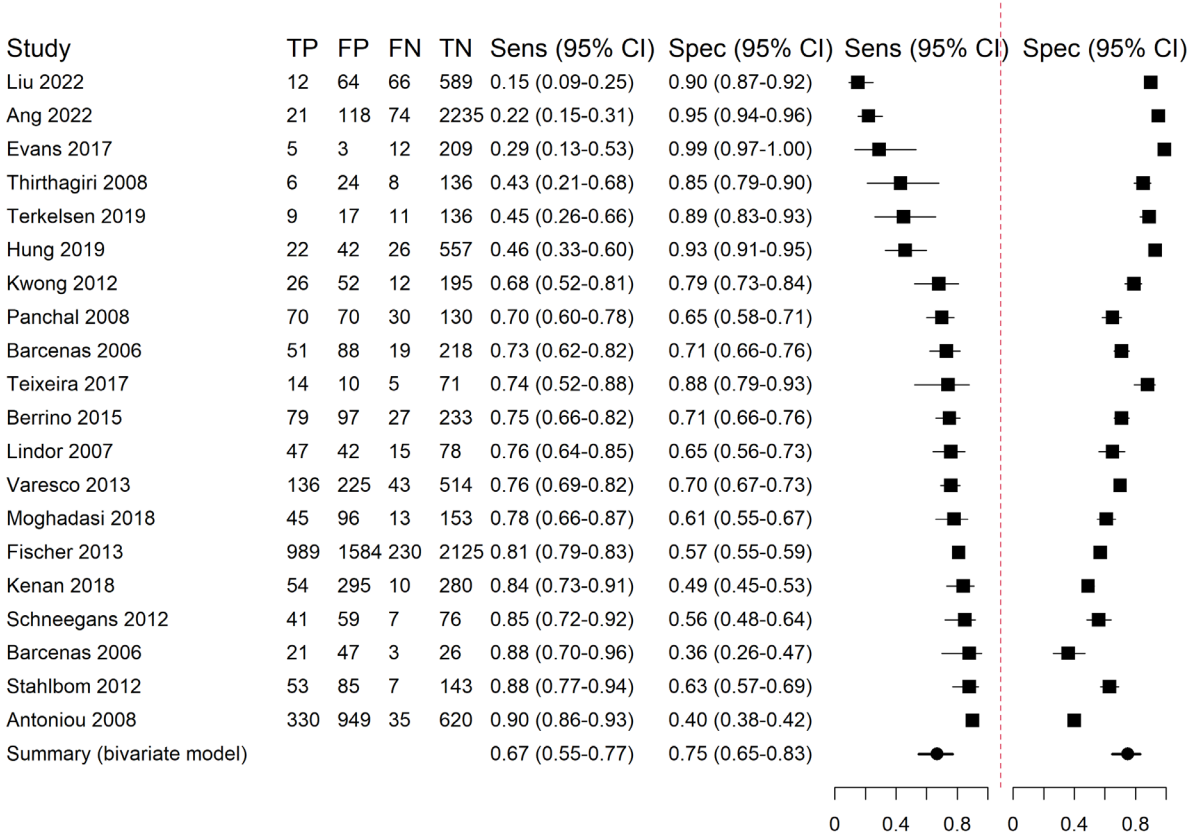
AUC: area under the ROC curve; CI: confidence interval; RE: random effects

Figure 3: Sensitivity and specificity of BOADICEA at carrier probability threshold of 5% for identification of pathogenic *BRCA1/2* variants



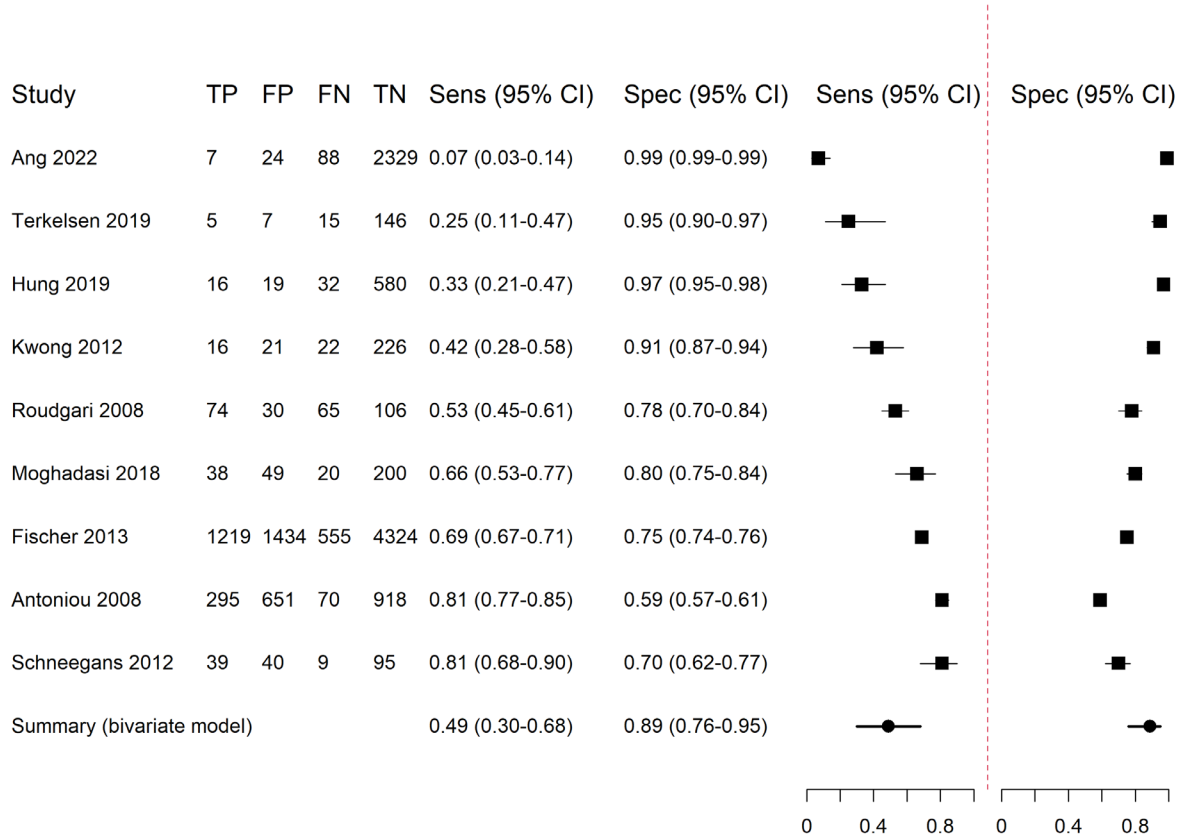
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 4: Sensitivity and specificity of BOADICEA at carrier probability threshold of 10% for identification of pathogenic *BRCA1/2* variants



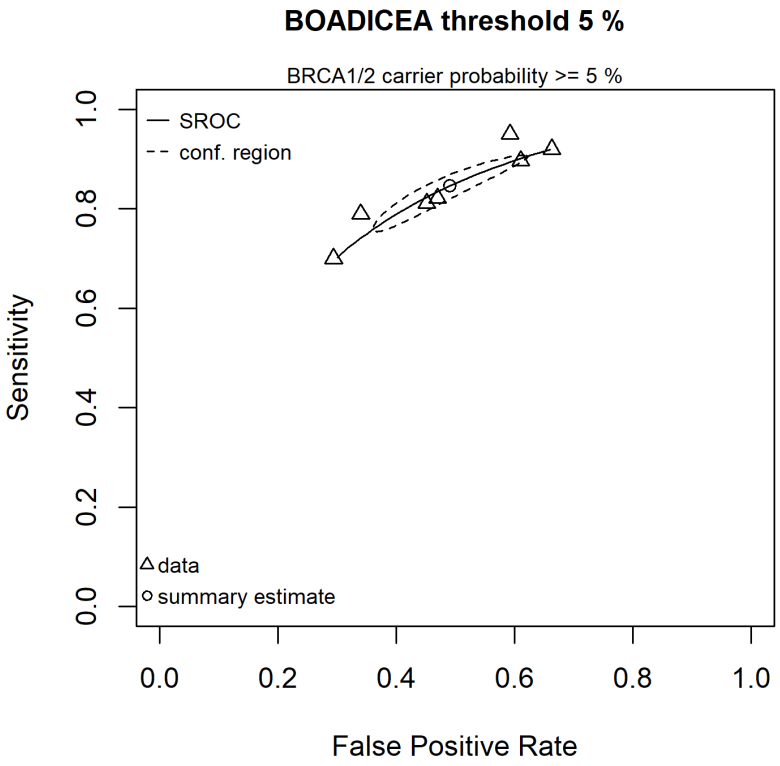
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 5: Sensitivity and specificity of BOADICEA at carrier probability threshold of 20% for identification of pathogenic *BRCA1/2* variants



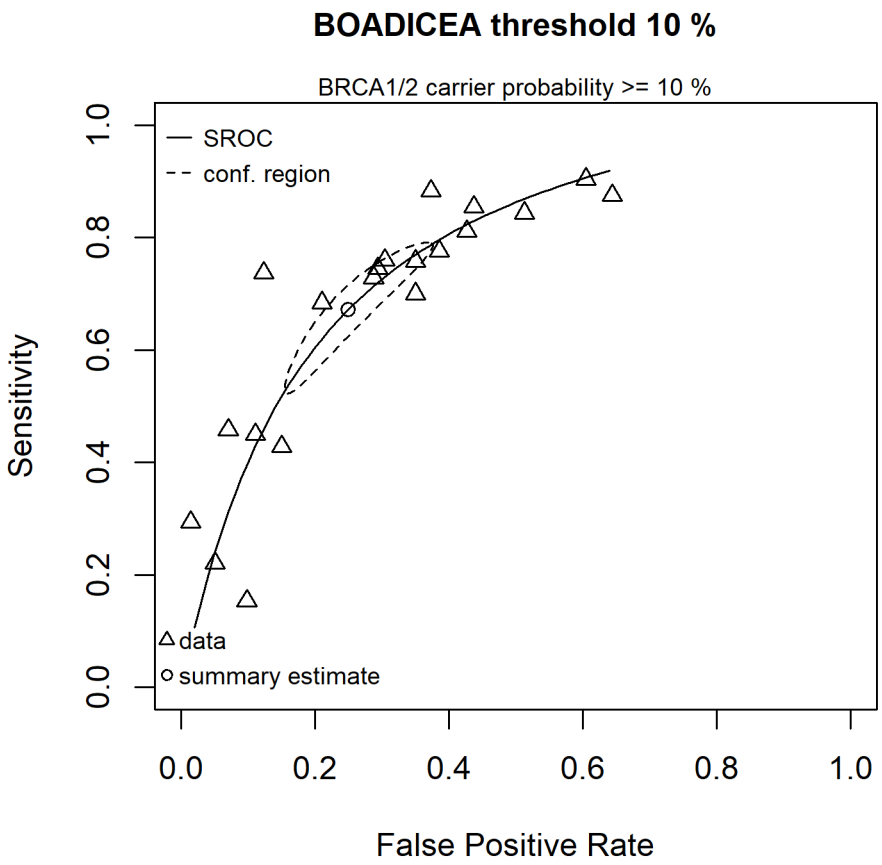
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 6: Summary ROC of BOADICEA at carrier probability threshold of 5% for identification of pathogenic *BRCA1/2* variants



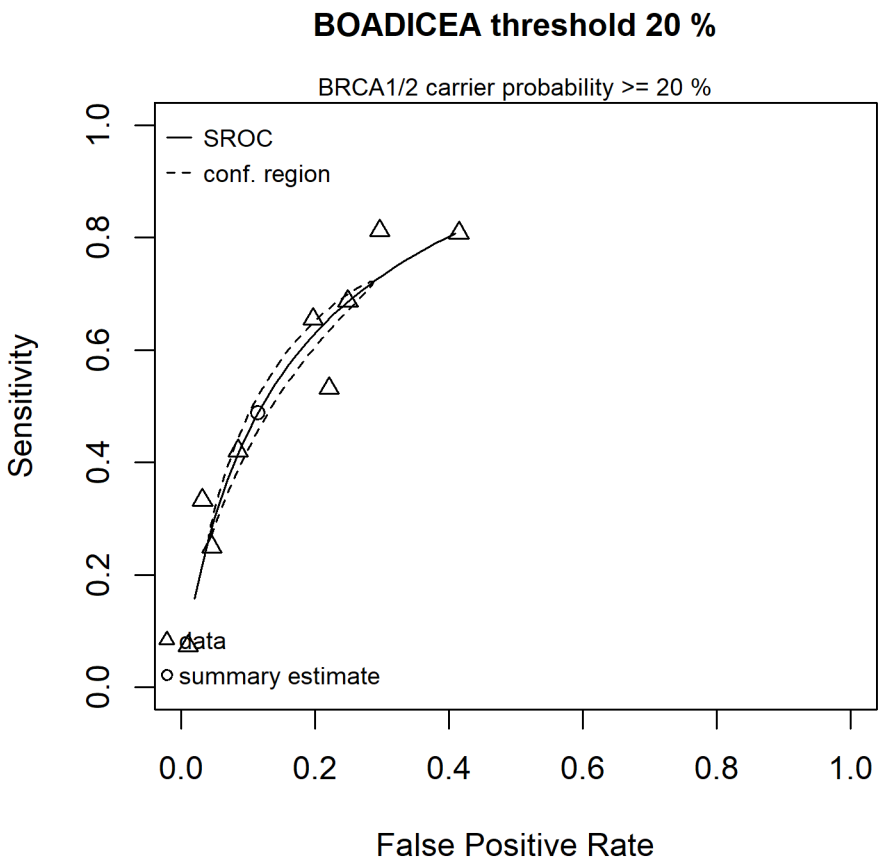
SROC: summary receiver operating characteristic curve

Figure 7: Summary ROC of BOADICEA at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



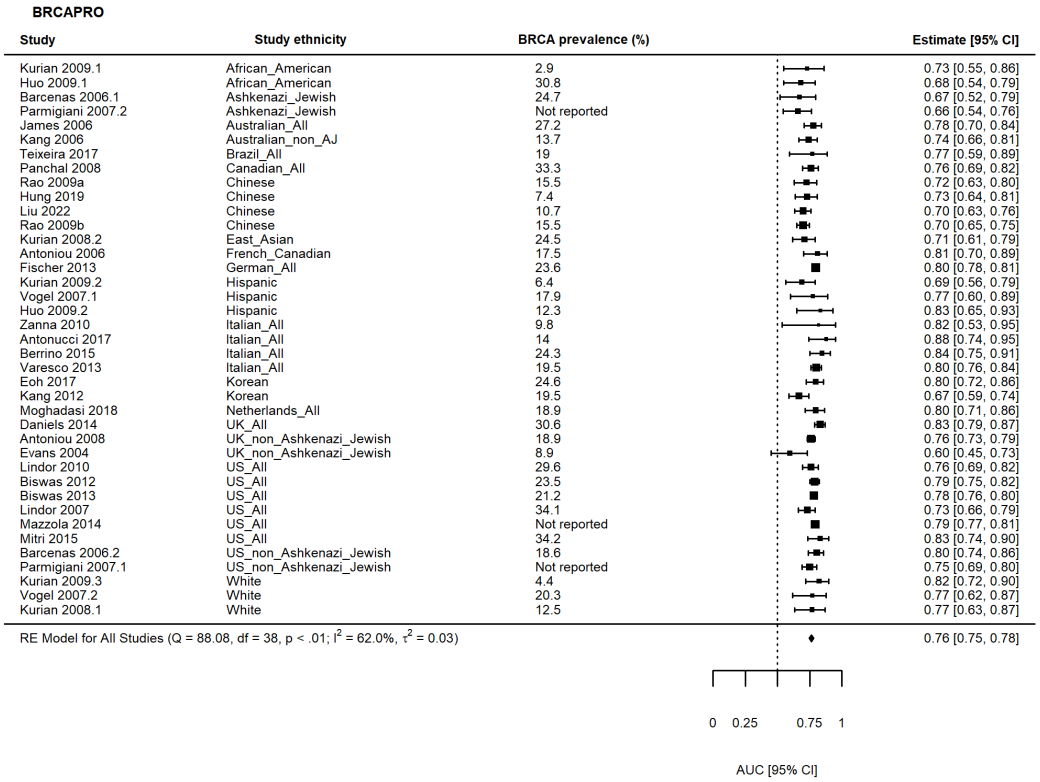
SROC: summary receiver operating characteristic curve

Figure 8: Summary ROC of BOADICEA at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



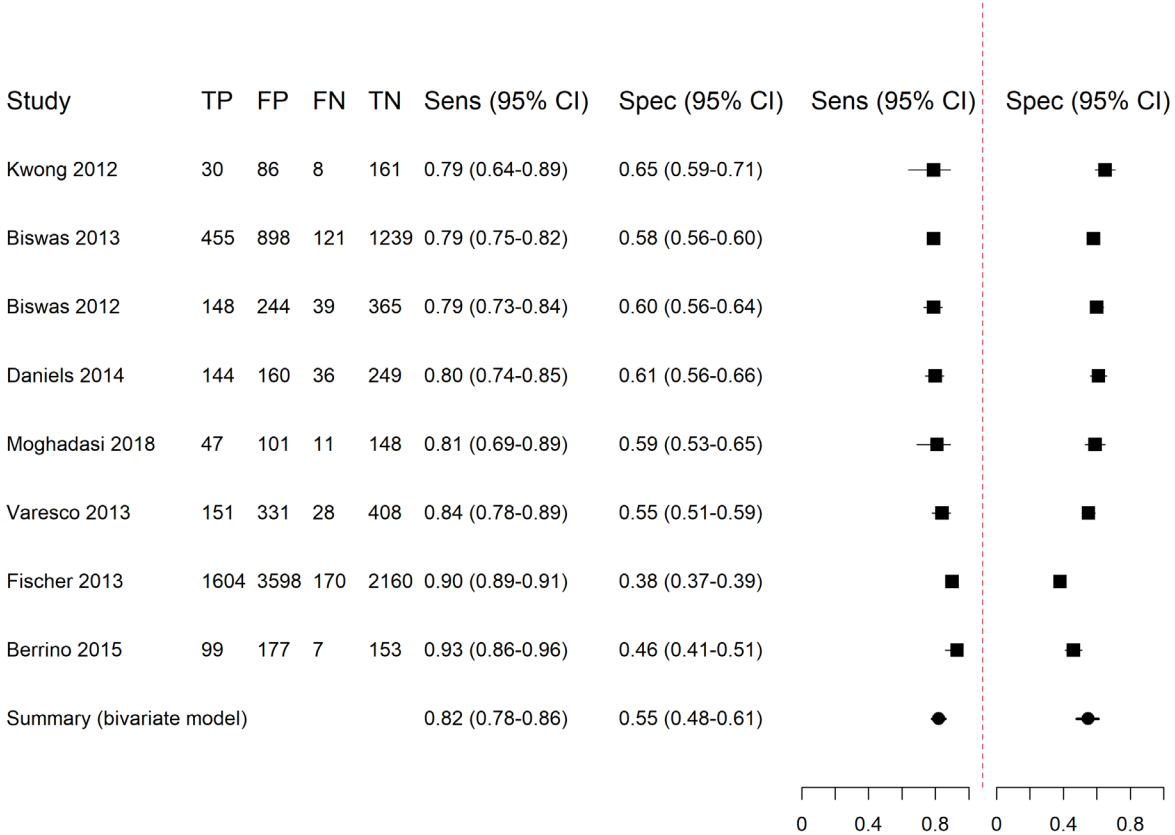
SROC: summary receiver operating characteristic curve

Figure 10: AUC of BRCAPRO for identification of pathogenic BRCA1/2 variants



AUC: area under the ROC curve; CI: confidence interval; RE: random effects

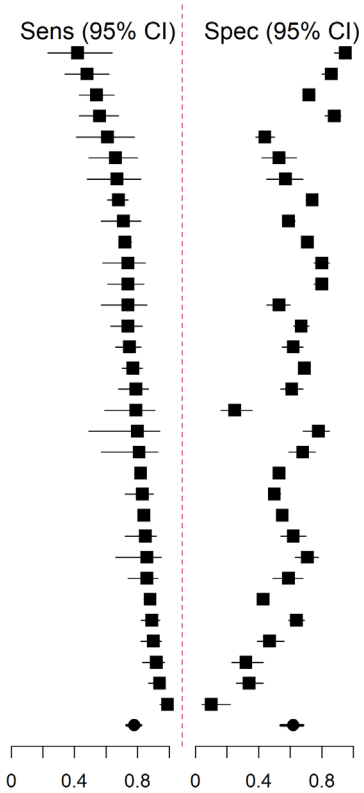
Figure 9: Sensitivity and specificity of BRCAPRO at carrier probability threshold of 5% for identification of pathogenic BRCA1/2 variants



CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

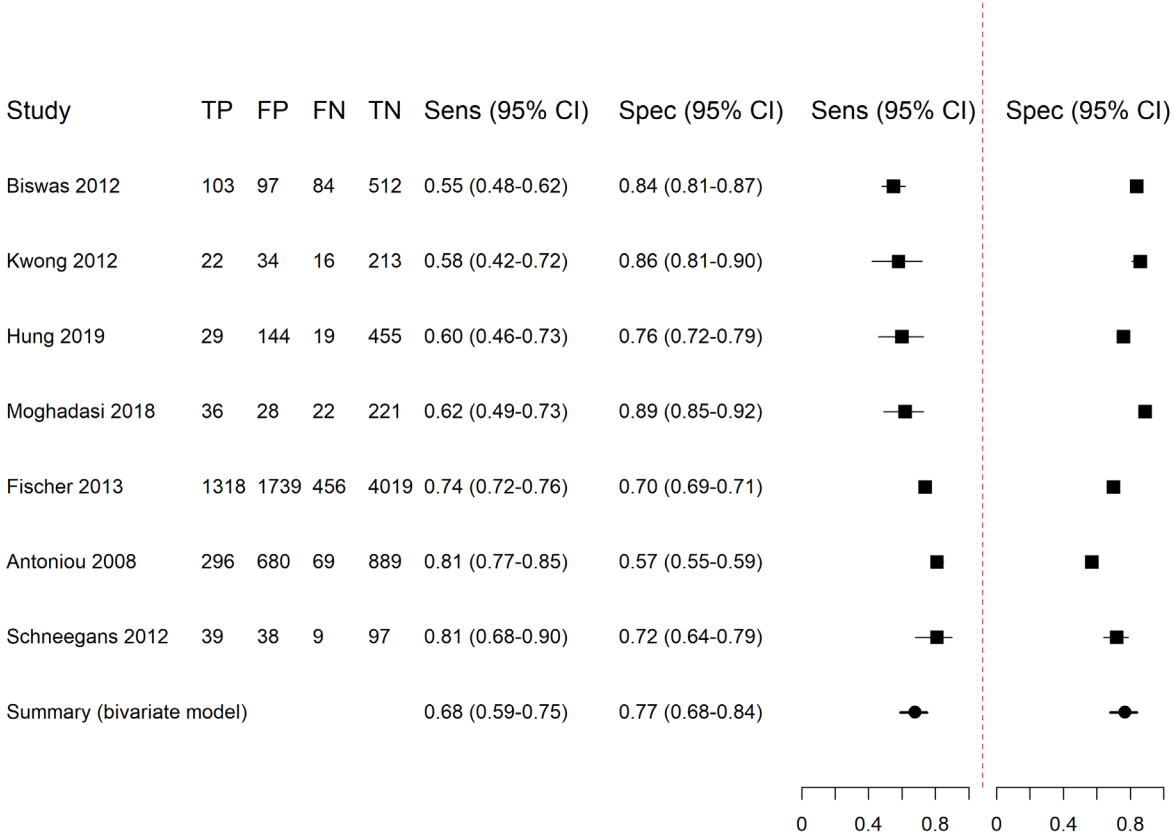
Figure 10: Sensitivity and specificity of BRCAPRO at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants

Study	TP	FP	FN	TN	Sens (95% CI)	Spec (95% CI)
Teixeira 2017	8	4	11	77	0.42 (0.23-0.64)	0.95 (0.88-0.98)
Kang 2012	22	27	24	163	0.48 (0.34-0.62)	0.86 (0.80-0.90)
Liu 2022	42	182	36	471	0.54 (0.43-0.65)	0.72 (0.68-0.75)
Eoh 2017	32	21	25	154	0.56 (0.43-0.68)	0.88 (0.82-0.92)
Evans 2004	14	131	9	104	0.61 (0.41-0.78)	0.44 (0.38-0.50)
Huo 2009	21	34	11	38	0.66 (0.49-0.80)	0.53 (0.42-0.64)
Capalbo 2006	18	31	9	41	0.67 (0.48-0.82)	0.57 (0.45-0.68)
Biswas 2012	127	158	60	451	0.68 (0.61-0.74)	0.74 (0.70-0.77)
Hung 2019	34	243	14	356	0.71 (0.57-0.82)	0.59 (0.55-0.63)
Biswas 2013	415	620	161	1517	0.72 (0.68-0.76)	0.71 (0.69-0.73)
Kwong 2012	28	50	10	197	0.74 (0.58-0.85)	0.80 (0.75-0.85)
Moghadasi 2018	43	50	15	199	0.74 (0.61-0.84)	0.80 (0.75-0.84)
Rao 2009b	23	79	8	90	0.74 (0.57-0.86)	0.53 (0.45-0.60)
Barcenas 2006	52	101	18	205	0.74 (0.63-0.83)	0.67 (0.62-0.72)
Panchal 2008	75	76	25	124	0.75 (0.66-0.82)	0.62 (0.55-0.68)
Varesco 2013	137	229	42	510	0.77 (0.70-0.83)	0.69 (0.66-0.72)
James 2006	53	70	14	109	0.79 (0.68-0.87)	0.61 (0.54-0.68)
Barcenas 2006	19	55	5	18	0.79 (0.59-0.91)	0.25 (0.16-0.36)
Zanna 2010	8	20	2	71	0.80 (0.49-0.94)	0.78 (0.68-0.85)
Huo 2009	13	36	3	78	0.81 (0.57-0.93)	0.68 (0.59-0.76)
Parmigiani 2007	352	522	75	579	0.82 (0.78-0.85)	0.53 (0.50-0.56)
Kenan 2018	53	285	11	289	0.83 (0.72-0.90)	0.50 (0.46-0.54)
Fischer 2013	1490	2591	284	3167	0.84 (0.82-0.86)	0.55 (0.54-0.56)
Schneegans 2012	41	51	7	84	0.85 (0.72-0.92)	0.62 (0.54-0.70)
Antonucci 2017	18	37	3	92	0.86 (0.66-0.95)	0.71 (0.63-0.78)
Mitri 2015	43	39	7	57	0.86 (0.74-0.93)	0.59 (0.49-0.68)
Antoniou 2008	322	893	43	676	0.88 (0.84-0.91)	0.43 (0.41-0.45)
Berrino 2015	94	118	12	212	0.89 (0.82-0.94)	0.64 (0.59-0.69)
Oros 2006	86	68	10	60	0.90 (0.82-0.95)	0.47 (0.39-0.56)
Euhus 2002	58	58	5	27	0.92 (0.83-0.97)	0.32 (0.23-0.43)
Berry 2002	85	76	5	39	0.94 (0.87-0.97)	0.34 (0.26-0.43)
Berry 2002	77	43	1	5	0.99 (0.94-1.00)	0.10 (0.04-0.22)
Summary (bivariate model)					0.78 (0.73-0.82)	0.62 (0.54-0.68)



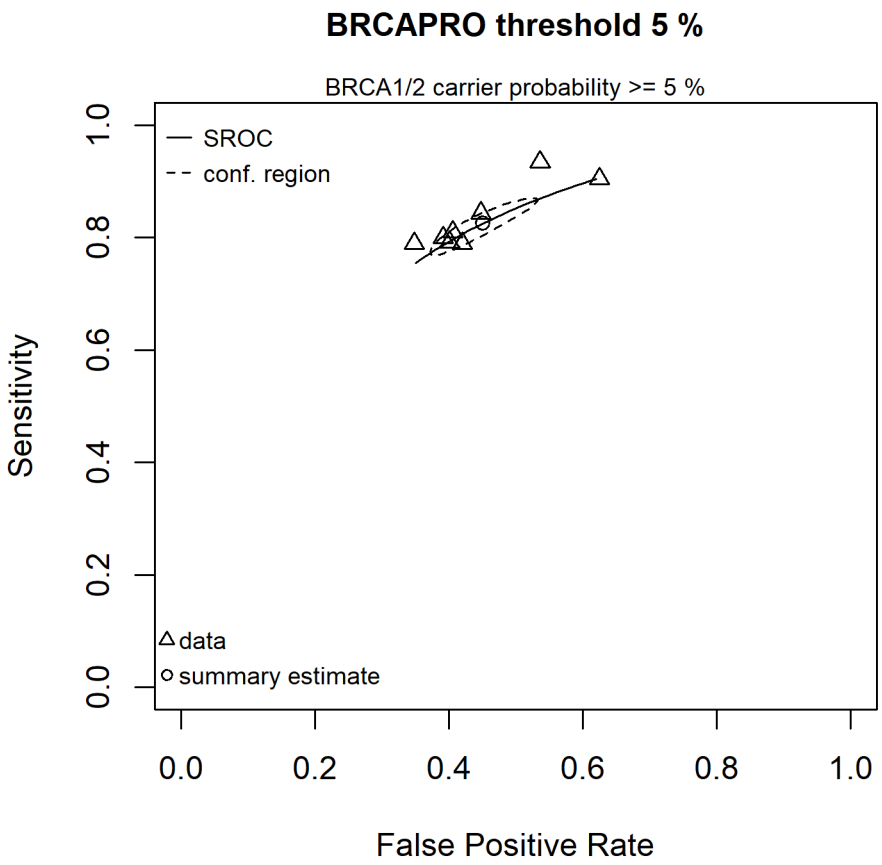
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 11: Sensitivity and specificity of BRCAPRO at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



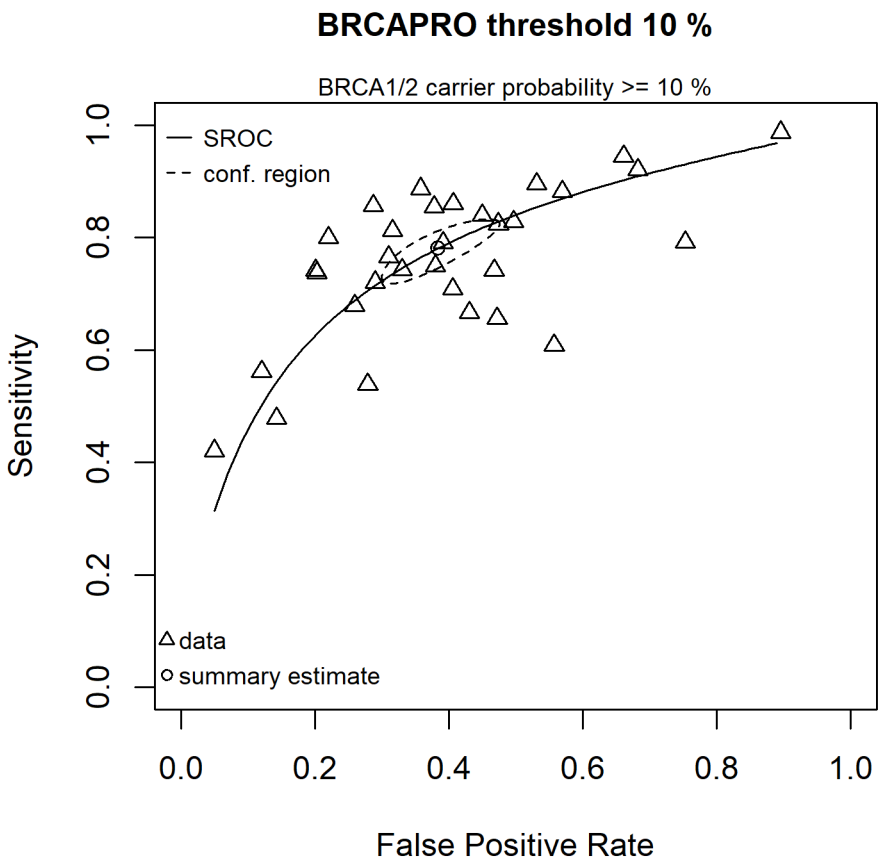
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 12: Summary ROC of BRCAPRO at carrier probability threshold of 5% for identification of pathogenic BRCA1/2 variants



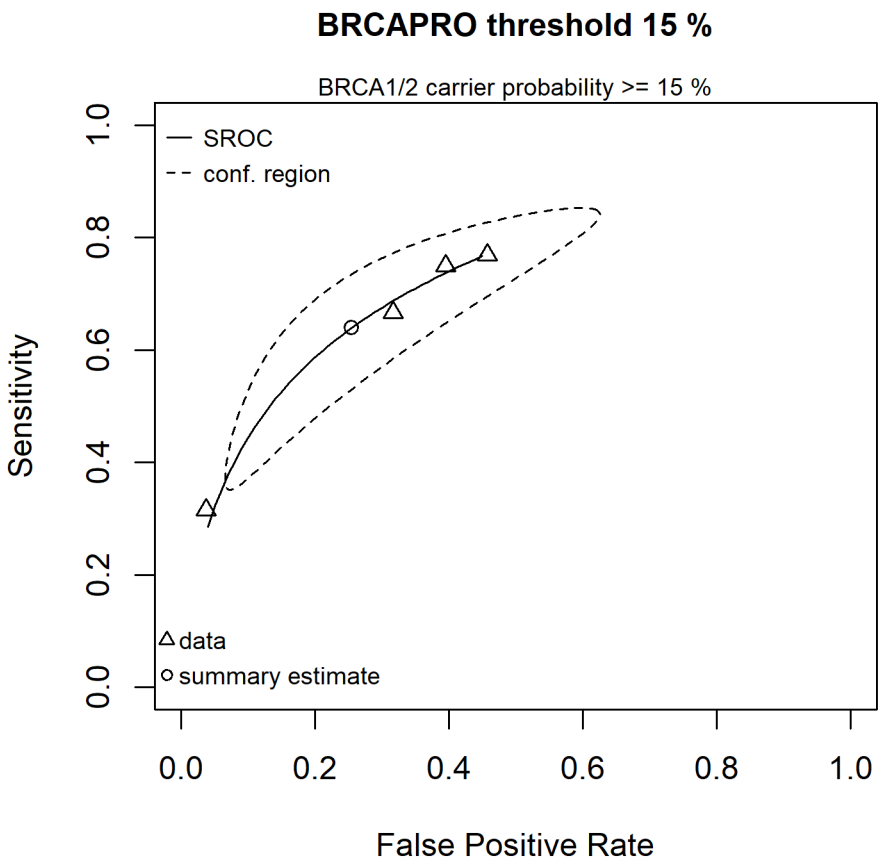
SROC: summary receiver operating characteristic curve

Figure 13: Summary ROC of BRCAPRO at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



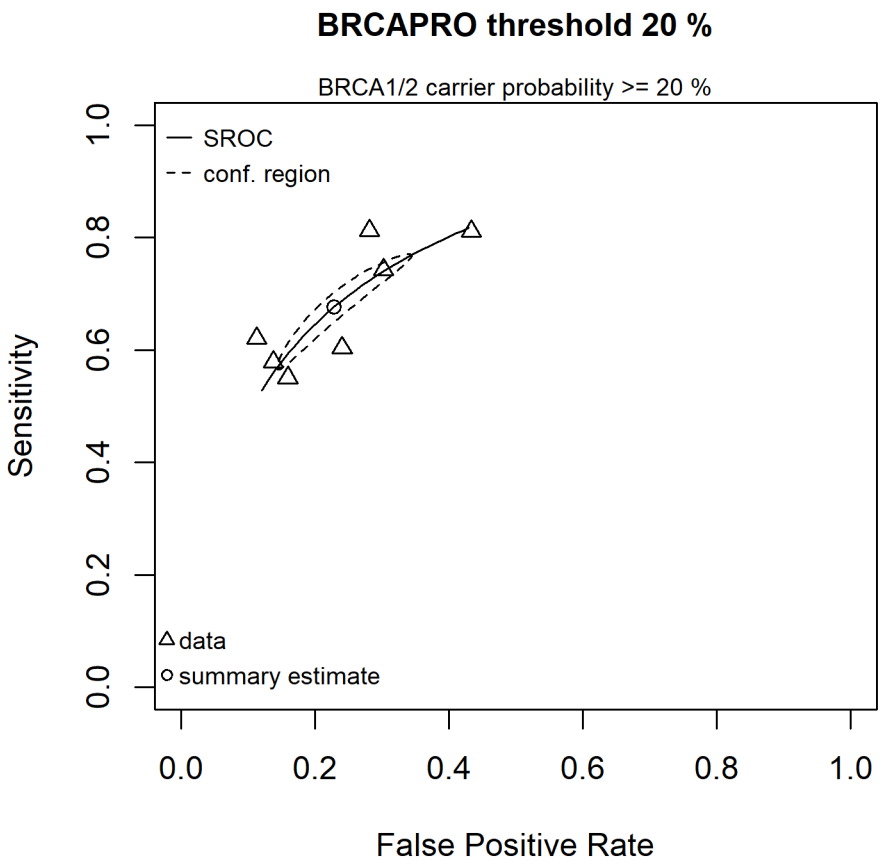
SROC: summary receiver operating characteristic curve

Figure 14: Summary ROC of BRCAPRO at carrier probability threshold of 15% for identification of pathogenic BRCA1/2 variants



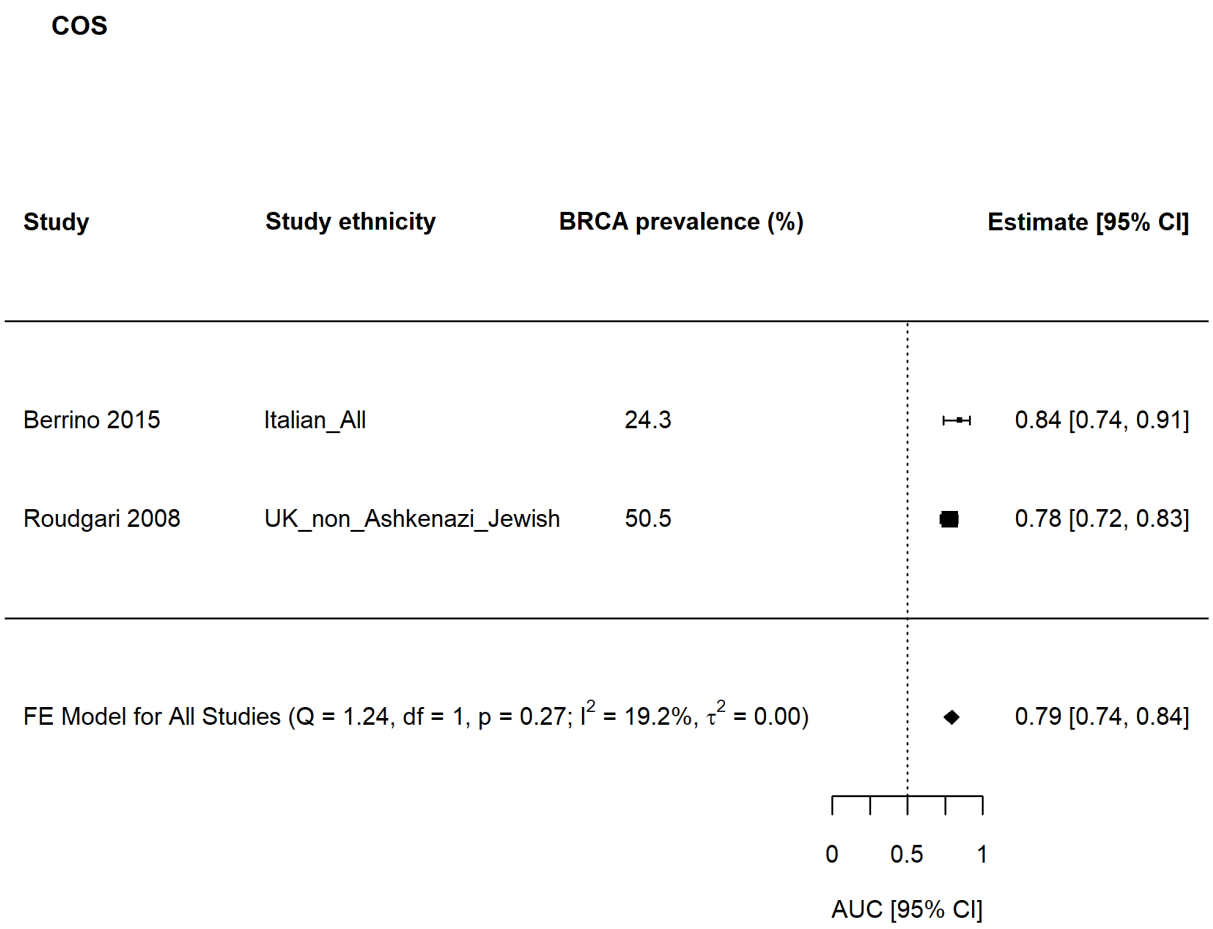
SROC: summary receiver operating characteristic curve

Figure 15: Summary ROC of BRCAPRO at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



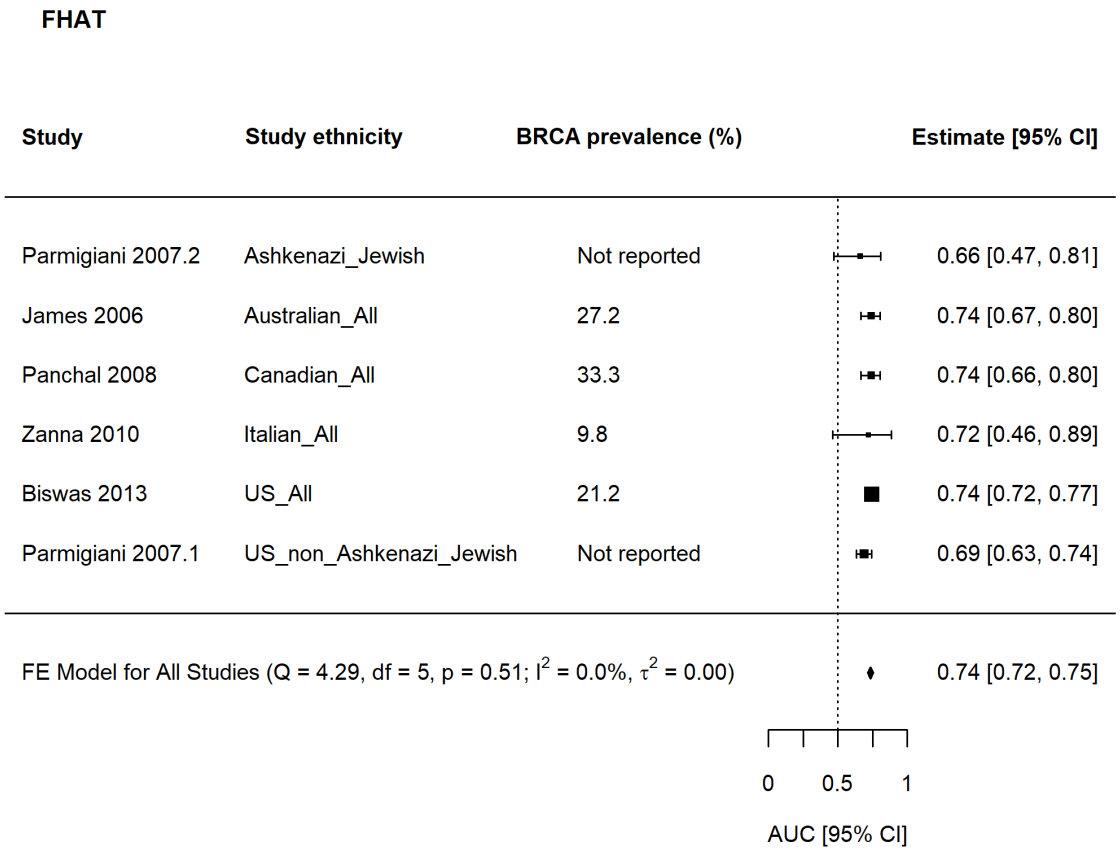
SROC: summary receiver operating characteristic curve

Figure 16: AUC of COS for identification of pathogenic BRCA1/2 variants



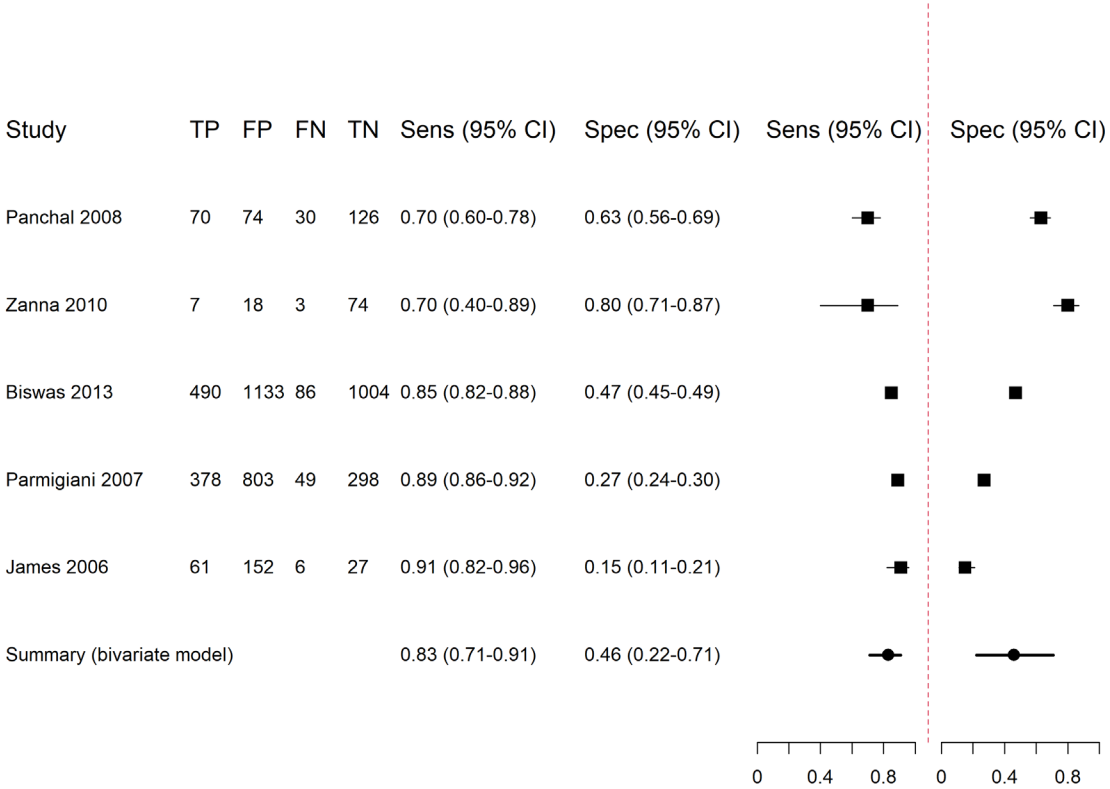
AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 17: AUC of FHAT for identification of pathogenic BRCA1/2 variants



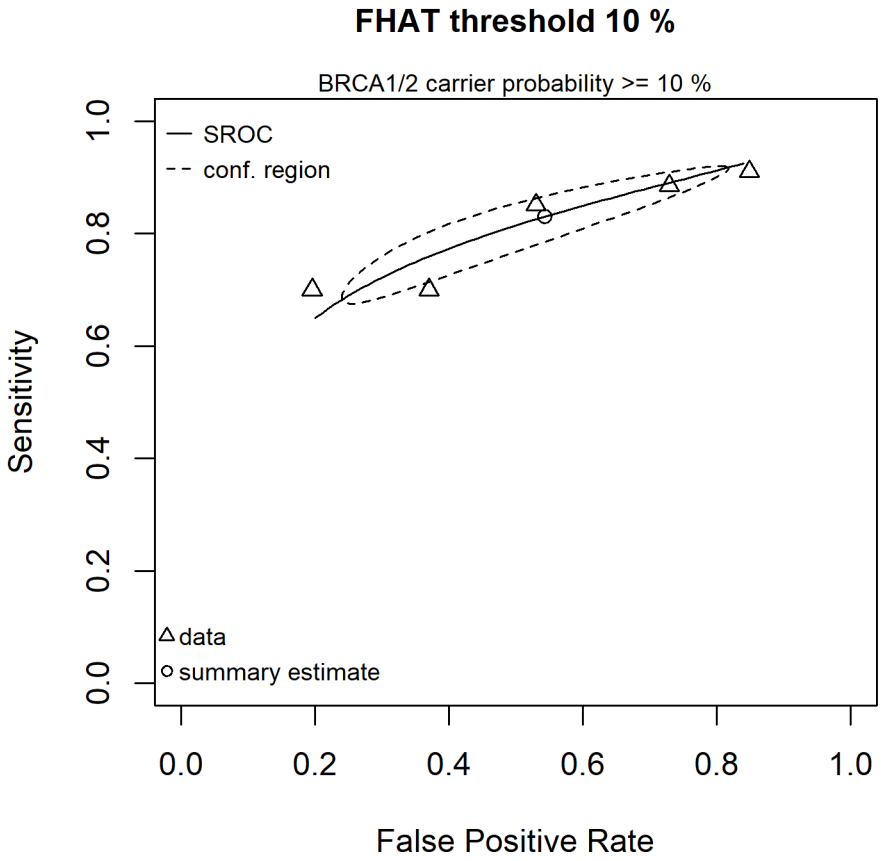
AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 18: Sensitivity and specificity of FHAT at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



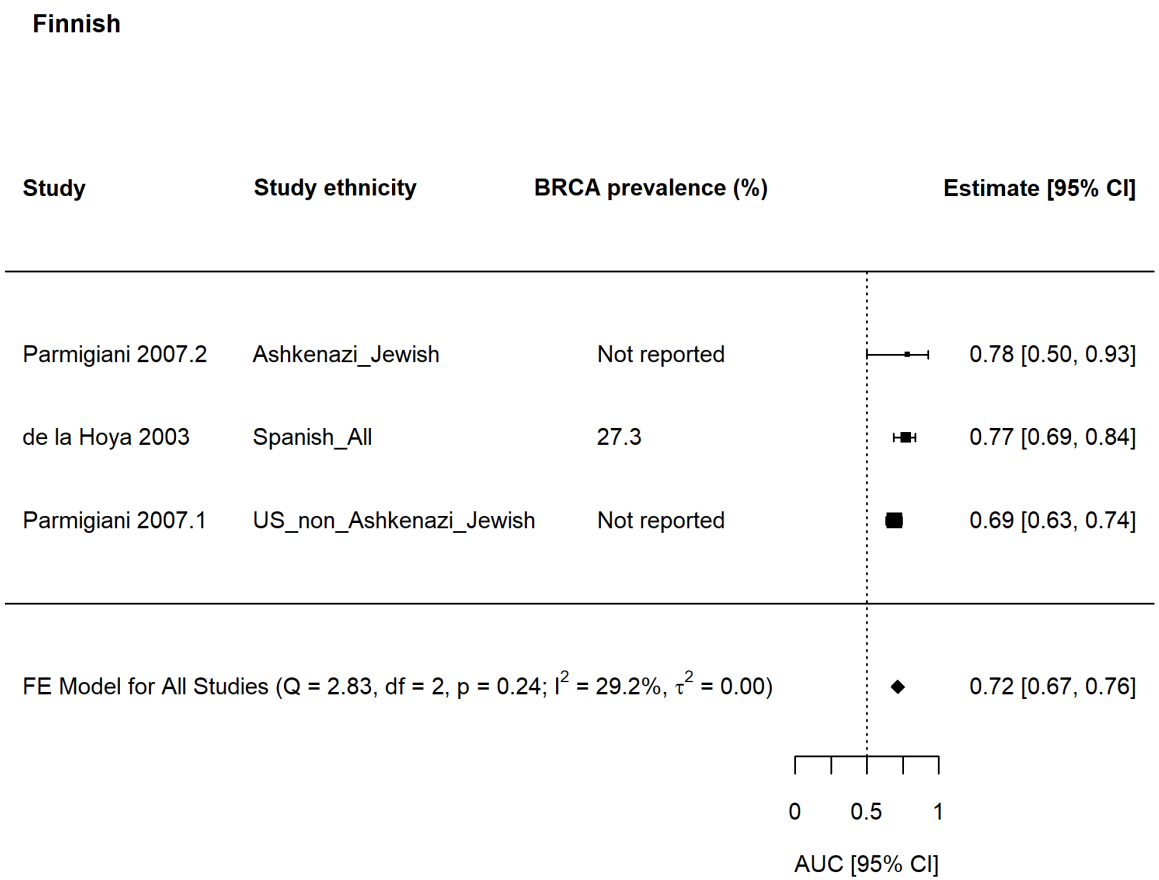
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 19: Summary ROC of FHAT at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



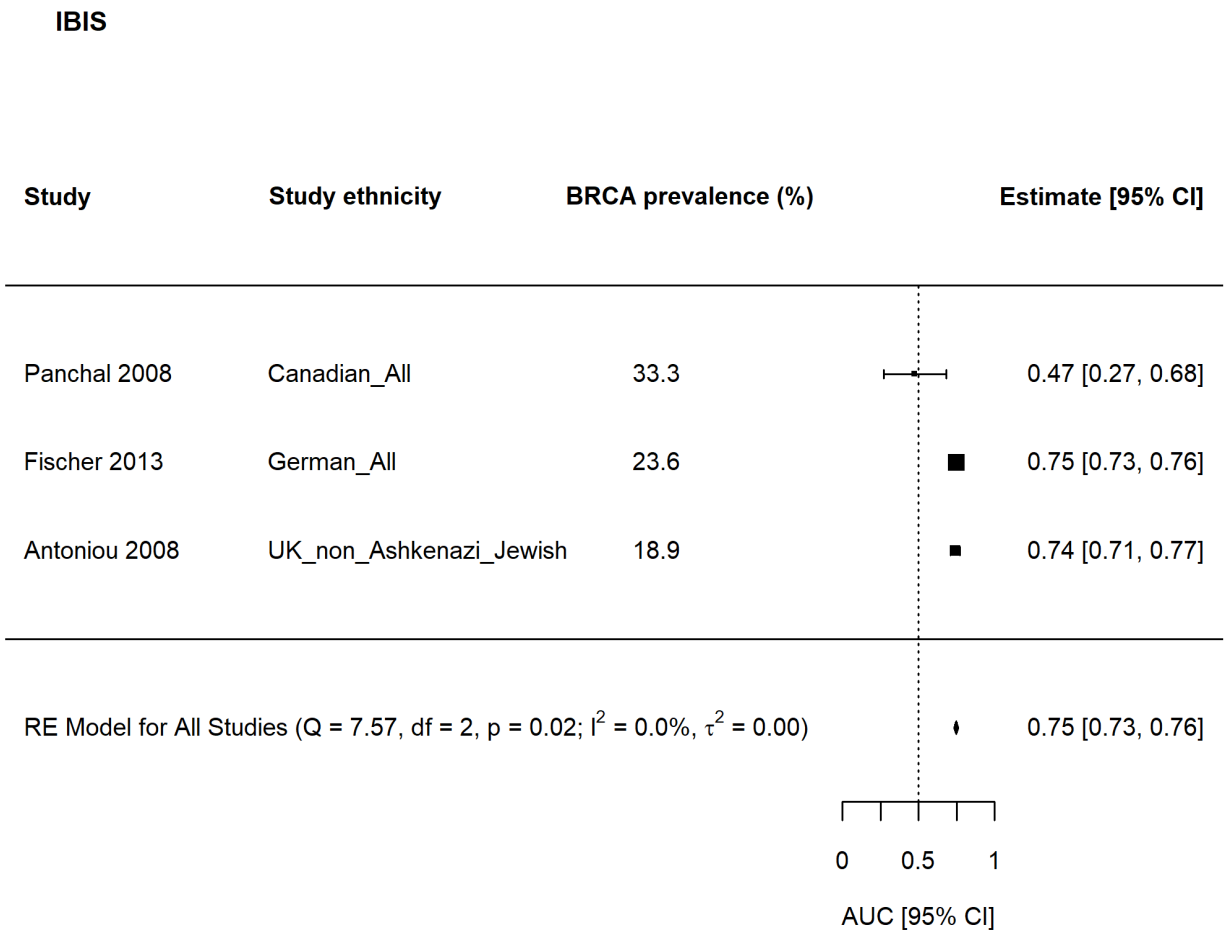
SROC: summary receiver operating characteristic curve

Figure 20: AUC of Finnish model for identification of pathogenic BRCA1/2 variants



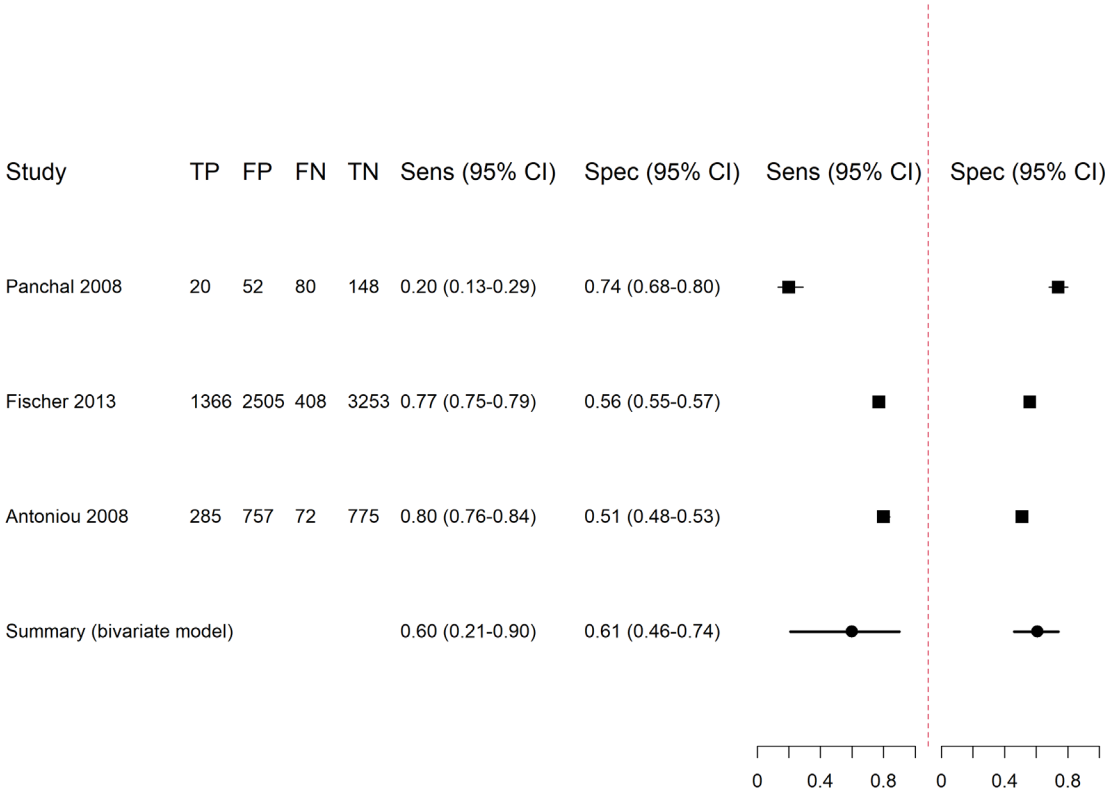
AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 21: AUC of IBIS for identification of pathogenic BRCA1/2 variants



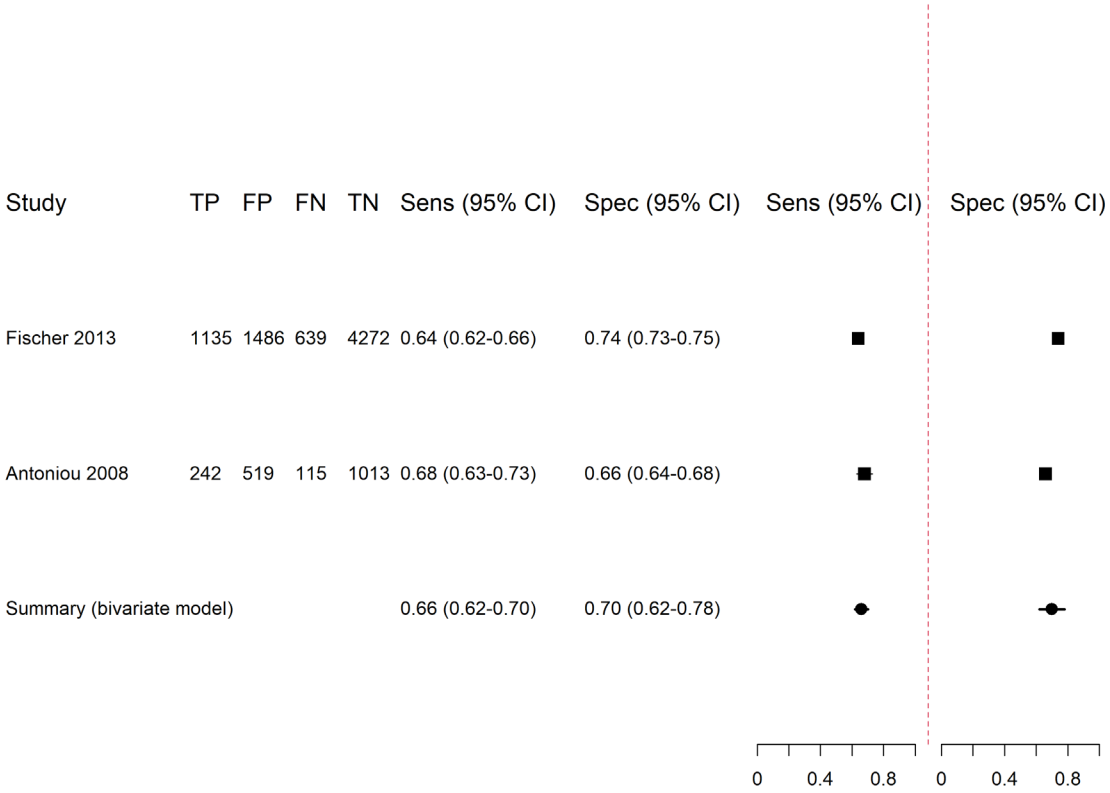
AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 22: Sensitivity and specificity of IBIS at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



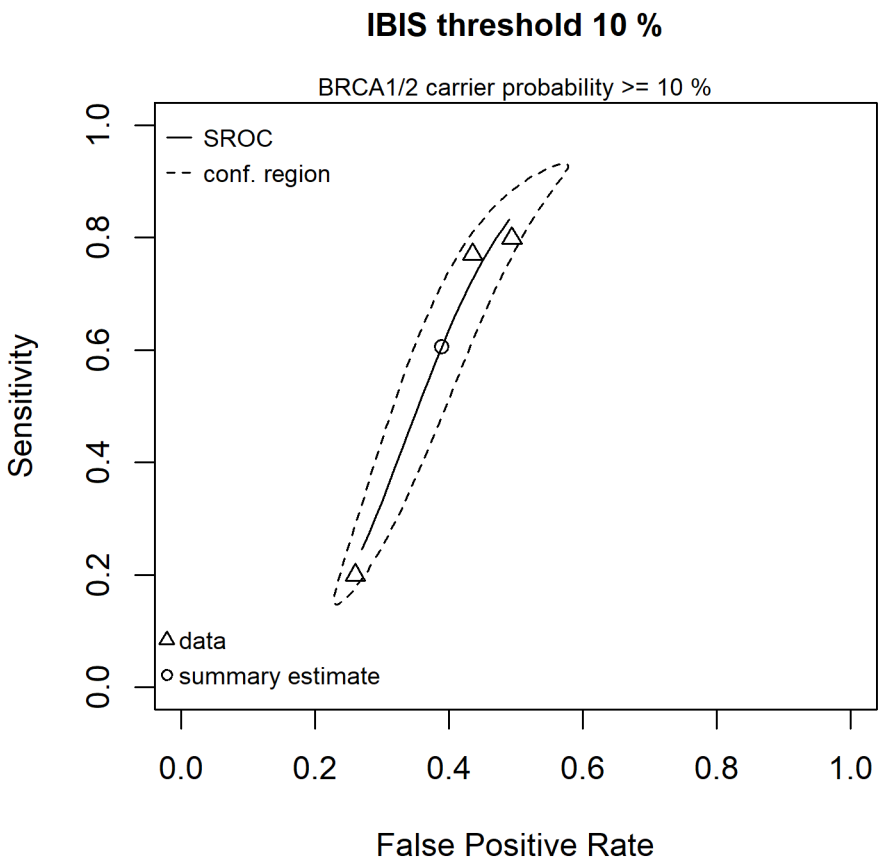
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 23: Sensitivity and specificity of IBIS at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



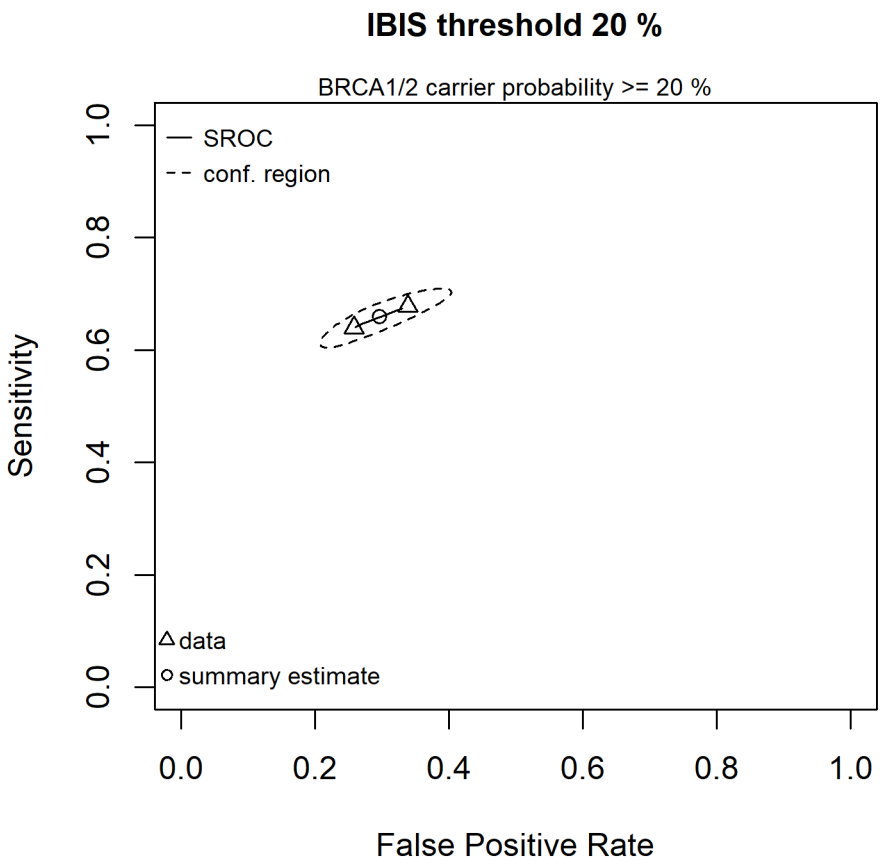
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 24: Summary ROC of IBIS at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



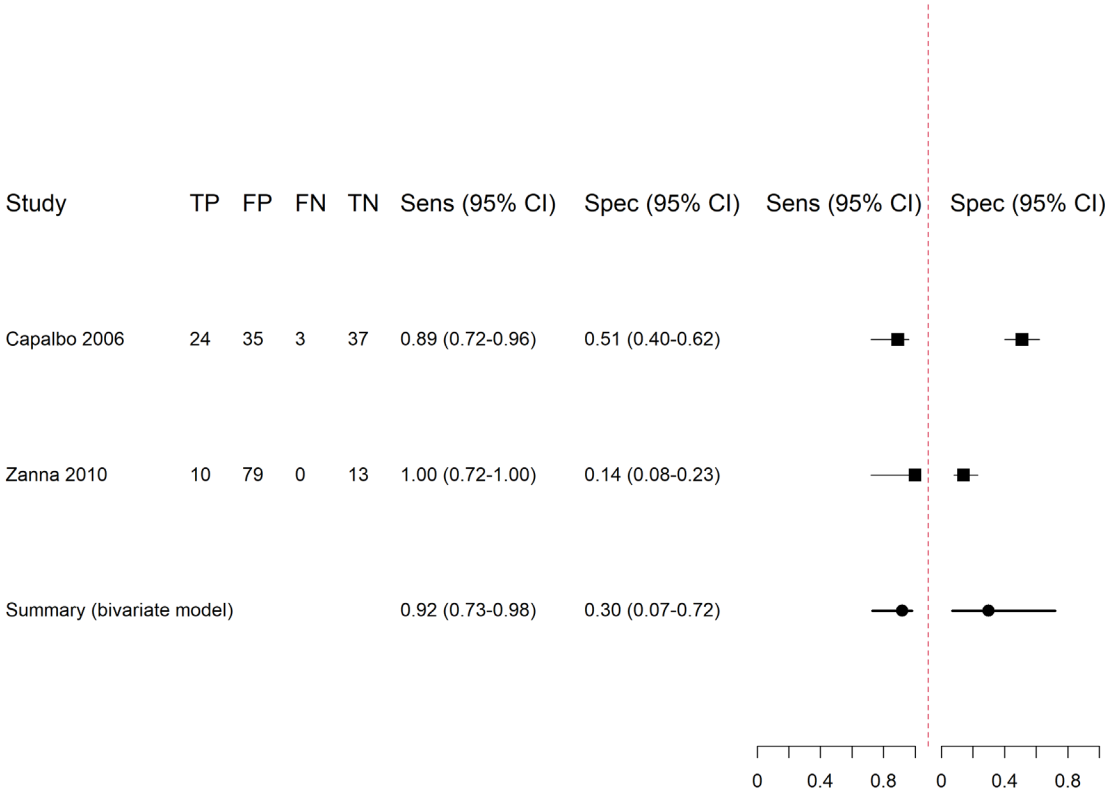
SROC: summary receiver operating characteristic curve

Figure 25: Summary ROC of IBIS at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



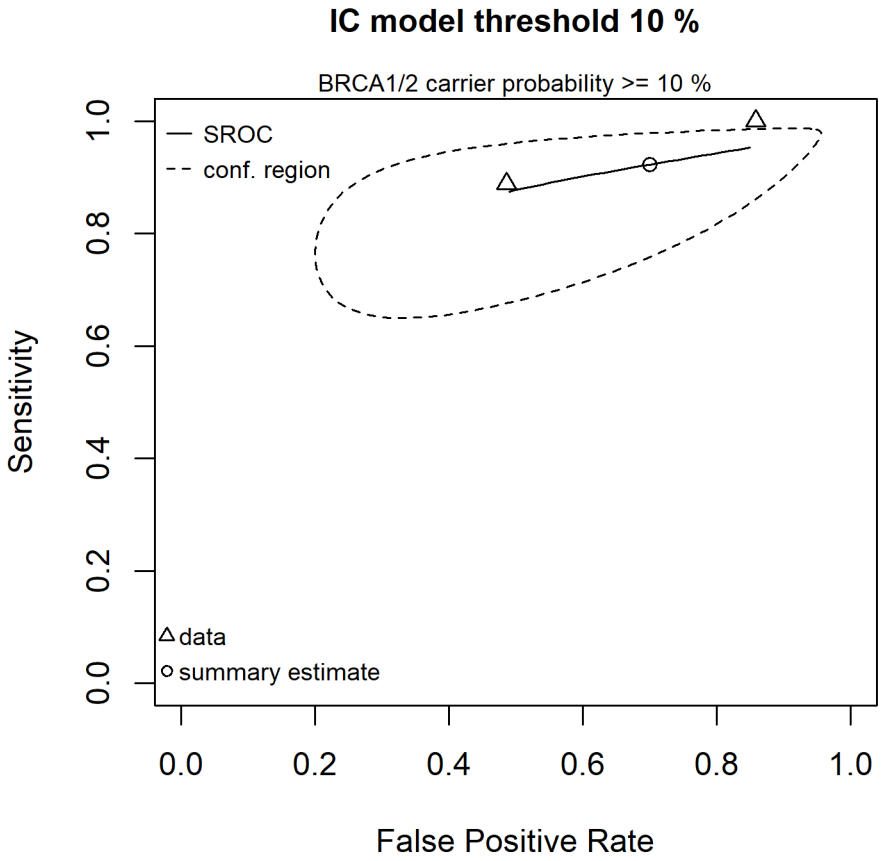
SROC: summary receiver operating characteristic curve

Figure 26: Sensitivity and specificity of IC model at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



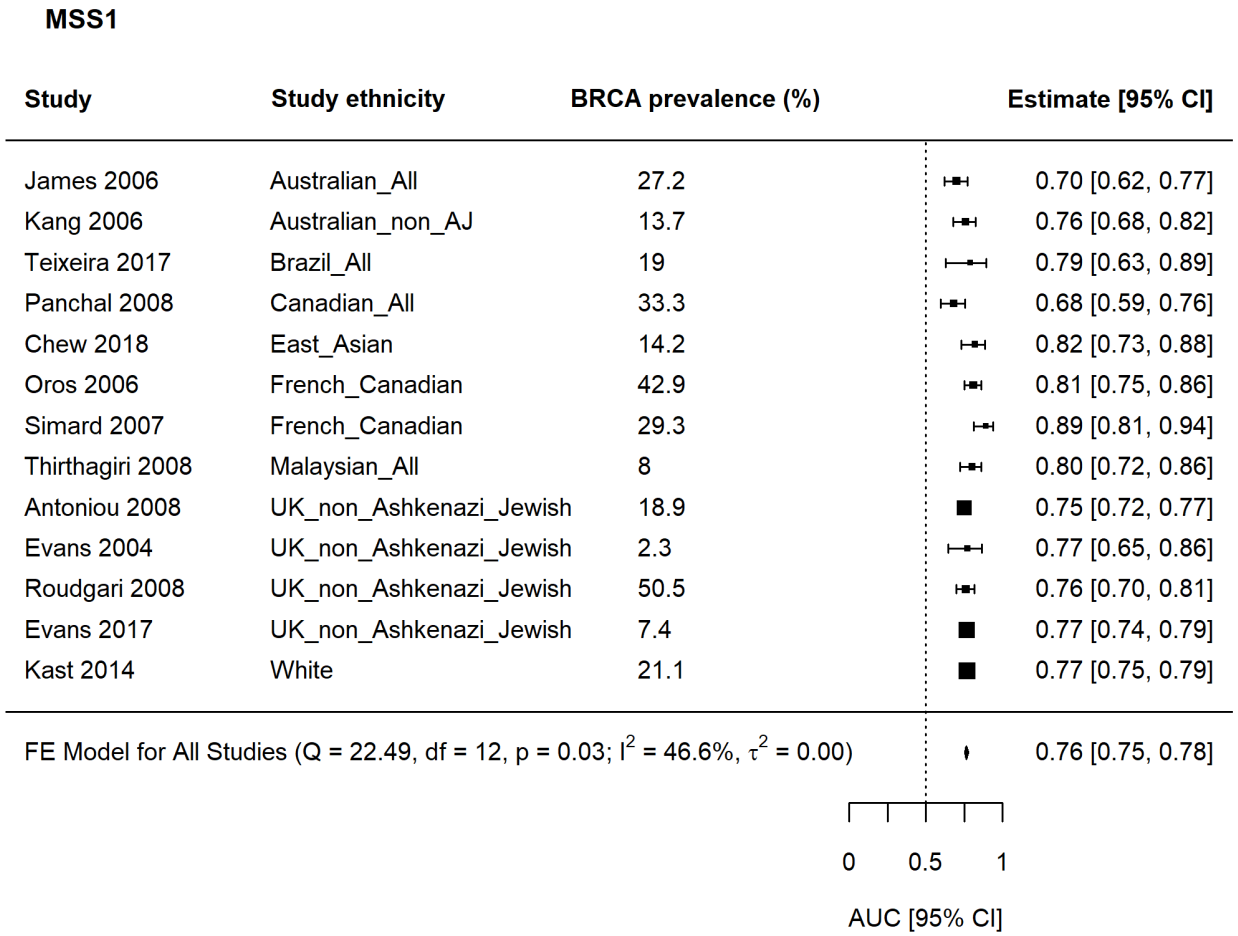
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 27: Summary ROC of IC model at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



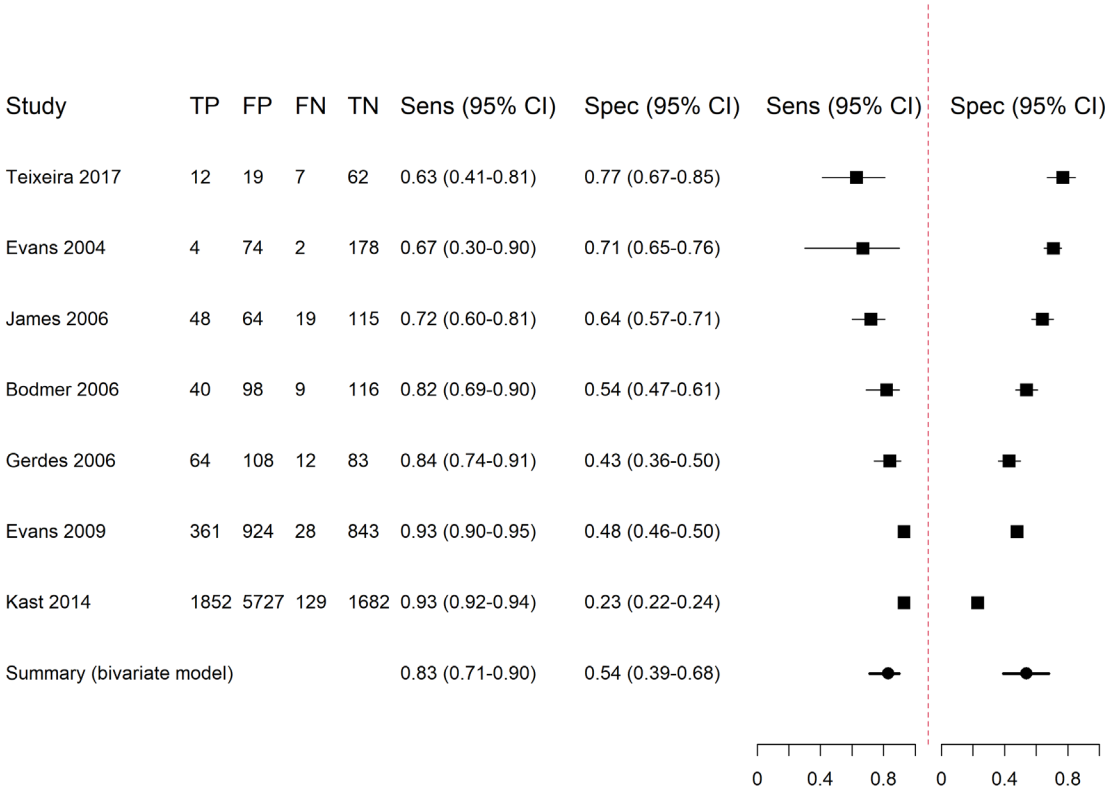
SROC: summary receiver operating characteristic curve

Figure 28: AUC of Manchester Scoring System v1 (MSS1) for identification of pathogenic BRCA1/2 variants



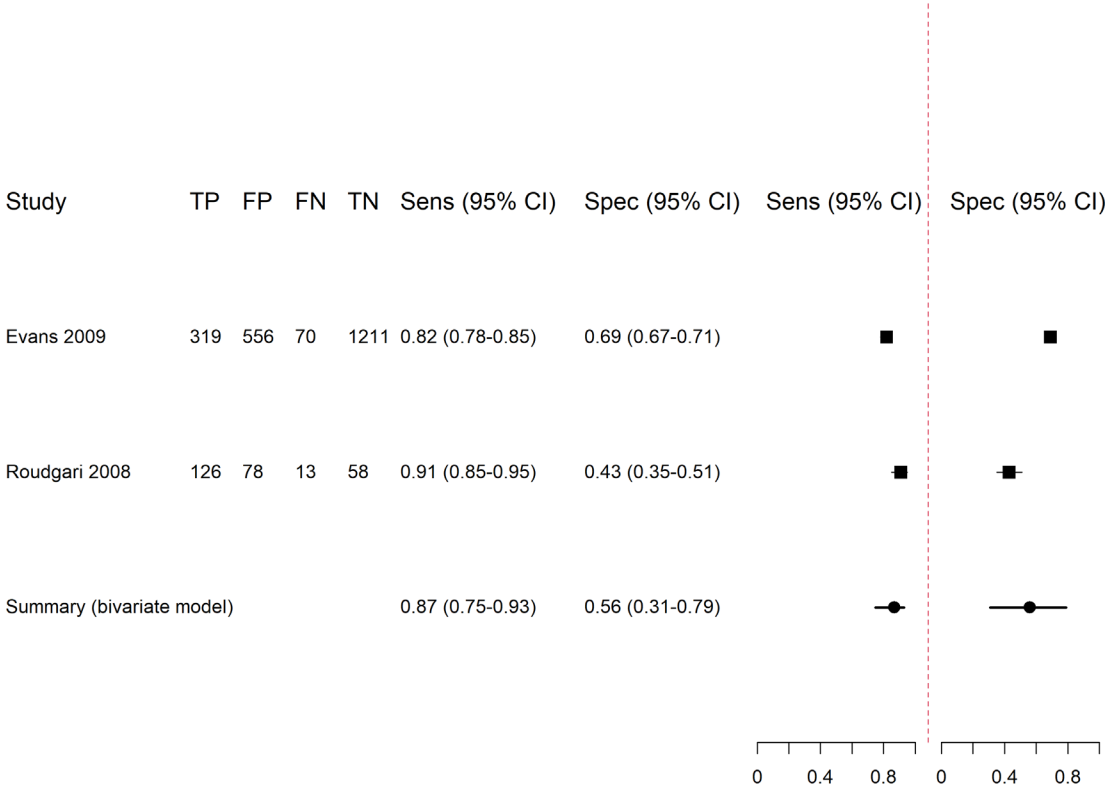
AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 29: Sensitivity and specificity of Manchester Scoring System v1 (MSS1) at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



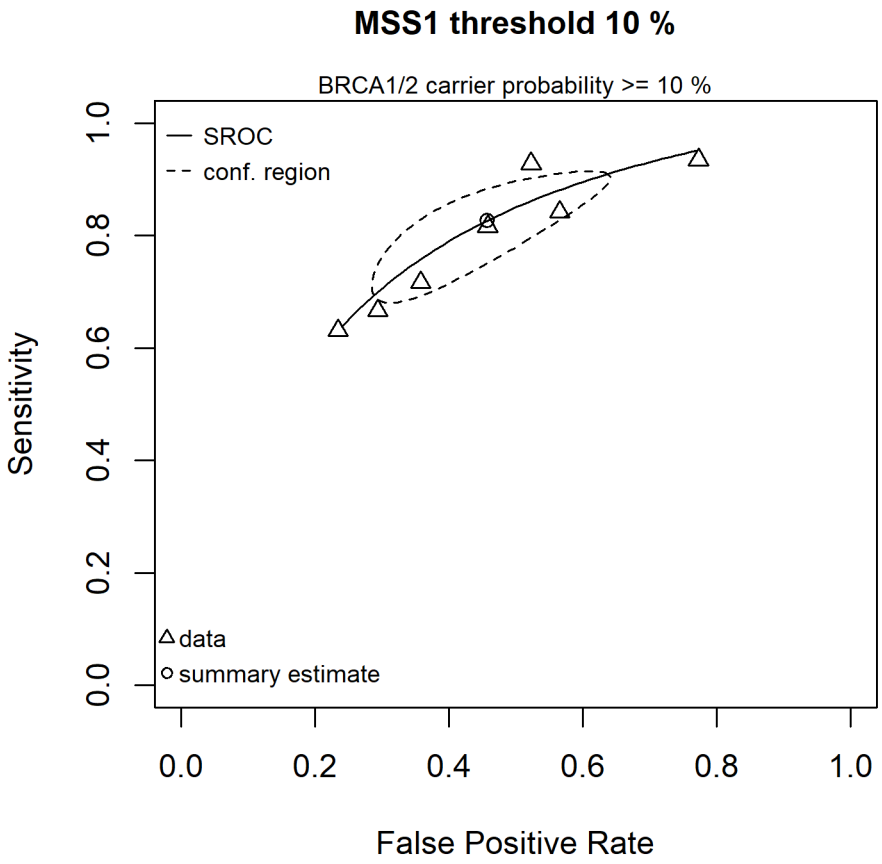
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 30:Sensitivity and specificity of Manchester Scoring System v1 (MSS1) at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



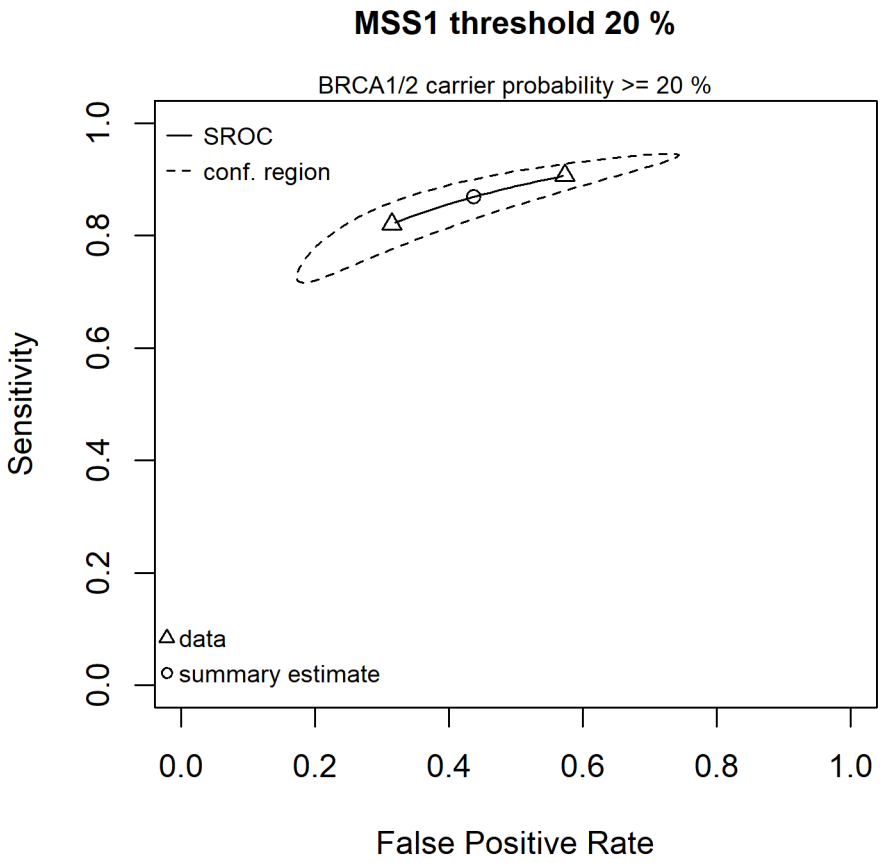
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 31: Summary ROC of Manchester Scoring System (version 1) at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



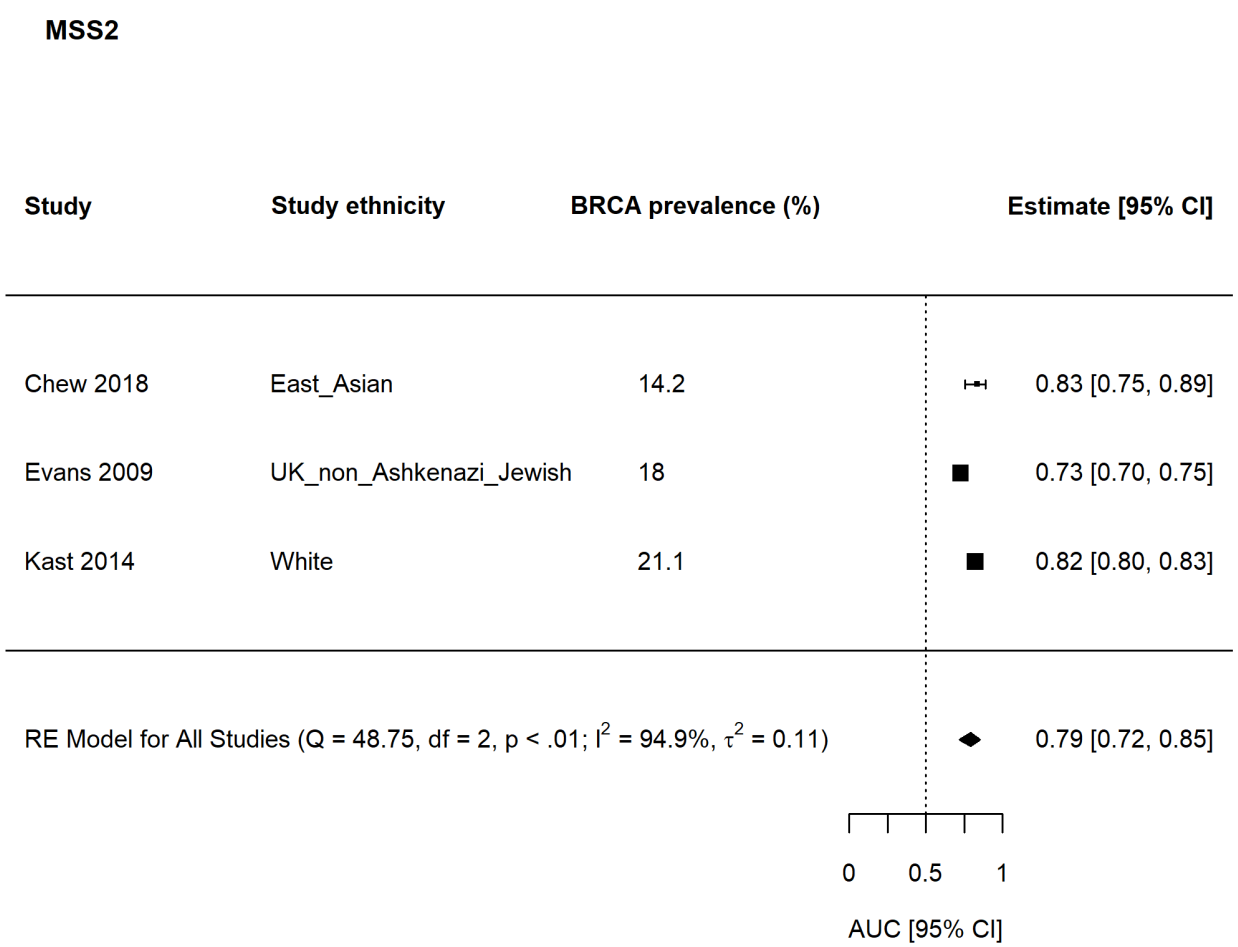
SROC: summary receiver operating characteristic curve

Figure 32: Summary ROC of Manchester Scoring System (version 1) at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



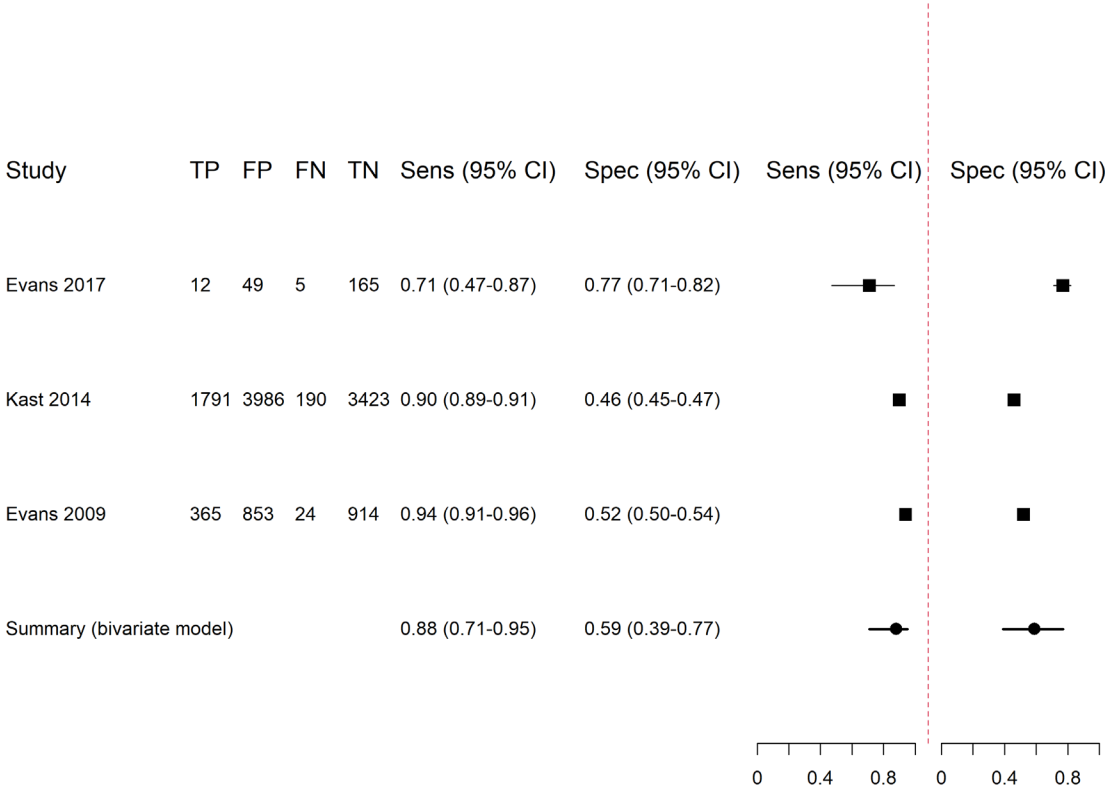
SROC: summary receiver operating characteristic curve

Figure 33: AUC of Manchester scoring system v2 (MSS2) for identification of pathogenic BRCA1/2 variants



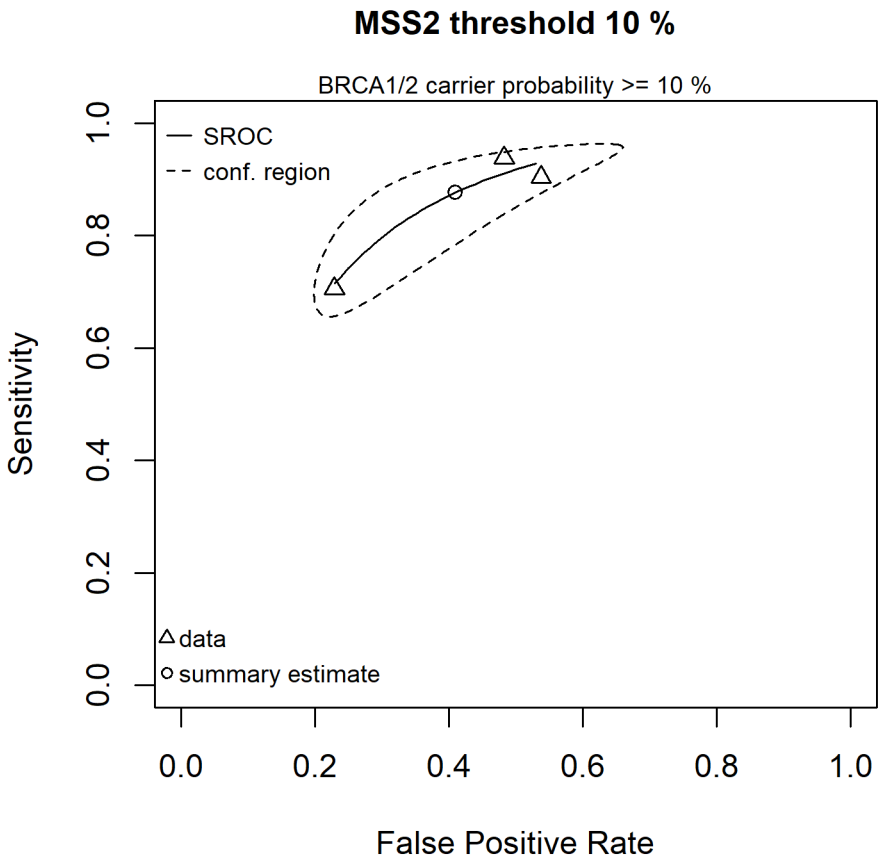
AUC: area under the ROC curve; CI: confidence interval; RE: random effects

Figure 34: Sensitivity and specificity of Manchester Scoring System v2 (MSS2) at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



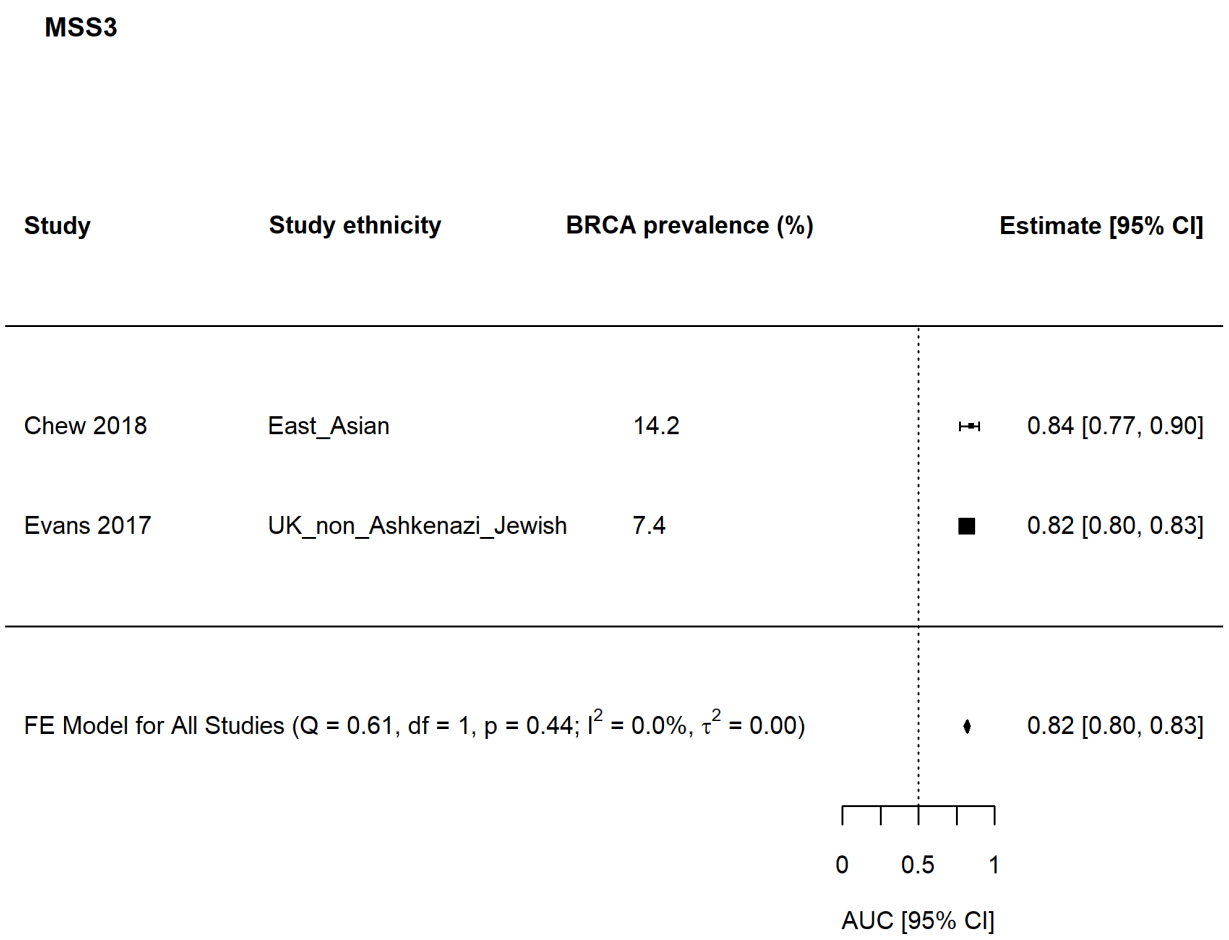
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 35: Summary ROC of Manchester Scoring System v2 (MSS2) at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



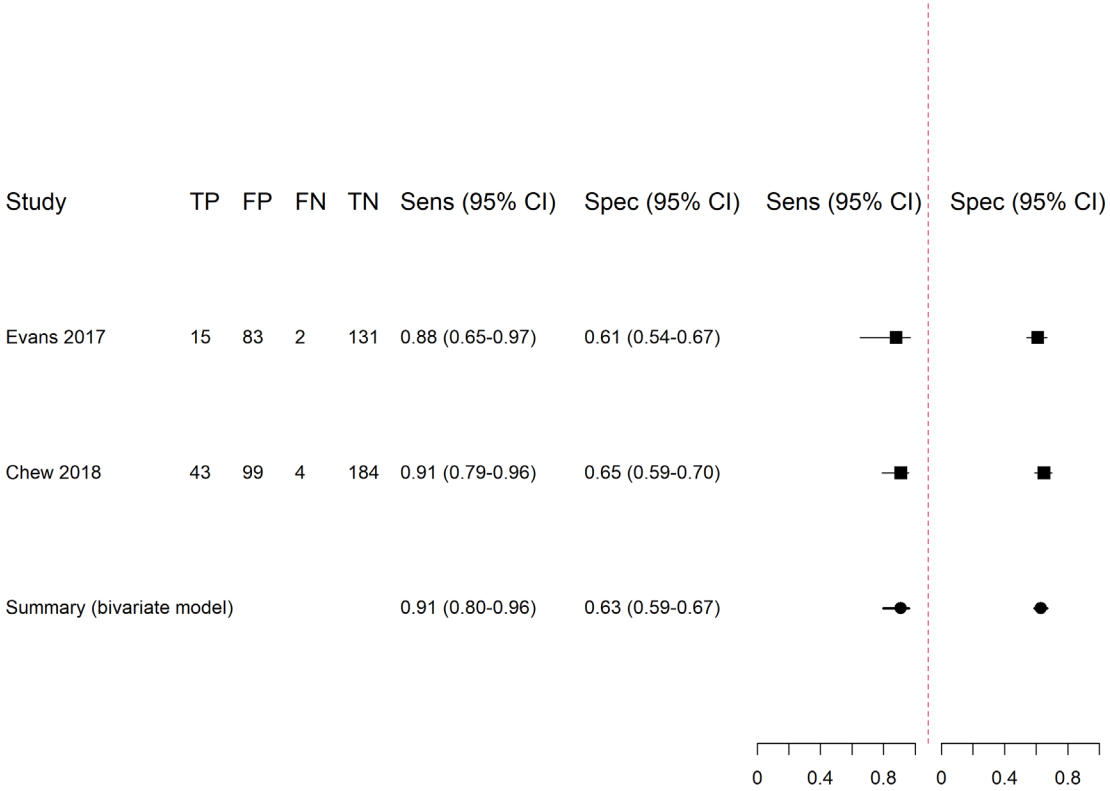
SROC: summary receiver operating characteristic curve

Figure 36: AUC of Manchester scoring system v3 (MSS3) for identification of pathogenic BRCA1/2 variants



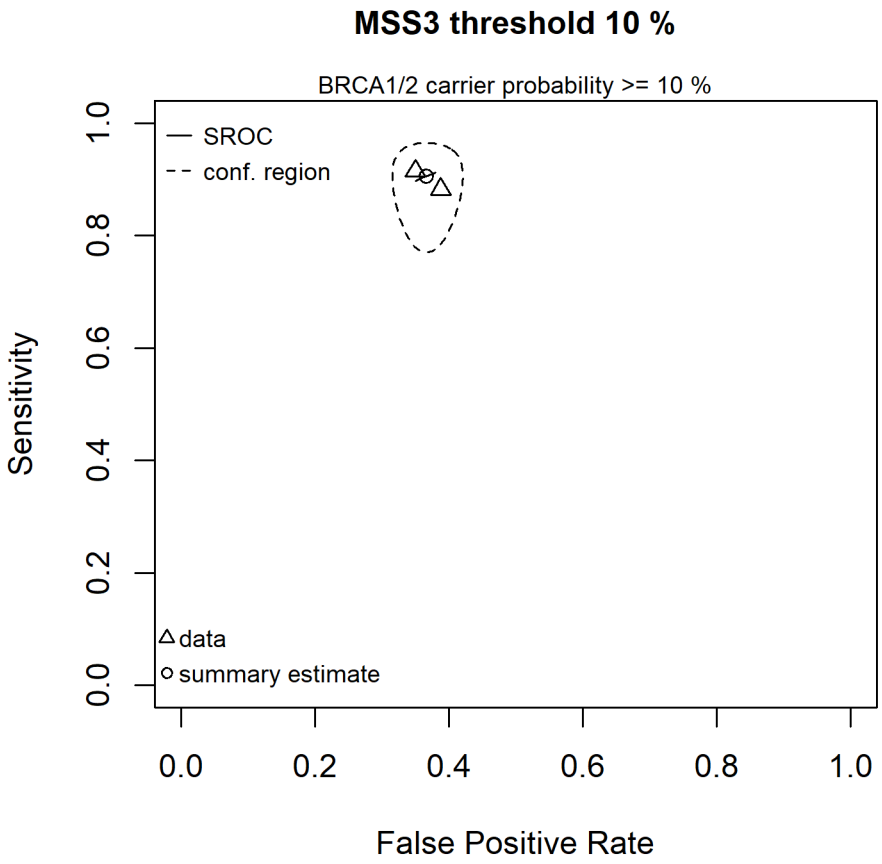
AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 37: Sensitivity and specificity of Manchester Scoring System v3 (MSS3) at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



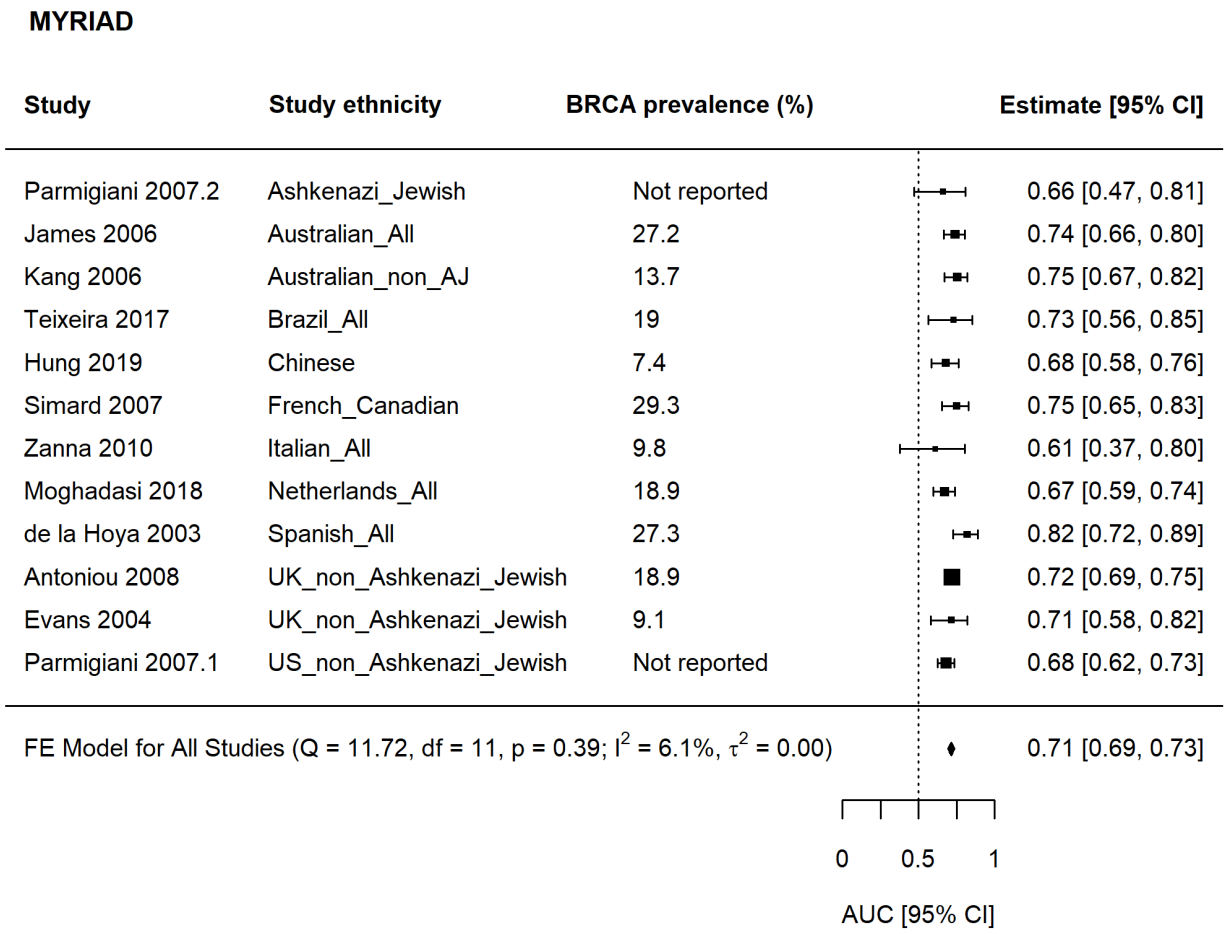
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 38: Summary ROC of Manchester Scoring System v3 (MSS3) at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



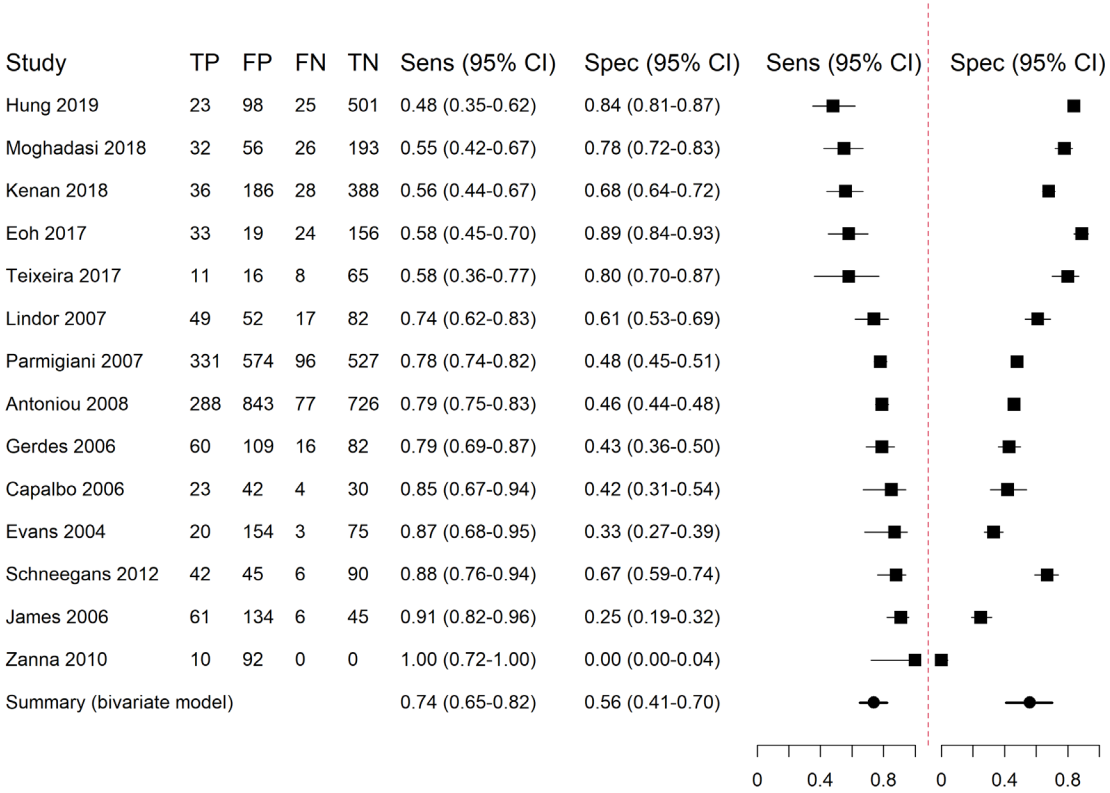
SROC: summary receiver operating characteristic curve

Figure 39: AUC of MYRIAD for identification of pathogenic BRCA1/2 variants



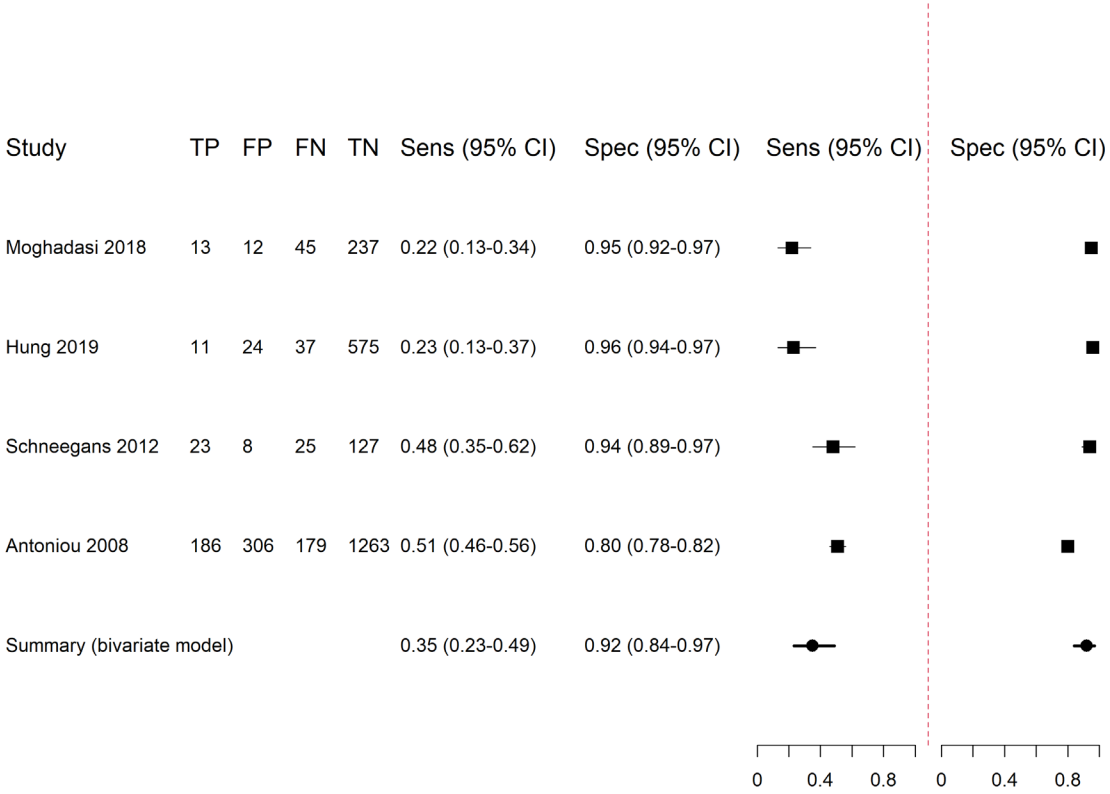
AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 40: Sensitivity and specificity of MYRIAD at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



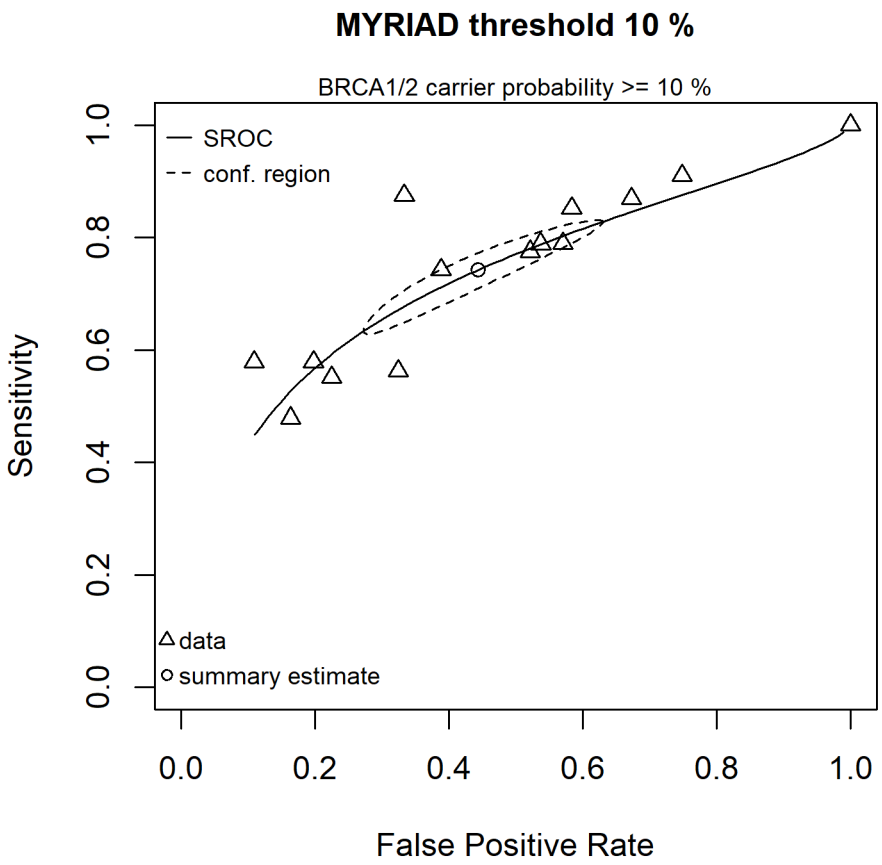
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 41: Sensitivity and specificity of MYRIAD at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



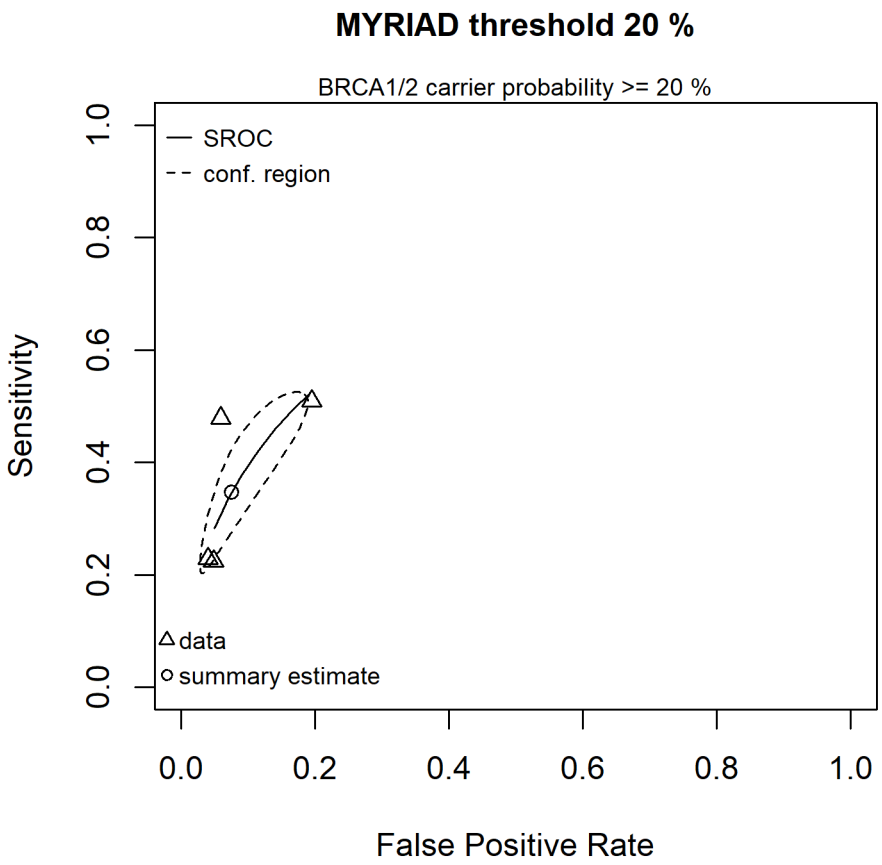
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 42: Summary ROC of MYRIAD at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



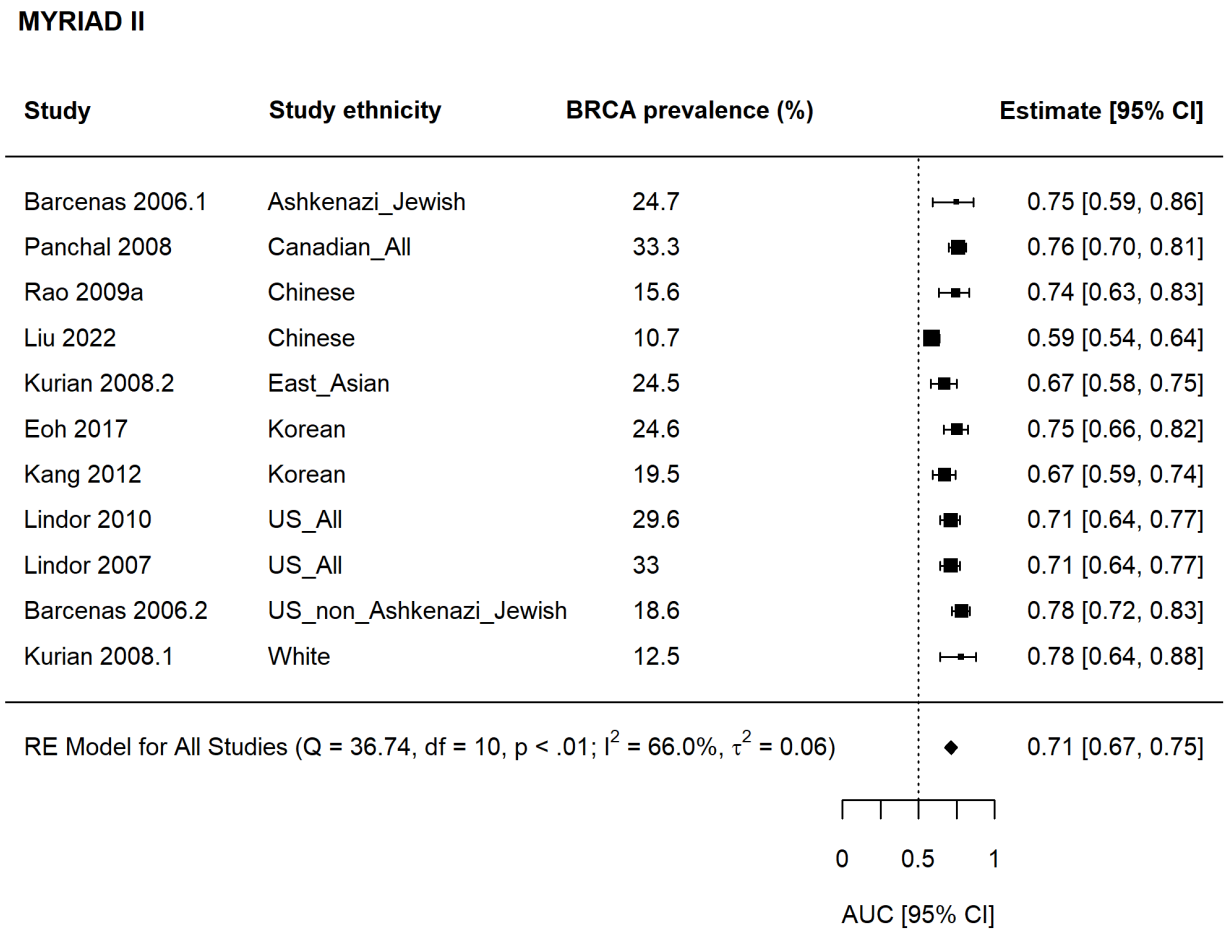
SROC: summary receiver operating characteristic curve

Figure 43: Summary ROC of MYRIAD at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



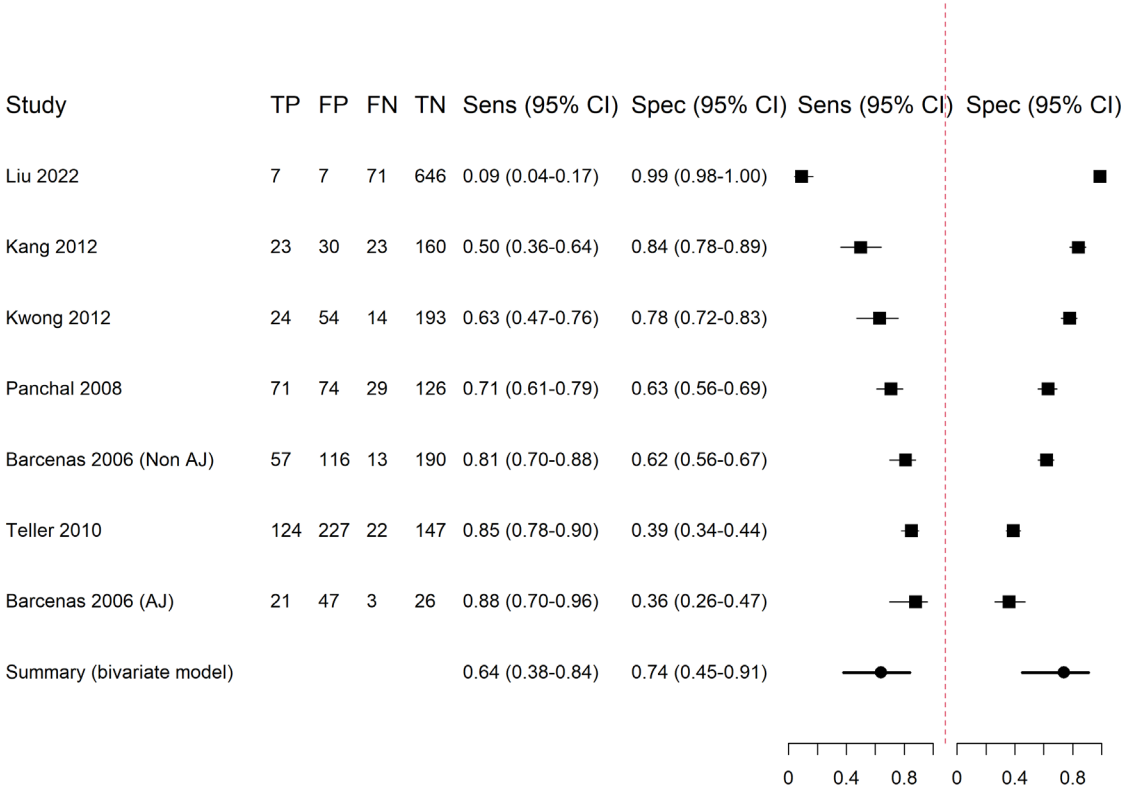
SROC: summary receiver operating characteristic curve

Figure 44: AUC of MYRIAD II for identification of pathogenic BRCA1/2 variants



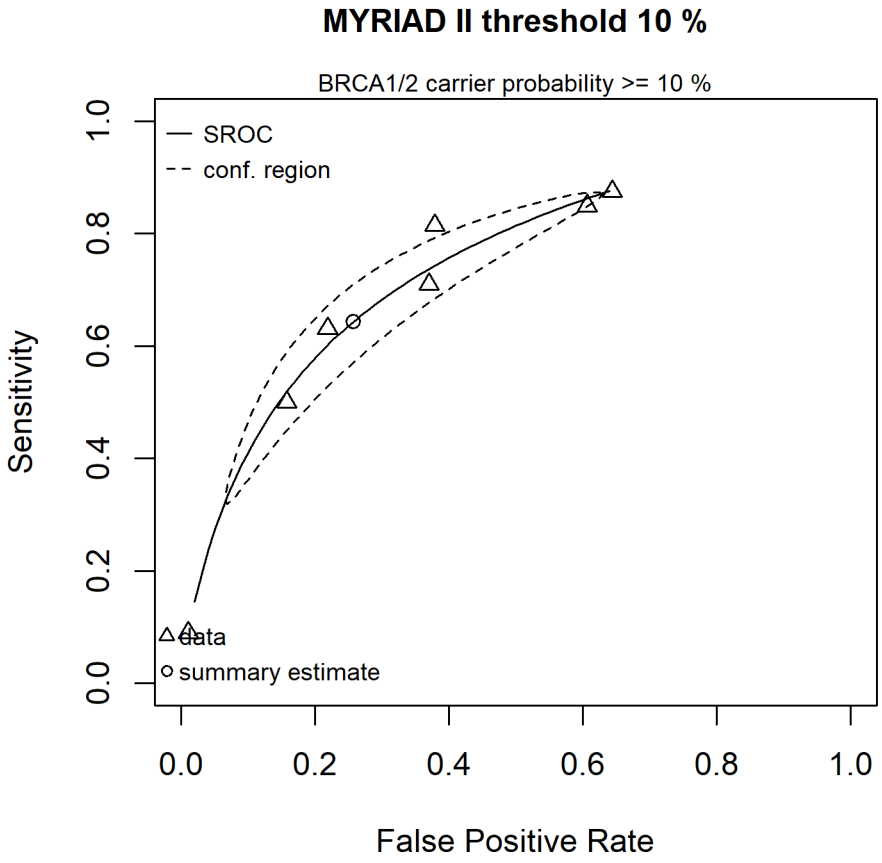
AUC: area under the ROC curve; CI: confidence interval; RE: random effects

Figure 45: Sensitivity and specificity of MYRIAD II at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



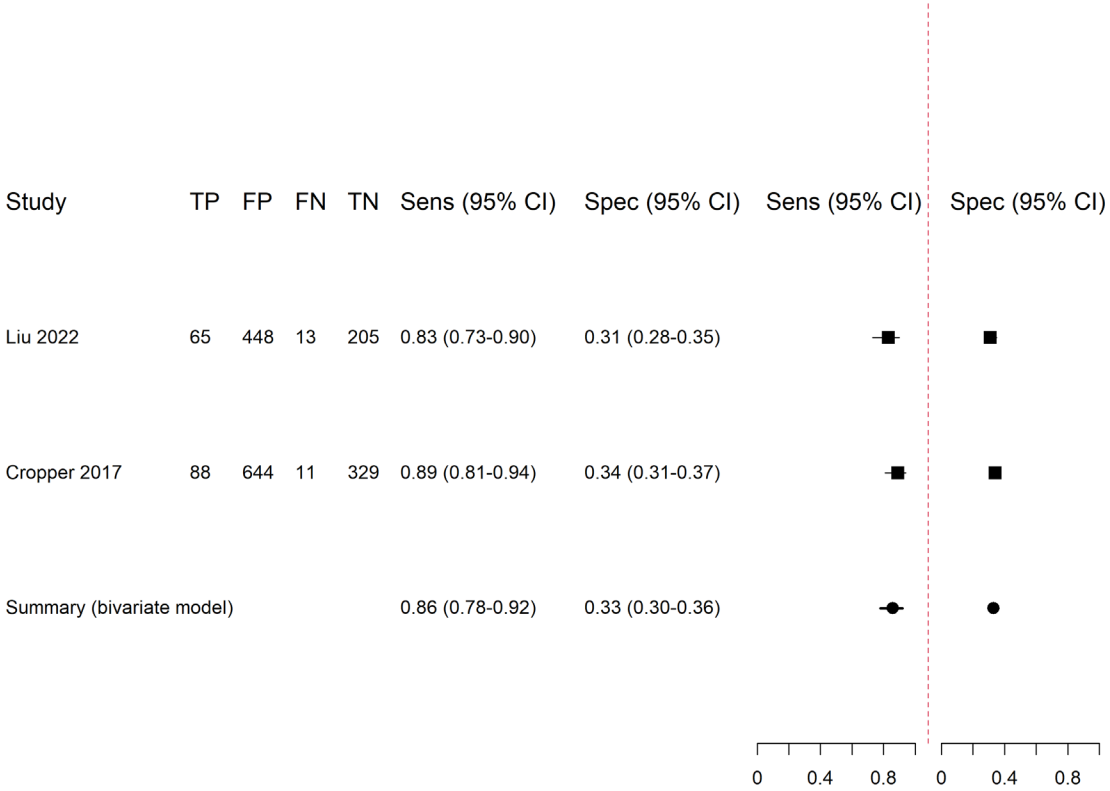
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 46: Summary ROC of MYRIAD II at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



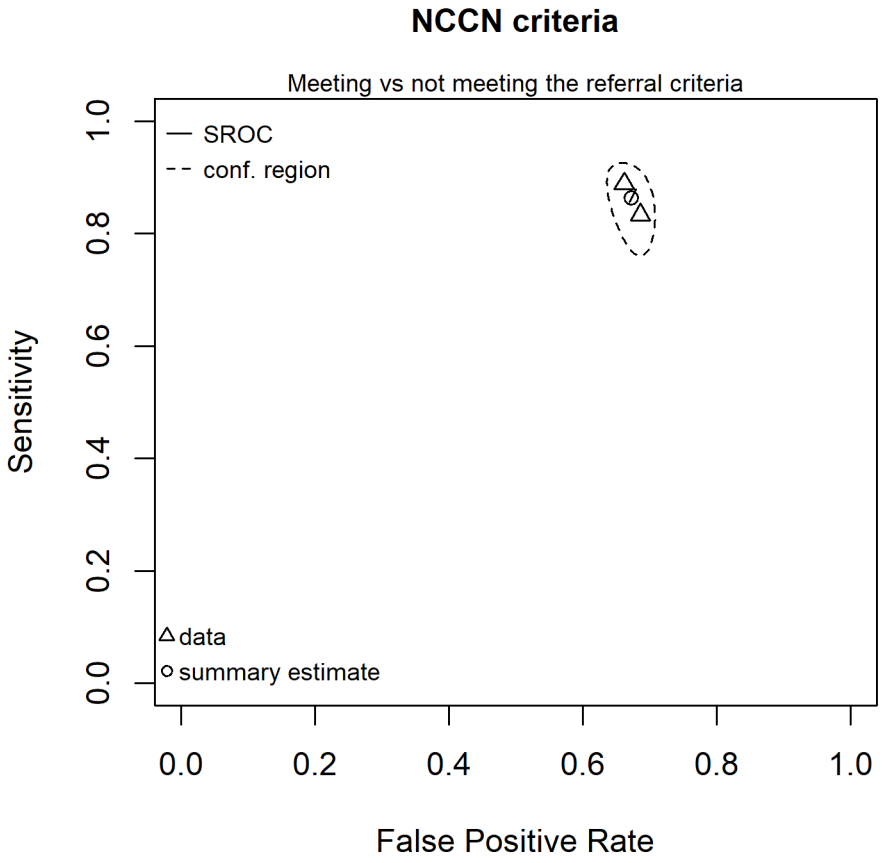
SROC: summary receiver operating characteristic curve

Figure 47:Sensitivity and specificity of NCCN referral criteria for testing for identification of pathogenic BRCA1/2 variants



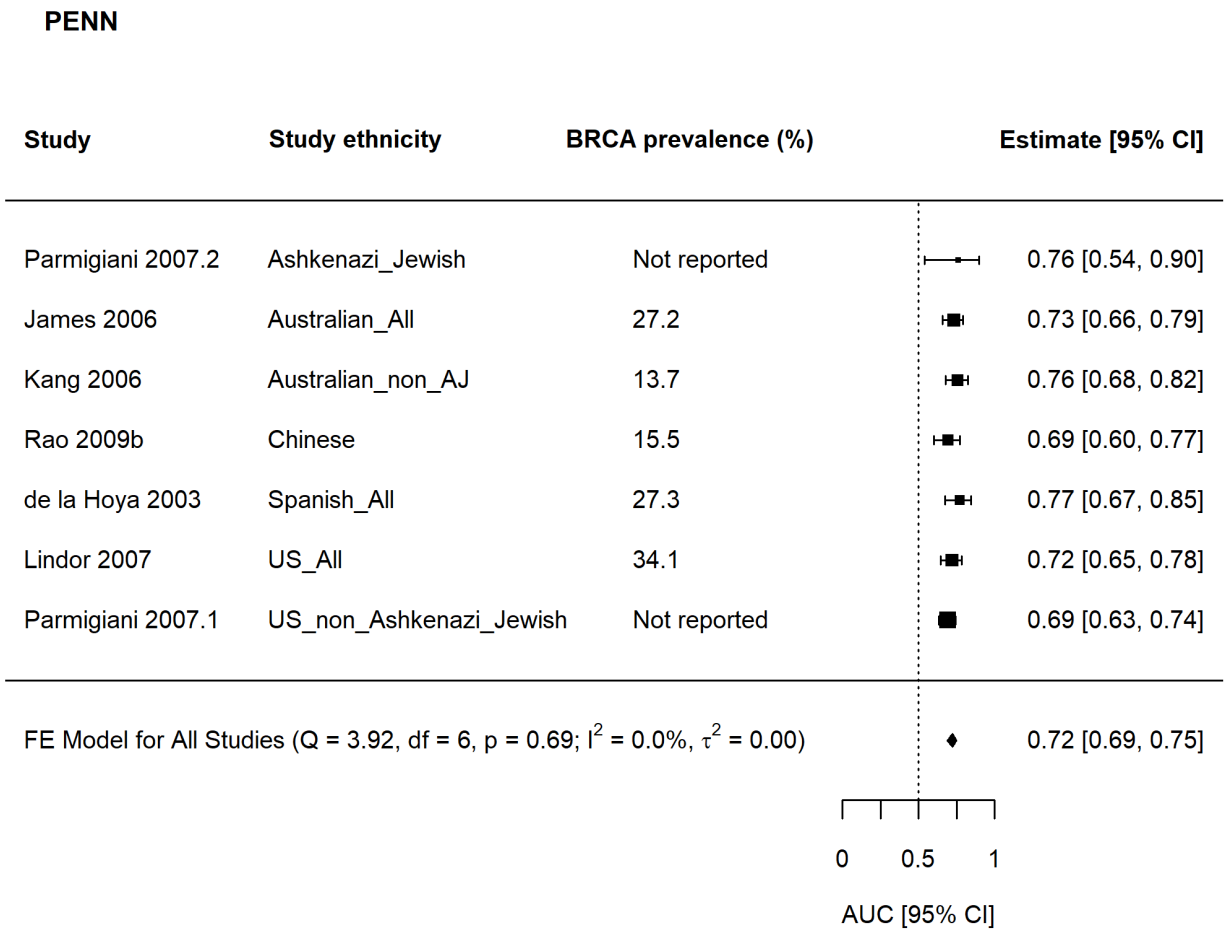
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 48: Summary ROC of NCCN referral criteria for testing for identification of pathogenic BRCA1/2 variants



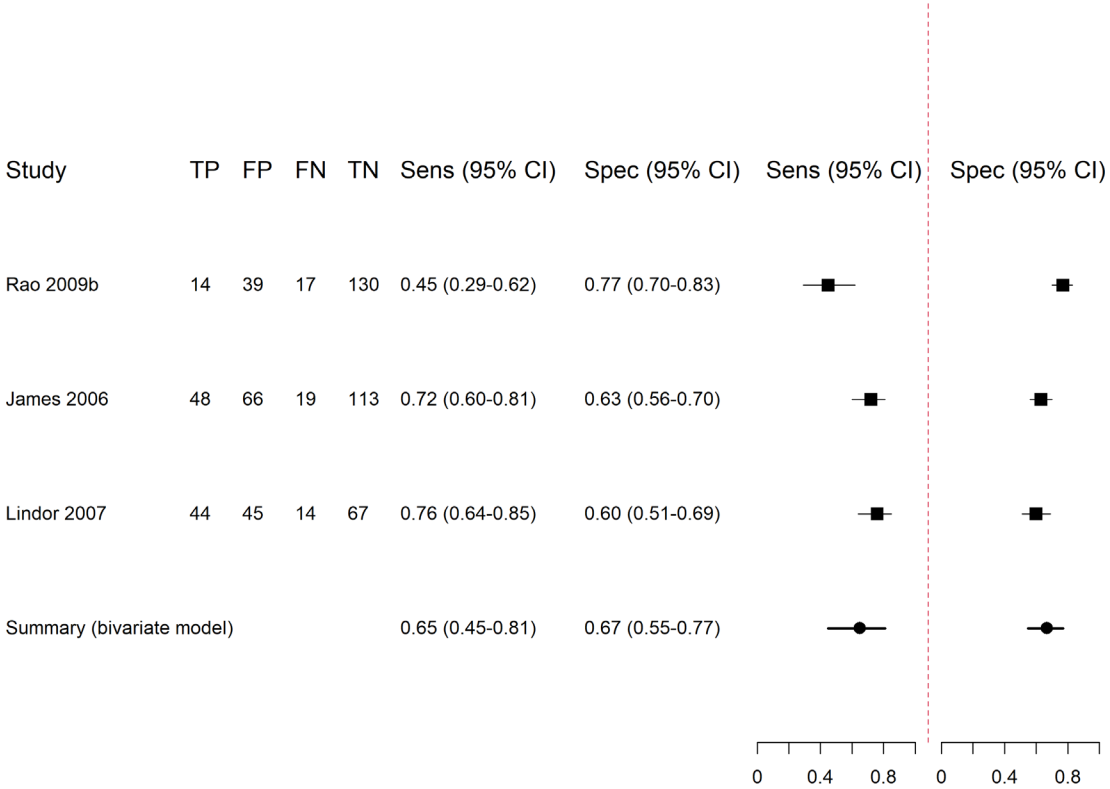
SROC: summary receiver operating characteristic curve

Figure 49: AUC of PENN for identification of pathogenic BRCA1/2 variants



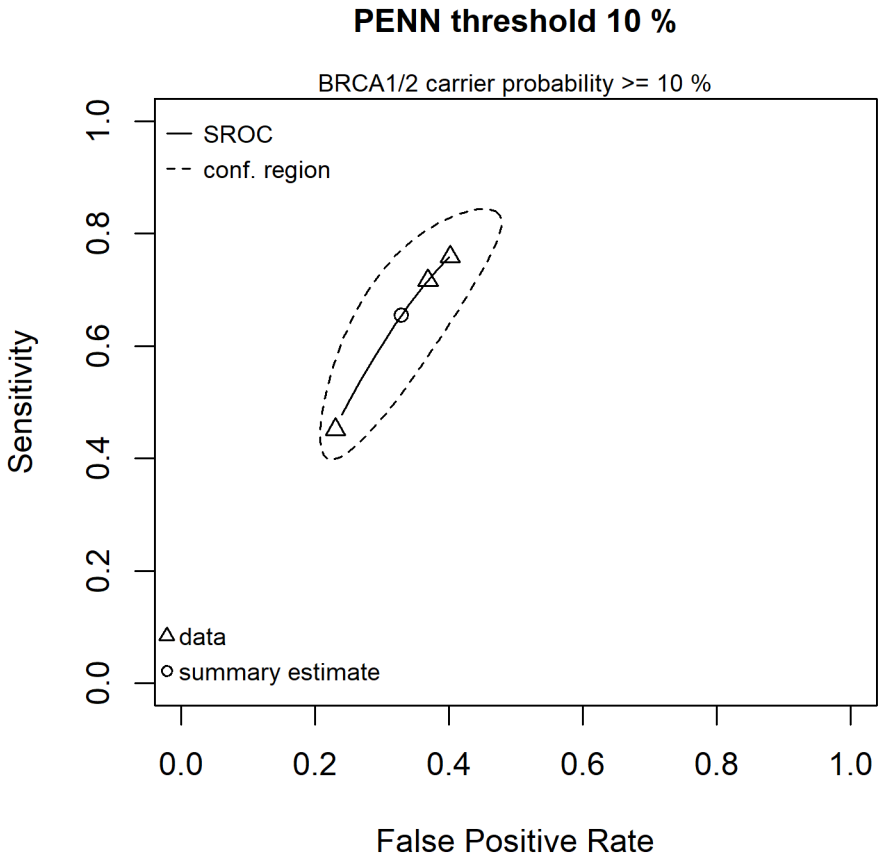
AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 50: Sensitivity and specificity of PENN at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



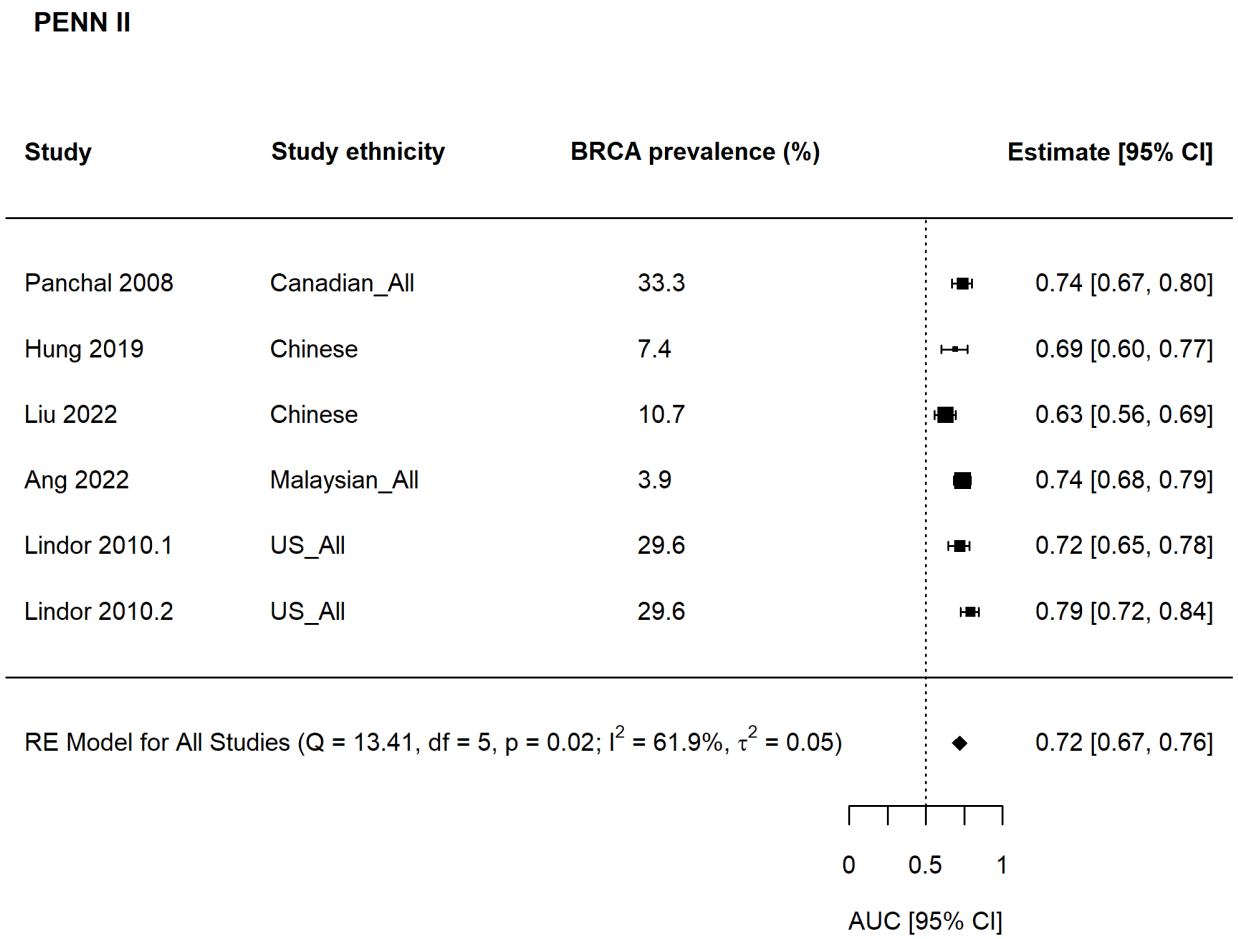
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 51: Summary ROC of PENN at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



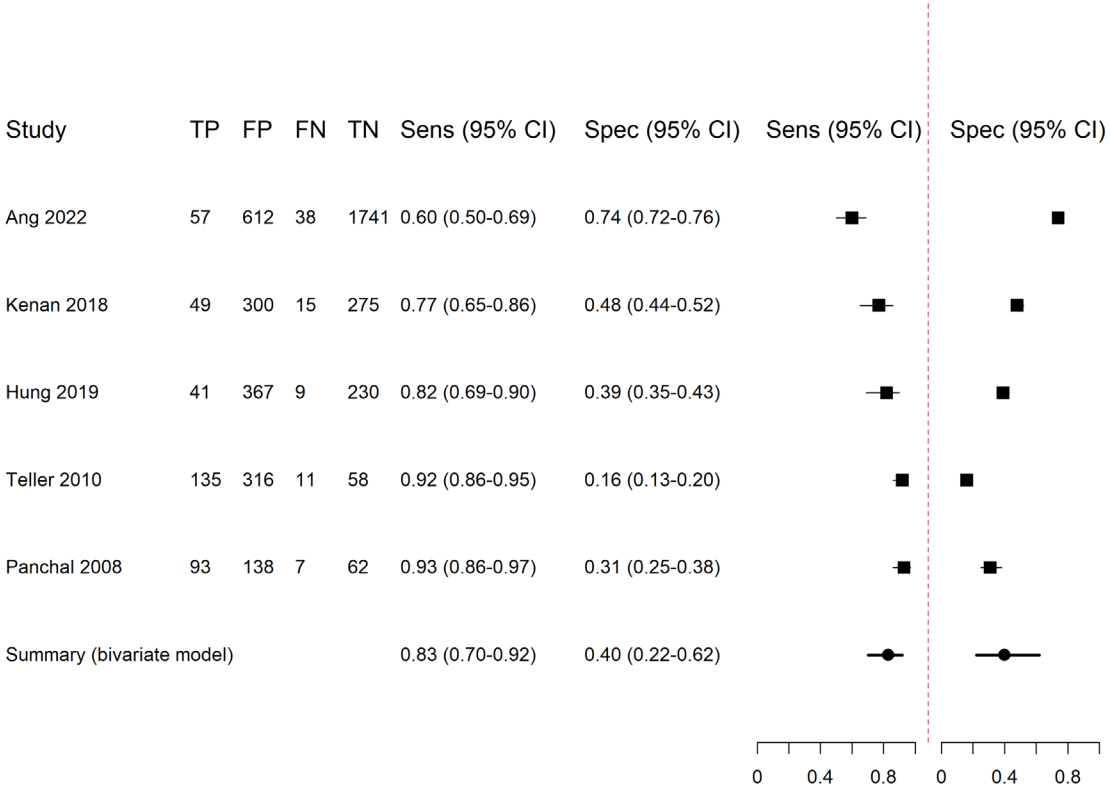
SROC: summary receiver operating characteristic curve

Figure 52: AUC of PENN II for identification of pathogenic BRCA1/2 variants



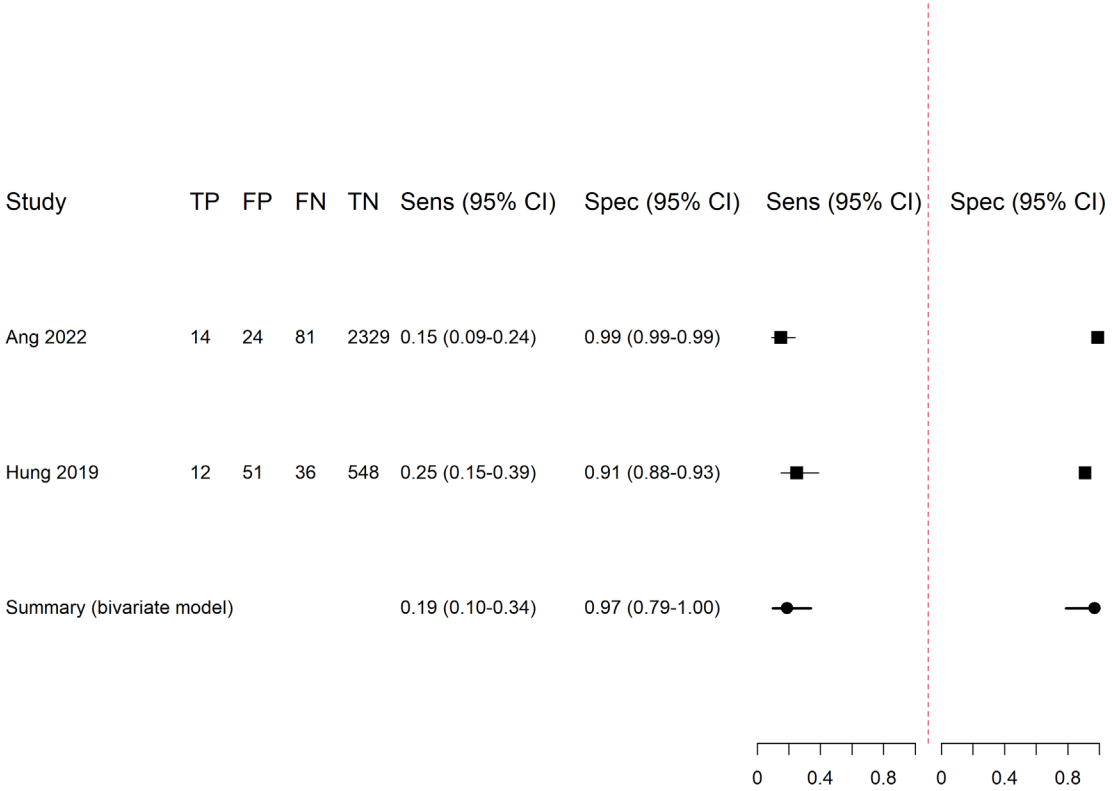
AUC: area under the ROC curve; CI: confidence interval; RE: random effects

Figure 53: Sensitivity and specificity of PENN II at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



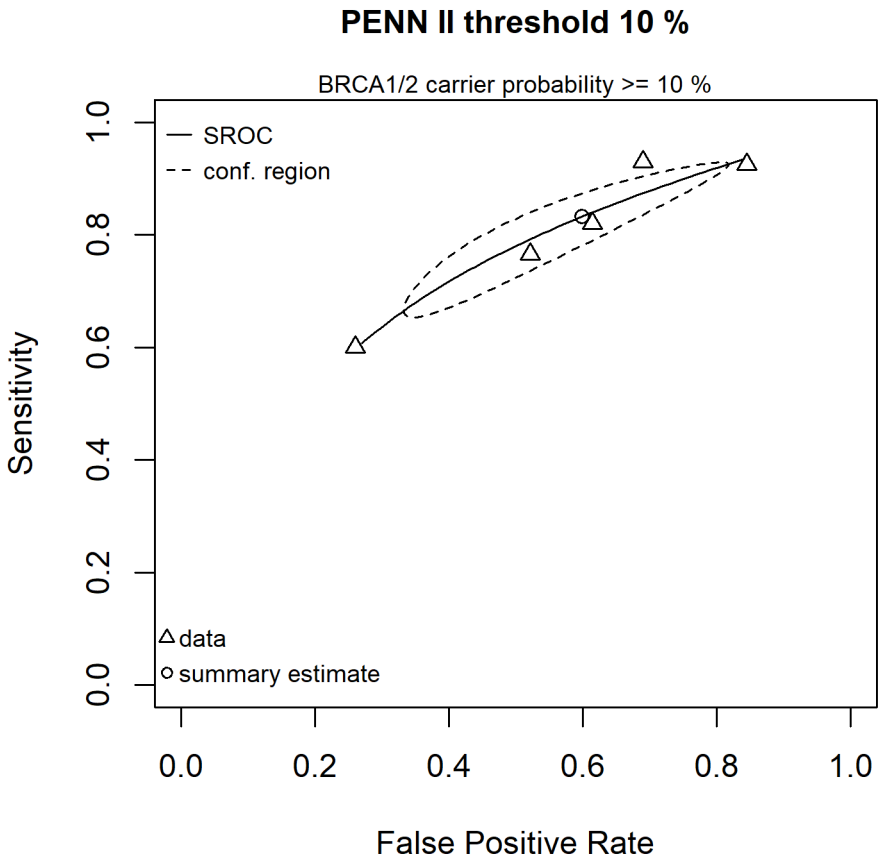
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 54: Sensitivity and specificity of PENN II at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



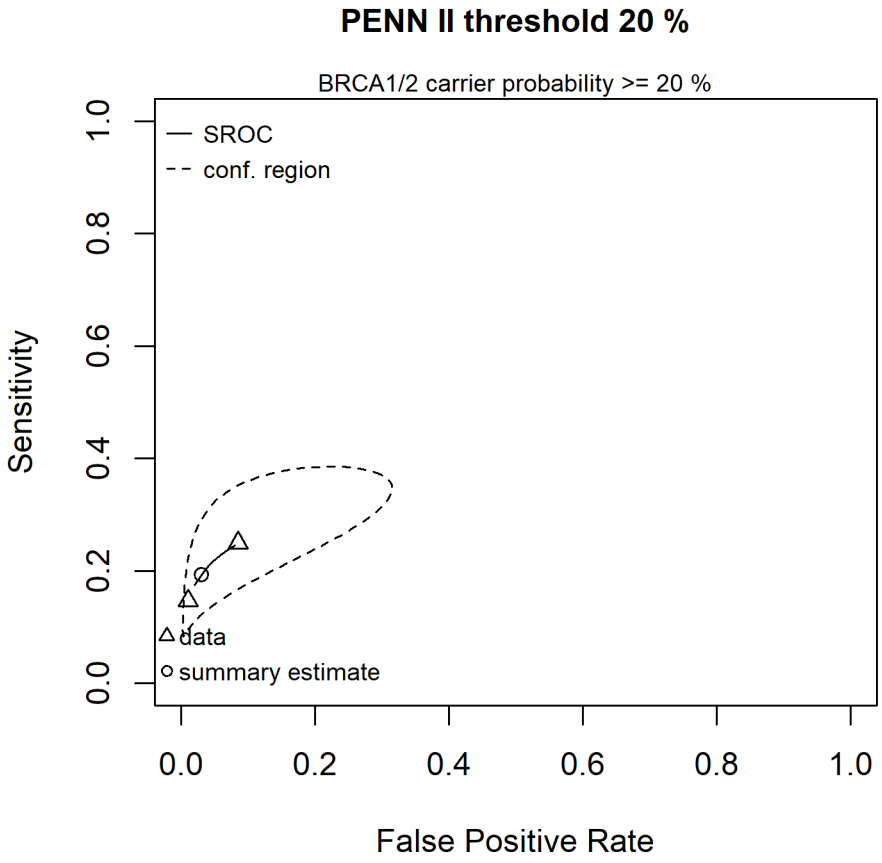
CI: confidence interval; FN: false negative; FP: false positive; Sens: sensitivity; Spec: specificity; TN: true negative; TP: true positive

Figure 55: Summary ROC of PENN II at carrier probability threshold of 10% for identification of pathogenic BRCA1/2 variants



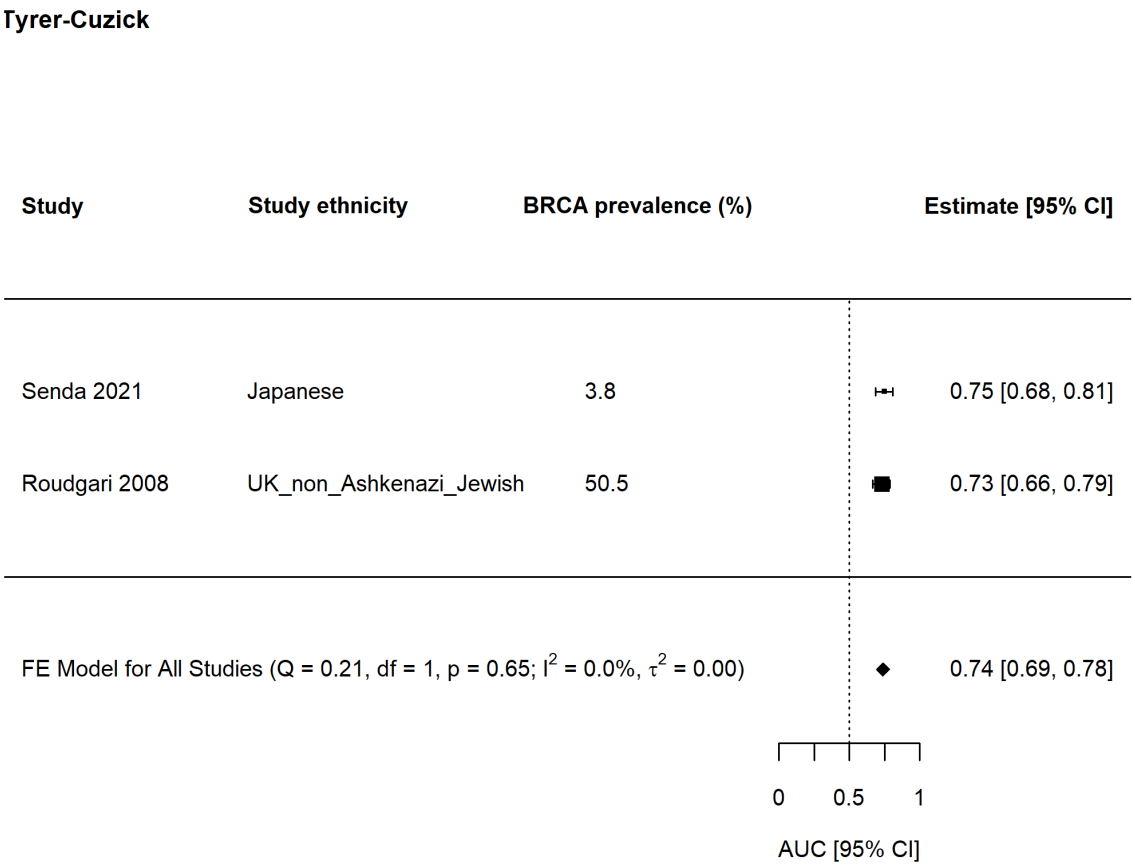
SROC: summary receiver operating characteristic curve

Figure 56: Summary ROC of PENN II at carrier probability threshold of 20% for identification of pathogenic BRCA1/2 variants



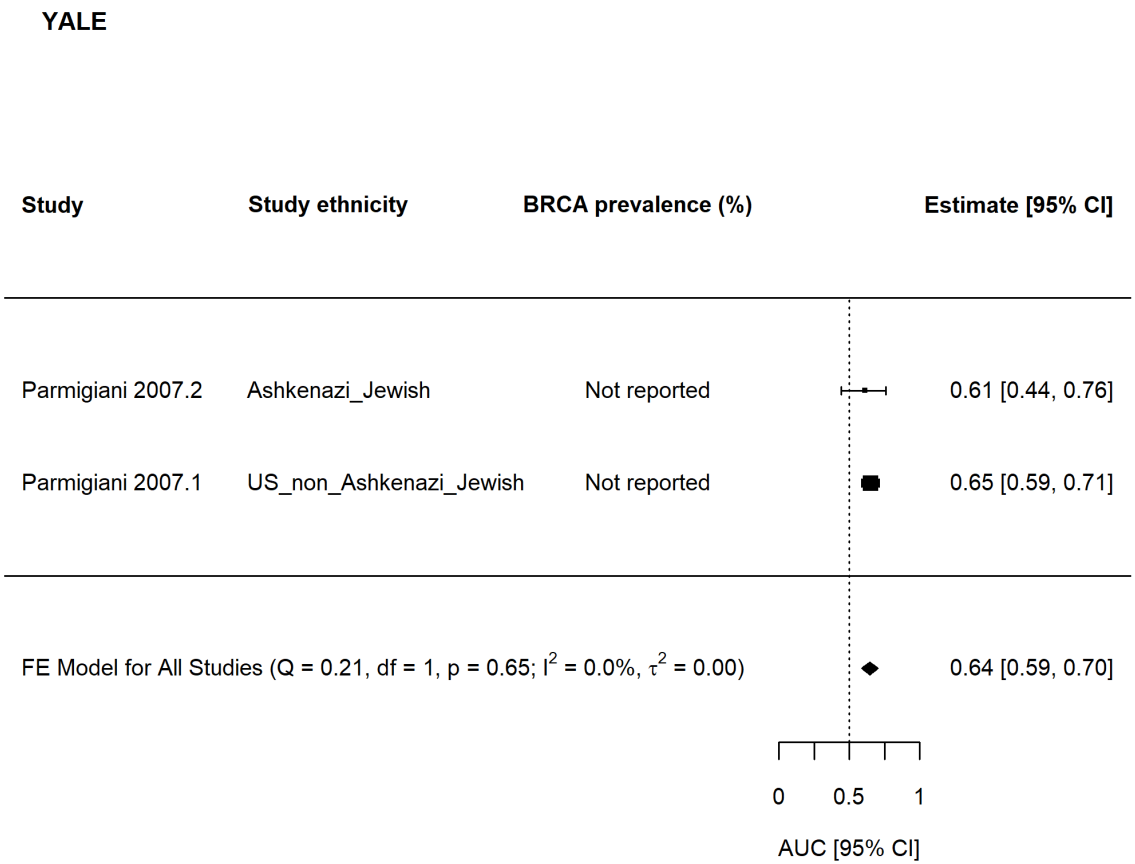
SROC: summary receiver operating characteristic curve

Figure 57: AUC of Tyrer-Cuzick for identification of pathogenic BRCA1/2 variants



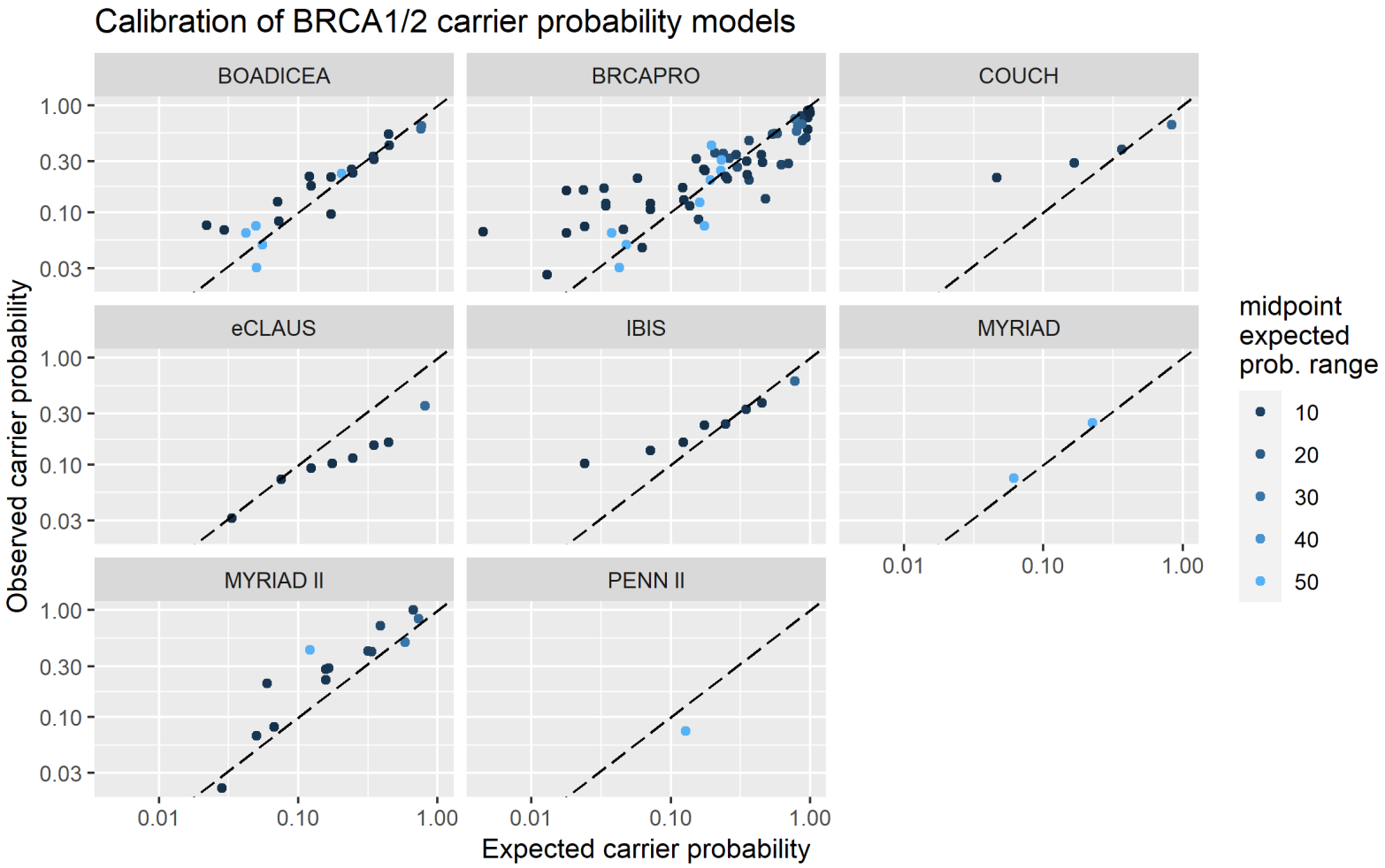
AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 58: AUC of YALE for identification of pathogenic BRCA1/2 variants



AUC: area under the ROC curve; CI: confidence interval; FE: fixed effects

Figure 59: Calibration of BRCA1/2 carrier probability models (see also Appendix M for calibration analyses)



Points are plotted from individual studies which reported observed and expected carrier probability within probability ranges. Points above the line are when the model underestimates carrier probability and those below the line are when the model overestimates carrier probability.

Appendix F Modified GRADE tables

GRADE tables for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

Table 4: Evidence profile for ARiCA to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
Ang 2022	Cohort study	2448	-	-	AUC 0.8 [0.75–0.84]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
Ang 2022	Cohort study	2448	0.34 [0.25–0.44]	0.94 [0.93–0.95]	LR+ 5.63 [4.08–7.77]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
					LR- 0.7 [0.61–0.81]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
Ang 2022	Cohort study	2448	0.15 [0.09–0.24]	0.99 [0.99–0.99]	LR+ 14.51 [7.83–26.88]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.86 [0.79–0.93]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 95% CI crosses 1 decision making threshold

Table 5: Evidence profile for BOADICEA to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[5]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
19[1]	Cohort studies	15355	-	-	AUC 0.76 [0.74–0.79]	Not serious	Serious[6]	Not serious	Not serious	MODERATE	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
7[2]	Cohort studies	9914	0.85 [0.77–0.90]	0.51 [0.40–0.61]	LR+ 1.73 [1.50–2.02]	Not serious	Serious[6]	Not serious	Serious[7]	LOW	CRITICAL
					LR- 0.31 [0.25–0.37]	Not serious	Serious[6]	Not serious	Not serious	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
20[3]	Cohort studies	15363	0.67 [0.55 – 0.77]	0.75 [0.65 – 0.83]	LR+ 2.70 [2.18–3.32]	Not serious	Very serious[8]	Not serious	Not serious	LOW	CRITICAL
					LR- 0.44 [0.35–0.54]	Not serious	Very serious[8]	Not serious	Not serious	LOW	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
9[4]	Cohort studies	13784	0.49 [0.30–0.68]	0.89 [0.76–0.95]	LR+ 4.3 [2.78–6.07]	Not serious	Very serious[8]	Not serious	Serious[7]	VERY LOW	CRITICAL
					LR- 0.58 [0.42–0.74]	Not serious	Very serious[8]	Not serious	Not serious	LOW	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Ang 2022, Antoniou 2006, Antoniou 2008, Barcenas 2006 (Ashkenazi-Jewish and US datasets), Berrino 2015, Fischer 2013, Hung 2019, Kurian 2009 (African-American, Hispanic and White datasets), Liu 2022, Moghadasi 2018, Panchal 2008, Stahlbom 2012, Teixeira 2017, Terkelsen 2019, Thirthagiri 2008, Varesco 2013
2 Berrino 2015, Fischer 2013, Kwong 2012, Moghadasi 2018, Stahlbom 2012, Terkelsen 2019, Varesco 2013
3 Ang 2022, Antoniou 2008, Barcenas 2006 (Ashkenazi-Jewish and US datasets), Berrino 2015, Evans 2017, Fischer 2013, Hung 2019, Kenan 2018, Kwong 2012, Lindor 2007, Liu 2022, Moghadasi 2018, Panchal 2008, Schneegans 2012, Stahlbom 2012, Teixeira 2017, Terkelsen 2019, Thirthagiri 2008, Varesco 2013
4 Antoniou 2008, Roudgari 2008, Ang 2022, Fischer 2013, Hung 2019, Kwong 2012, Moghadasi 2018, Schneegans 2012, Terkelsen 2019
5 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
6 Serious heterogeneity unexplained by subgroup analysis
7 95% CI crosses 1 decision making threshold
8 Very serious heterogeneity unexplained by subgroup analysis

Table 6: Evidence profile for BRCAPRO to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[5]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
39[1]	Cohort studies	24071	-	-	AUC 0.76 [0.75–0.78]	Not serious	Serious[6]	Not serious	Not serious	MODERATE	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
8[2]	Cohort studies	13576	0.82 [0.78–0.86]	0.55 [0.48–0.61]	LR+ 1.83 [1.66–2.03]	Not serious	Not serious	Not serious	Serious[7]	MODERATE	CRITICAL
					LR- 0.32 [0.28–0.36]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
32[3]	Cohort studies	22127	0.78 [0.73 – 0.82]	0.62 [0.54 – 0.68]	LR+ 2.04 [1.78–2.36]	Not serious	Very serious[8]	Not serious	Serious[7]	VERY LOW	CRITICAL
					LR- 0.36 [0.31–0.41]	Not serious	Very serious[8]	Not serious	Not serious	LOW	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
7[4]	Cohort studies	11684	0.68 [0.59–0.75]	0.77 [0.68–0.84]	LR+ 4.3 [2.78–6.07]	Not serious	Not serious	Not serious	Serious[7]	MODERATE	CRITICAL
					LR- 0.58 [0.42–0.74]	Not serious	Not serious	Not serious	Serious[7]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Antoniou 2006, Antoniou 2008, Antonucci 2017, Barcenas 2006 (Ashkenazi-Jewish and US datasets), Berrino 2015, Biswas 2012, Biswas 2013, Daniels 2014, Eoh 2017, Evans 2004, Fischer 2013, Hung 2019, Huo 2009 (African-American and Hispanic datasets), James 2006, Kang 2006, Kang 2012, Kurian 2008 (white and east Asian datasets), Kurian 2009 (African-American, Hispanic and white datasets), Lindor 2007, Lindor 2010, Liu 2022, Mazzola 2014, Mitri 2015, Moghadasi 2018, Panchal 2008, Parmigiani 2007 (Ashkenazi-Jewish and US datasets), Rao 2009a, Rao 2009b, Teixeira 2017, Varesco 2013, Vogel 2007 (Hispanic and white datasets), Zanna 2010,
2 Berrino 2015, Biswas 2012, Biswas 2013, Daniels 2014, Fischer 2013, Kwong 2012, Moghadasi 2018, Varesco 2013
3 Antoniou 2008, Antonucci 2017, Barcenas 2006 (Ashkenazi-Jewish and US datasets), Berrino 2015, Berry 2002 (Ashkenazi-Jewish and US datasets), Biswas 2012, Biswas 2013, Capalbo 2006, Eoh 2017, Euhus 2002, Evans 2004, Fischer 2013, Hung 2019, Huo 2009 (African-American and Hispanic datasets),, James 2006,, Kang 2012, Kenan 2018, Kwong 2012, Liu 2022, Mitri 2015, Moghadasi 2018, Oros 2006, Panchal 2008, Parmigiani 2007, Rao 2009b, Schneegans 2012, Teixeira 2017, Varesco 2013, Zanna 2010,
4 Antoniou 2008, Biswas 2012, Fischer 2013, Hung 2019, Kwong 2012, Moghadasi 2018, Schneegans 2012
5 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
6 Serious heterogeneity unexplained by subgroup analysis
7 95% CI crosses 1 decision making threshold

Table 7: Evidence profile for BRCAPROLYTE to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
Biswas 2013	Cohort studies	2713	-	-	AUC 0.76 [0.74–0.79]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
Biswas 2013	Cohort studies	2713	0.92 [0.89–0.94]	0.3 [0.28–0.32]	LR+ 1.31 [1.27–1.36]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
					LR- 0.27 [0.2–0.36]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
Biswas 2013	Cohort studies	2713	0.86 [0.83–0.89]	0.47 [0.45–0.49]	LR+ 1.62 [1.54–1.71]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
					LR- 0.3 [0.25–0.37]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2

Table 8: Evidence profile for BRCAPROLYTE-Plus to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
Biswas 2013	Cohort studies	2713	-	-	AUC 0.77 [0.75–0.80]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
Biswas 2013	Cohort studies	2713	0.76 [0.72–0.79]	0.62 [0.6–0.64]	LR+ 2 [1.86–2.15]	Serious[2]	Not serious	Not serious	Serious[3]	LOW	CRITICAL
					LR- 0.39 [0.33–0.45]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
Biswas 2013	Cohort studies	2713	0.66 [0.62–0.7]	0.76 [0.74–0.78]	LR+ 2.75 [2.5–3.02]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
					LR- 0.45 [0.4–0.5]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
3 95% CI crosses 1 decision making threshold

Table 9: Evidence profile for BRCAPROLYTE-Simple to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
Biswas 2013	Cohort studies	2713	-	-	AUC 0.77 [0.75–0.79]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
Biswas 2013	Cohort studies	2713	0.84 [0.81–0.87]	0.52 [0.5–0.54]	LR+ 1.75 [1.65–1.85]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
					LR- 0.31 [0.26–0.37]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
Biswas 2013	Cohort studies	2713	0.74 [0.7–0.77]	0.65 [0.63–0.67]	LR+ 2.11 [1.96–2.28]	Serious[2]	Not serious	Not serious	Serious[3]	LOW	CRITICAL
					LR- 0.4 [0.35–0.46]	Serious[2]	Not serious	Not serious	Not serious	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 Serious risk of bias in the evidence contributing to the outcomes as per QUADAS-2
3 95% CI crosses 1 decision making threshold

Table 10: Evidence profile for COS to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[2]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
2[1]	Cohort studies	711	-	-	AUC 0.79 [0.74–0.84]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
Berrino 2015	Cohort studies	436	0.93 [0.87–0.97]	0.48 [0.43–0.53]	LR+ 1.78 [1.59–2]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
					LR- 0.15 [0.07–0.3]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
Berrino 2015	Cohort studies	436	0.9 [0.83–0.95]	0.64 [0.59–0.69]	LR+ 2.52 [2.15–2.95]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.15 [0.09–0.27]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
Roudgari 2008	Cohort studies	275	0.92 [0.86–0.95]	0.43 [0.35–0.51]	LR+ 1.6 [1.38–1.87]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.19 [0.11–0.35]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Berrino 2015, Roudgari 2008
2 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
3 95% CI crosses 1 decision making threshold

Table 11: Evidence profile for DrABC to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
Liu 2022	Cohort studies	711	-	-	AUC 0.79 [0.74–0.85]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
Diagnostic accuracy											
Liu 2022	Cohort studies	436	0.82 [0.72–0.89]	0.63 [0.59–0.67]	LR+ 2.21 [1.91–2.56]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
					LR- 0.29 [0.18–0.47]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 95% CI crosses 1 decision making threshold

Table 12: Evidence profile for eCLAUS to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
Fischer 2013	Cohort studies	7532	-	-	AUC 0.75 [0.73–0.76]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
Fischer 2013	Cohort studies	7532	1 [0.99–1]	0.03 [0.02–0.03]	LR+ 1.02 [1.02–1.03]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.12 [0.05–0.27]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
Fischer 2013	Cohort studies	7532	0.98 [0.97–0.99]	0.1 [0.09–0.1]	LR+ 1.08 [1.07–1.1]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.21 [0.15–0.29]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
Fischer 2013	Cohort studies	7532	0.93 [0.92–0.94]	0.25 [0.24–0.26]	LR+ 1.23 [1.21–1.26]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.29 [0.24–0.34]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 95% CI crosses 1 decision making threshold

Table 13: Evidence profile for FHAT to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[2]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
5[1]	Cohort studies	4889	-	-	AUC 0.74 [0.72–0.75]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
5[1]	Cohort studies	4889	0.83 [0.71–0.91]	0.46 [0.22–0.71]	LR+ 1.60 [1.16–2.47]	Not serious	Serious[3]	Not serious	Serious[4]	LOW	CRITICAL
					LR- 0.39 [0.31–0.48]	Not serious	Serious[3]	Not serious	Not serious	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Biswas 2013, James 2006, Panchal 2008, Parmigiani 2007, Zanna 2010
2 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
3 Serious heterogeneity unexplained by subgroup analysis
4 95% CI crosses 1 decision making threshold

Table 14: Evidence profile for Finnish model to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[2]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
2[1]	Cohort studies	1330	-	-	AUC 0.72 [0.67–0.76]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
Diagnostic accuracy at 5.4% carrier probability threshold											
de la Hoya 2003	Cohort study	109	0.91 [0.75–0.97]	0.34 [0.24–0.45]	LR+ 1.37 [1.12–1.67]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.27 [0.08–0.91]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
Parmigiani 2007	Cohort study	1421	0.73 [0.68–0.77]	0.65 [0.62–0.68]	LR+ 2.1 [1.89–2.32]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
					LR- 0.42 [0.35–0.49]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 de la Hoya 2003, Parmigiani 2007
2 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
3 95% CI crosses 1 decision making threshold

Table 15: Evidence profile for HCSC to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
De la Hoya 2003	Cohort study	109	-	-	AUC 0.82 [0.73–0.88]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
Diagnostic accuracy at 11.4% carrier probability threshold											
De la Hoya 2003	Cohort study	109	0.91 [0.75–0.97]	0.46 [0.35–0.57]	LR+ 1.68 [1.32–2.14]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
					LR- 0.2 [0.06–0.65]	Not serious	Not serious	Not serious	Very serious[3]	LOW	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 95% CI crosses 1 decision making threshold
3 95% CI crosses 2 decision making thresholds

Table 16: Evidence profile for IBIS to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[3]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
3[1]	Cohort studies	9721	-	-	AUC 0.75 [0.73–0.76]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
Fischer 2013	Cohort study	7532	0.87 [0.85–0.88]	0.36 [0.34–0.37]	LR+ 1.35 [1.31–1.38]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.37 [0.33–0.42]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
3[1]	Cohort studies	9721	0.60 [0.21–0.90]	0.61 [0.46–0.74]	LR+ 1.47 [0.81–1.79]	Not serious	Very serious[5]	Not serious	Not serious	LOW	CRITICAL
					LR- 0.65 [0.22–1.07]	Not serious	Very serious[5]	Not serious	Serious[4]	VERY LOW	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
2[2]	Cohort study	9421	0.66 [0.62–0.70]	0.70 [0.62–0.78]	LR+ 2.24 [1.82–2.78]	Not serious	Not serious	Not serious	Serious[4]	MODERATE	CRITICAL
					LR- 0.49 [0.46–0.52]	Not serious	Not serious	Not serious	Serious[4]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Antoniou 2008, Fischer 2013, Panchal 2008
2 Antoniou 2008, Fischer 2013
3 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios

4 95% CI crosses 1 decision making threshold
5 Very serious heterogeneity unexplained by subgroup analysis

Table 17: Evidence profile for IC model to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[2]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
Zanna 2010	Cohort study	102	-	-	AUC 0.79 [0.66–0.93]	Not serious	Not serious	Not serious	Very serious[3]	LOW	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
2[1]	Cohort study	201	0.92 [0.73–0.98]	0.30 [0.07–0.72]	LR+ 1.46 [1.02–2.87]	Not serious	Very serious[4]	Not serious	Serious[5]	VERY LOW	CRITICAL
					LR- 0.32 [0.10–0.76]	Not serious	Very serious[4]	Not serious	Very serious[3]	VERY LOW	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1. *Capalbo 2006, Zanna 2010*
2 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
3 95% CI crosses 2 decision making thresholds
4 Very serious heterogeneity unexplained by subgroup analysis
5 95% CI crosses 1 decision making threshold

Table 18: Evidence profile KOHCal to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
Ang 2022	Cohort study	2448	-	-	AUC 0.71 [0.65–0.76]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
Ang 2022	Cohort study	2448	0.44 [0.35–0.54]	0.88 [0.87–0.89]	LR+ 3.69 [2.87–4.74]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.63 [0.53–0.76]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
Ang 2022	Cohort study	2448	0.22 [0.15–0.32]	0.97 [0.96–0.98]	LR+ 7.37 [4.76–11.41]	Not serious	Not applicable	Not serious	Serious[2]	MODERATE	CRITICAL
					LR- 0.8 [0.72–0.89]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 95% CI crosses 1 decision making threshold

Table 19: Evidence profile for LUMC to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
De la Hoya 2003	Cohort study	109	-	-	AUC 0.71 [0.65–0.76]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
Diagnostic accuracy at 7.5% carrier probability threshold											
De la Hoya 2003	Cohort study	109	0.91 [0.75–0.97]	0.54 [0.43–0.65]	LR+ 1.99 [1.51–2.61]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
					LR- 0.17 [0.05–0.55]	Not serious	Not serious	Not serious	Very serious[3]	LOW	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 95% CI crosses 1 decision making threshold
3 95% CI crosses 2 decision making thresholds

Table 20: Evidence profile for Manchester Scoring System version 1 (MSS1) to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[4]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
13[1]	Cohort studies	17886	-	-	AUC 0.76 [0.75–0.78]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
7[2]	Cohort studies	12680	0.83 [0.71–0.90]	0.54 [0.39–0.68]	LR+ 1.83 [1.46–2.35]	Not serious	Very serious[5]	Not serious	Serious[6]	VERY LOW	CRITICAL
					LR- 0.33 [0.23–0.45]	Not serious	Very serious[5]	Not serious	Not serious	LOW	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
2[3]	Cohort studies	2431	0.87 [0.75–0.94]	0.56 [0.31–0.79]	LR+ 2.11 [1.35–3.57]	Not serious	Serious[7]	Not serious	Serious[6]	LOW	CRITICAL
					LR- 0.24 [0.18–0.32]	Not serious	Serious[7]	Not serious	Serious[6]	LOW	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Antoniou 2008, Chew 2018, Evans 2004, Evans 2017, James 2006, Kang 2006, Kast 2014, Oros 2006, Panchal 2008, Roudgari 2008, Simard 2007, Teixeira 2017, Thirthagiri 2008
2 Bodmer 2006, Evans 2004, Evans 2009, Gerdes 2006, James 2006, Kast 2014, Teixeira 2017
3 Evans 2009, Roudgari 2008
4 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
5 Very serious heterogeneity unexplained by subgroup analysis
6 95% CI crosses 1 decision making threshold
7 Serious heterogeneity unexplained by subgroup analysis

Table 21: Evidence profile for Manchester Scoring System version 2 (MSS2) to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[3]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
3[1]	Cohort studies	10836	-	-	AUC 0.79 [0.72–0.85]	Not serious	Not serious	Not serious	Serious[4]	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
3[2]	Cohort studies	11777	0.88 [0.71–0.95]	0.59 [0.39–0.77]	LR+ 2.19 [1.54–3.21]	Not serious	Serious[5]	Not serious	Serious[4]	LOW	CRITICAL
					LR- 0.22 [0.11–0.39]	Not serious	Serious[5]	Not serious	Serious[4]	LOW	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
Evans 2009	Cohort study	2156	0.84 [0.8–0.88]	0.72 [0.7–0.75]	LR+ 3.06 [2.8–3.33]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.22 [0.17–0.27]	Not serious	Not serious	Not serious	Serious[4]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Chew 2018, Evans 2009, Kast 2014
2 Evans 2009, Evans 2017, Kast 2014
3 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios

4 95% CI crosses 1 decision making threshold
5 Serious heterogeneity unexplained by subgroup analysis

Table 22: Evidence profile for Manchester Scoring System version 3 (MSS3) to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[2]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
2[1]	Cohort studies	4443	-	-	AUC 0.82 [0.80–0.83]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
2[1]	Cohort studies	561	0.91 [0.80–0.96]	0.63 [0.59–0.67]	LR+ 2.46 [2.11–2.82]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.16 [0.07–0.31]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Chew 2018, Evans 2017
2 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
3 95% CI crosses 1 decision making threshold

Table 23: Evidence profile for MYRIAD to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[4]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
11[1]	Cohort studies	2334	-	-	AUC 0.71 [0.69–0.73]	Not serious	Not serious	Not serious	Serious[5]	MODERATE	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
Moghadasi 2018	Cohort study	307	0.99 [0.92–1]	0 [0–0.02]	LR+ 0.99 [0.97–1.02]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 4.24 [0.09–211.36]	Not serious	Not serious	Not serious	Very serious[6]	LOW	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
14[2]	Cohort studies	6735	0.74 [0.65–0.82]	0.56 [0.41–0.70]	LR+ 1.7 [1.36–2.17]	Not serious	Very serious[7]	Not serious	Serious[5]	VERY LOW	CRITICAL
					LR- 0.47 [0.42–0.52]	Not serious	Very serious[7]	Not serious	Serious[5]	VERY LOW	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
4[3]	Cohort studies	3071	0.35 [0.23–0.49]	0.92 [0.84–0.97]	LR+ 4.69 [2.90–7.20]	Not serious	Not serious	Not serious	Serious[5]	MODERATE	CRITICAL
					LR- 0.71 [0.60–0.80]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Antoniou 2008, de la Hoya 2003, Evans 2004, Hung 2019, James 2006, Kang 2006, Moghadasi 2018, Parmigiani 2007, Simard 2007, Teixeira 2017, Zanna 2010
2 Antoniou 2008, Capalbo 2006, Eoh 2017, Evans 2004, Gerdes 2006, Hung 2019, James 2006, Kenan 2018, Lindor 2007, Moghadasi 2018, Parmigiani 2007, Schneegans 2012, Teixeira 2017, Zanna 2010
3 Antoniou 2008, Hung 2019, Moghadasi 2018, Schneegans 2012
4 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
5 95% CI crosses 1 decision making threshold
6 95% CI crosses 2 decision making thresholds
7 Very serious heterogeneity unexplained by subgroup analysis

Table 24: Evidence profile for MYRIAD II to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[3]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
9[1]	Cohort studies	2983	-	-	AUC 0.71 [0.67–0.75]	Not serious	Serious[4]	Not serious	Serious[5]	LOW	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
Kwong 2012	Cohort study	285	0.96 [0.85–0.99]	0.18 [0.14–0.24]	LR+ 1.18 [1.08–1.28]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[3]	Quality	Importance
					LR- 0.21 [0.04–1.03]	Not serious	Not serious	Not serious	Very serious[5]	LOW	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
6[2]	Cohort studies	2545	0.64 [0.38–0.84]	0.74 [0.45–0.91]	LR+ 2.6 [1.51–4.42]	Not serious	Very serious[6]	Not serious	Serious[5]	VERY LOW	CRITICAL
					LR- 0.49 [0.34–0.68]	Not serious	Very serious[6]	Not serious	Serious[5]	VERY LOW	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
Kwong 2012	Cohort study	285	0.35 [0.22–0.5]	0.92 [0.88–0.95]	LR+ 4.4 [2.4–8.07]	Not serious	Not serious	Not serious	Serious[5]	MODERATE	CRITICAL
					LR- 0.71 [0.56–0.89]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 *Barcenas 2006, Eoh 2017, Kang 2012, Kurian 2008, Lindor 2007, Lindor 2010, Liu 2022, Panchal 2008, Rao 2009a*
2 Barcenas 2006, Kang 2012, Kwong 2012, Liu 2022, Panchal 2008, Teller 2010
3 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios

4 Serious heterogeneity unexplained by subgroup analysis
5 95% CI crosses 1 decision making threshold
6 Very serious heterogeneity unexplained by subgroup analysis
7 95% CI crosses 2 decision making thresholds

Table 25: Evidence profile for NCCN criteria to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[2]	Quality	Importance
Diagnostic accuracy of NCCN Criteria											
2[1]	Cohort studies	1803	0.86 [0.78–0.92]	0.33 [0.30–0.36]	LR+ 1.28 [1.14–1.4]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.43 [0.25–0.69]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Cropper 2017, Liu 2022
2 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
3 95% CI crosses 1 decision making threshold

Table 26: Evidence profile for PENN to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[3]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
6[1]	Cohort studies	1099	-	-	AUC 0.72 [0.69–0.75]	Not serious	Not serious	Not serious	Serious[4]	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
3[2]	Cohort studies	616	0.65 [0.45–0.81]	0.67 [0.55–0.77]	LR+ 1.7 [1.63–2.38]	Not serious	Not serious	Not serious	Serious[4]	MODERATE	CRITICAL
					LR- 0.52 [0.32–0.71]	Not serious	Not serious	Not serious	Serious[4]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 *de la Hoya 2003, James 2006, Kang 2006, Lindor 2007, Parmigiani 2007, Rao 2009b*
2 James 2006, Lindor 2007, Rao 2009b
3 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
4 95% CI crosses 1 decision making threshold

Table 27: Evidence profile for PENN II to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[4]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
5[1]	Cohort studies	4581	-	-	AUC 0.72 [0.67–0.76]	Not serious	Serious[5]	Not serious	Serious[6]	LOW	CRITICAL
Diagnostic accuracy at 5% carrier probability threshold											
Liu 2022	Cohort study	731	0.61 [0.5–0.71]	0.62 [0.58–0.65]	LR+ 1.6 [1.31–1.95]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.63 [0.47–0.83]	Not serious	Not serious	Not serious	Serious[6]	MODERATE	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
5[2]	Cohort studies	4554	0.83 [0.70–0.92]	0.40 [0.22–0.62]	LR+ 1.42 [1.16–1.85]	Not serious	Serious[5]	Not serious	Not serious	MODERATE	CRITICAL
					LR- 0.43 [0.33–0.53]	Not serious	Serious[5]	Not serious	Serious[6]	LOW	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
2[3]	Cohort studies	3095	0.19 [0.10–0.34]	0.97 [0.79–1.00]	LR+ 9.07 [1.42–33.00]	Not serious	Not serious	Not serious	Very serious[7]	LOW	CRITICAL
					LR- 0.84 [0.75–0.92]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 *Ang 2022, Hung 2019, Lindor 2010, Lindor 2012, Liu 2022, Panchal 2008*
2 Ang 2022, Hung 2019, Kenan 2018, Panchal 2008, Teller 2010

3 Ang 2022, Hung 2019
4 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
5 Serious heterogeneity unexplained by subgroup analysis
6 95% CI crosses 1 decision making threshold
7 95% CI crosses 2 decision making thresholds

Table 28: Evidence profile for Tyrer-Cuzick to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[2]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
2[1]	Cohort studies	2270	-	-	AUC 0.74 [0.69–0.78]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
Diagnostic accuracy at 20% carrier probability threshold											
Roudgari 2008	Cohort study	275	0.62 [0.54–0.69]	0.75 [0.67–0.81]	LR+ 2.45 [1.79–3.37]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL
					LR- 0.51 [0.41–0.64]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 Roudgari 2008, Senda 2021
2 Imprecision assessment for diagnostic accuracy based on likelihood ratios
3 95% CI crosses 1 decision making threshold

Table 29: Evidence profile for YALE to identify *BRCA1/2* mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
AUC for discrimination between carriers and non-carriers											
Parmigiani 2007	Cohort study	N.R.	-	-	AUC 0.64 [0.59–0.70]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
Diagnostic accuracy at 10% carrier probability threshold											
Parmigiani 2007	Cohort study	1528	0.64 [0.59–0.68]	0.57 [0.55–0.6]	LR+ 1.5 [1.36–1.66]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL
					LR- 0.63 [0.55–0.72]	Not serious	Not serious	Not serious	Not serious	HIGH	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios

Table 30: Evidence profile for Brief Family History Questionnaire to identify Lynch Syndrome mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
Diagnostic accuracy											
Kim 2022	Cohort study	169	0.81 [0.54–0.94]	0.67 [0.59–0.74]	LR+ 2.43 [1.72–3.43]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
					LR- 0.29 [0.09–0.88]	Not serious	Not serious	Not serious	Very serious[3]	LOW	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 95% CI crosses 1 decision making threshold
3 95% CI crosses 2 decision making thresholds

Table 31: Evidence profile for Extended Family History Questionnaire to identify Lynch Syndrome mutation carriers

No. of studies	Study design	Sample size	Sensitivity (95% CI)	Specificity (95% CI)	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision[1]	Quality	Importance
Diagnostic accuracy											
Kim 2022	Cohort study	169	0.54 [0.29–0.78]	0.92 [0.86–0.95]	LR+ 6.45 [3.02–13.79]	Not serious	Not serious	Not serious	Serious[2]	MODERATE	CRITICAL
					LR- 0.5 [0.27–0.93]	Not serious	Not serious	Not serious	Serious[3]	MODERATE	CRITICAL

AUC: area under ROC curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio
1 In rows where both sensitivity, specificity and likelihood ratios are presented, the imprecision assessments were based on the likelihood ratios
2 95% CI crosses 1 decision making threshold
3 95% CI crosses 2 decision making thresholds

Appendix G Economic evidence study selection

Study selection for: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

One global search was undertaken – please see Supplement 2 for details on study selection.

Appendix H Economic evidence tables

Economic evidence tables for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

No economic evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

Excluded effectiveness studies

Table 32: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Apicella, C, Dowty, J G, Dite, G S et al. (2007) Validation study of the LAMBDA model for predicting the BRCA1 or BRCA2 mutation carrier status of North American Ashkenazi Jewish women. Clinical genetics 72(2): 87-97	- Outcomes in study do not match those specified in this review protocol
Arnold, Angela G, Otegbeye, Ebunoluwa, Fleischut, Megan Harlan et al. (2014) Assessment of individuals with BRCA1 and BRCA2 large rearrangements in high-risk breast and ovarian cancer families. Breast cancer research and treatment 145(3): 625-34	- Outcomes in study do not match those specified in this review protocol
Arts-de Jong, Marieke, de Bock, Geertruida H, van Asperen, Christi J et al. (2016) Germline BRCA1/2 mutation testing is indicated in every patient with epithelial ovarian cancer: A systematic review. European journal of cancer (Oxford, England: 1990) 61: 137-45	- Systematic review used as source of primary studies
Azzollini, Jacopo, Scuvera, Giulietta, Bruno, Eleonora et al. (2016) Mutation detection rates associated with specific selection criteria for BRCA1/2 testing in 1854 high-risk families: A monocentric Italian study. European journal of internal medicine 32: 65-71	- Outcomes in study do not match those specified in this review protocol
Bansal, A, Critchfield, G C, Frank, T S et al. (2000) The predictive value of BRCA1 and BRCA2 mutation testing. Genetic testing 4(1): 45-8	- Insufficient data for 2 x 2 table
Bekos, C., Grimm, C., Kranawetter, M. et al. (2021) Reliability of tumor testing compared to germline testing for detecting brca1 and brca2 mutations in patients with epithelial ovarian cancer. Journal of Personalized Medicine 11(7): 593	- Outcomes in study do not match those specified in this review protocol
Bellcross, Cecelia A, Lemke, Amy A, Pape, Laura S et al. (2009) Evaluation of a breast/ovarian cancer genetics referral screening tool in a mammography population. Genetics in medicine: official journal of the American College of Medical Genetics 11(11): 783-9	- Outcomes in study do not match those specified in this review protocol
Berry, D A, Parmigiani, G, Sanchez, J et al. (1997) Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. Journal of the National Cancer Institute 89(3): 227-38	- Outcomes in study do not match those specified in this review protocol
Bonaiti, Bernard, Alarcon, Flora, Andrieu, Nadine et al. (2014) A new scoring system in cancer genetics: application to criteria for BRCA1 and BRCA2 mutation screening. Journal of medical genetics 51(2): 114-21	- Intervention in study does not match that specified in this review protocol
Capalbo, Carlo, Ricevuto, Enrico, Vestri, Annarita et al. (2006) Improving the accuracy of BRCA1/2 mutation prediction: validation of the novel country-customized IC software. European journal of human genetics: EJHG 14(1): 49-54	- Outcomes do not match those specified in this review protocol

Study	Reason for exclusion
Chang-Claude, J, Becher, H, Caligo, M et al. (1999) Risk estimation as a decision-making tool for genetic analysis of the breast cancer susceptibility genes. EC Demonstration Project on Familial Breast Cancer. Disease markers 15(13): 53-65	- Outcomes in study do not match those specified in this review protocol
Couch, F.J., DeShano, M.L., Blackwood, M.A. et al. (1997) BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. New England Journal of Medicine 336(20): 1409-1415	- Outcomes in study do not match those specified in this review protocol
Danzinger, S., Tan, Y.Y., Rudas, M. et al. (2018) Differential Claudin 3 and EGFR Expression Predicts BRCA1 Mutation in Triple-Negative Breast Cancer. Cancer Investigation 36(7): 378-388	- Insufficient data for 2 x 2 table
de la Cruz, Jeannine, Andre, Fabrice, Harrell, Robyn K et al. (2012) Tissue-based predictors of germ-line BRCA1 mutations: implications for triaging of genetic testing. Human pathology 43(11): 1932-9	- Outcomes in study do not match those specified in this review protocol
Eccles, Diana M, Balmana, Judith, Clune, Joe et al. (2016) Selecting Patients with Ovarian Cancer for Germline BRCA Mutation Testing: Findings from Guidelines and a Systematic Literature Review. Advances in therapy 33(2): 129-50	- Systematic review used as source of primary studies
Elsayegh, Nisreen, Barrera, Angelica M Gutierrez, Muse, Kimberly I et al. (2016) Evaluation of BRCAPRO Risk Assessment Model in Patients with Ductal Carcinoma In situ Who Underwent Clinical BRCA Genetic Testing. Frontiers in genetics 7: 71	- Population in study does not match that specified in this review protocol
Ernst, Corinna, Hahnen, Eric, Engel, Christoph et al. (2018) Performance of in silico prediction tools for the classification of rare BRCA1/2 missense variants in clinical diagnostics. BMC medical genomics 11(1): 35	- Outcomes in study do not match those specified in this review protocol
Evans, D Gareth, van Veen, Elke M, Woodward, Emma R et al. (2021) Gene Panel Testing for Breast Cancer Reveals Differential Effect of Prior BRCA1/2 Probability. Cancers 13(16)	- Outcomes in study do not match those specified in this review protocol
Evans, D.G.R., Moran, A., Hartley, R. et al. (2010) Long-term outcomes of breast cancer in women aged 30 years or younger, based on family history, pathology and BRCA1/BRCA2/TP53 status. British Journal of Cancer 102(7): 1091-1098	- Population in study does not match that specified in this review protocol
Goelen, G., Teugels, E., Sermijn, E. et al. (2003) Comparing the performance of family characteristics and predictive models for germline BRCA1/2 mutations in breast cancer families. Archives of Public Health 61(6): 297-312	- Insufficient data for 2 x 2 table
Gomez-Garcia, E.B., Ambergen, T., Blok, M.J. et al. (2005) Patients with an unclassified genetic variant in the BRCA1 or BRCA2 genes show different clinical features from those with a mutation. Journal of Clinical Oncology 23(10): 2185-2190	- Outcomes in study do not match those specified in this review protocol
Hart, Steven N, Hoskin, Tanya, Shimelis, Hermela et al. (2019) Comprehensive annotation of BRCA1 and BRCA2 missense variants by functionally validated sequence-based computational prediction models. Genetics in medicine: official journal of the American College of Medical Genetics 21(1): 71-80	- Outcomes in study do not match those specified in this review protocol
Hassanein, Mohamed, Huiart, Laetitia, Bourdon, Violaine et al. (2013) Prediction of BRCA1 germ-line mutation status in patients with breast cancer using histoprognosis grade, MS110, Lys27H3, vimentin, and KI67. Pathobiology: journal of immunopathology, molecular and cellular biology 80(5): 219-27	- Outcomes in study do not match those specified in this review protocol

Study	Reason for exclusion
Hoskins, Kent F; Zwaagstra, Alice; Ranz, Michael (2006) Validation of a tool for identifying women at high risk for hereditary breast cancer in population-based screening. Cancer 107(8): 1769-76	- Outcomes in study do not match those specified in this review protocol
Hoyer, Juliane, Vasileiou, Georgia, Uebe, Steffen et al. (2018) Addition of triple negativity of breast cancer as an indicator for germline mutations in predisposing genes increases sensitivity of clinical selection criteria. BMC cancer 18(1): 926	- Outcomes in study do not match those specified in this review protocol
Jacobi, Catharina E, van Ierland, Yvette, van Asperen, Christi J et al. (2007) Prediction of BRCA1/2 mutation status in patients with ovarian cancer from a hospital-based cohort. Genetics in medicine : official journal of the American College of Medical Genetics 9(3): 173-9	- Population in study does not match that specified in this review protocol
Katki, Hormuzd A, Blackford, Amanda, Chen, Sining et al. (2008) Multiple diseases in carrier probability estimation: accounting for surviving all cancers other than breast and ovary in BRCAPRO. Statistics in medicine 27(22): 4532-48	- Outcomes in study do not match those specified in this review protocol
Laforest, Flore, Kirkegaard, Pia, Mann, Baljinder et al. (2019) Genetic cancer risk assessment in general practice: systematic review of tools available, clinician attitudes, and patient outcomes. The British journal of general practice : the journal of the Royal College of General Practitioners 69(679): e97-e105	- Systematic review used as source of primary studies
Li, Meng-Ru, Liu, Ming-Zhu, Ge, Ya-Qiong et al. (2021) Assistance by Routine CT Features Combined With 3D Texture Analysis in the Diagnosis of BRCA Gene Mutation Status in Advanced Epithelial Ovarian Cancer. Frontiers in oncology 11: 696780	- Intervention in study does not match that specified in this review protocol
Lin, Hui-Heng, Xu, Hongyan, Hu, Hongbo et al. (2021) Predicting Ovarian/Breast Cancer Pathogenic Risks of Human BRCA1 Gene Variants of Unknown Significance. BioMed research international 2021: 6667201	- Outcomes in study do not match those specified in this review protocol
Maksimenko, J, Irmejs, A, Trofimovics, G et al. (2018) High frequency of pathogenic non-founder germline mutations in BRCA1 and BRCA2 in families with breast and ovarian cancer in a founder population. Hereditary cancer in clinical practice 16: 12	- Insufficient data for 2 x 2 table
Mingzhu, Liu, Yaqiong, Ge, Mengru, Li et al. (2021) Prediction of BRCA gene mutation status in epithelial ovarian cancer by radiomics models based on 2D and 3D CT images. BMC medical imaging 21(1): 180	- Outcomes in study do not match those specified in this review protocol
Ottini, L., Masala, G., D'Amico, C. et al. (2003) BRCA1 and BRCA2 mutation status and tumor characteristics in male breast cancer: a population-based study in Italy. Cancer Res 63(2): 342-7	- Outcomes in study do not match those specified in this review protocol
Parmigiani, G; Berry, D; Aguilar, O (1998) Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. American journal of human genetics 62(1): 145-58	- Outcomes in study do not match those specified in this review protocol
Phuah, Sze-Yee, Looi, Lai-Meng, Hassan, Norhashimah et al. (2012) Triple-negative breast cancer and PTEN (phosphatase and tensin homologue) loss are predictors of BRCA1 germline mutations in women with early-onset and familial breast cancer, but not in women with isolated late-onset breast cancer. Breast cancer research: BCR 14(6): r142	- Outcomes in study do not match those specified in this review protocol

Study	Reason for exclusion
Riahi, Aouatef, Ghourabi, Mohamel El, Fourati, Asma et al. (2017) Family history predictors of BRCA1/BRCA2 mutation status among Tunisian breast/ovarian cancer families. Breast cancer (Tokyo, Japan) 24(2): 238-244	- Outcomes in study do not match those specified in this review protocol
Rosati, S, Bianchi, F, Belvedersi, L et al. (2004) Correlation between brcapro risk estimate and incidence of brca1-brca2 mutation in 178 patients with familial breast and/or ovarian cancer from central Italy. Annals Of Oncology 15: ii11	- Study design does not match that specified in this review protocol
Rybchenko, L A, Bychkova, A M, Skyban, G V et al. (2013) Prognosis of probability of BRCA1 and BRCA2 mutations carriage in women with compromised family history of breast and/or ovarian cancer. Problemy radiatsiinoi medytsyny ta radiobiolohii: 253-60	- Population in study does not match that specified in this review protocol
Shannon, Kristen M, Lubratovich, Marcie L, Finkelstein, Dianne M et al. (2002) Model-based predictions of BRCA1/2 mutation status in breast carcinoma patients treated at an academic medical center. Cancer 94(2): 305-13	- Outcomes in study do not match those specified in this review protocol
Spurdle, Amanda B, Couch, Fergus J, Parsons, Michael T et al. (2014) Refined histopathological predictors of BRCA1 and BRCA2 mutation status: a large-scale analysis of breast cancer characteristics from the BCAC, CIMBA, and ENIGMA consortia. Breast cancer research: BCR 16(6): 3419	- Outcomes in study do not match those specified in this review protocol
Stadler, Zsofia K, Saloustros, Emmanuel, Hansen, Nichole A L et al. (2010) Absence of genomic BRCA1 and BRCA2 rearrangements in Ashkenazi breast and ovarian cancer families. Breast cancer research and treatment 123(2): 581-5	- Outcomes in study do not match those specified in this review protocol
Sun, Li, Brentnall, Adam, Patel, Shreeya et al. (2019) A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer. JAMA oncology	- Outcomes in study do not match those specified in this review protocol
Tabarestani, S., Motallebi, M., Akbari, M.E. et al. (2017) Analysis of BRCA1/2 mutations and performance of manchester scoring system in high risk iranian breast cancer patients: A pilot study. International Journal of Cancer Management 10(12): e60392	- Outcomes in study do not match those specified in this review protocol
van Harssel, J J T, van Roozendaal, C E P, Detisch, Y et al. (2010) Efficiency of BRCAPRO and Myriad II mutation probability thresholds versus cancer history criteria alone for BRCA1/2 mutation detection. Familial cancer 9(2): 193-201	- Insufficient data for 2 x 2 table
Vasileiou, Georgia, Costa, Maria J, Long, Christopher et al. (2020) Breast MRI texture analysis for prediction of BRCA-associated genetic risk. BMC medical imaging 20(1): 86	- Outcomes in study do not match those specified in this review protocol
Villarreal-Garza, Cynthia, Alvarez-Gomez, Rosa Maria, Perez-Plasencia, Carlos et al. (2015) Significant clinical impact of recurrent BRCA1 and BRCA2 mutations in Mexico. Cancer 121(3): 372-8	- Outcomes in study do not match those specified in this review protocol
Vos, Shoko, Elias, Sjoerd G, van der Groep, Petra et al. (2018) Comprehensive Proteomic Profiling-derived Immunohistochemistry-based Prediction Models for BRCA1 and BRCA2 Germline Mutation-related Breast Carcinomas. The American journal of surgical pathology 42(9): 1262-1272	- Outcomes in study do not match those specified in this review protocol
Walsh, T., Casadei, S., Coats, K.H. et al. (2006) Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. Journal of the American Medical Association 295(12): 1379-1388	- Outcomes in study do not match those specified in this review protocol
Weitzel, Jeffrey N, Lagos, Veronica I, Cullinane, Carey A et al. (2007) Limited family structure and BRCA gene mutation	- Insufficient data for 2 x 2 table

Study	Reason for exclusion
status in single cases of breast cancer. JAMA 297(23): 2587-95	
Witjes, Vera M, van Bommel, Majke H D, Ligtenberg, Marjolijn J L et al. (2022) Probability of detecting germline BRCA1/2 pathogenic variants in histological subtypes of ovarian carcinoma. A meta-analysis. Gynecologic oncology 164(1): 221-230	- Systematic review used as source of primary studies
Wong, Edward S Y, Shekar, Sandhya, Chan, Claire H T et al. (2015) Predictive Factors for BRCA1 and BRCA2 Genetic Testing in an Asian Clinic-Based Population. PloS one 10(7): e0134408	- Outcomes in study do not match those specified in this review protocol
Woods, Nicholas T, Baskin, Rebekah, Golubeva, Volha et al. (2016) Functional assays provide a robust tool for the clinical annotation of genetic variants of uncertain significance. NPJ genomic medicine 1	- Outcomes in study do not match those specified in this review protocol
Yadav, Siddhartha, Hu, Chunling, Hart, Steven N et al. (2020) Evaluation of Germline Genetic Testing Criteria in a Hospital-Based Series of Women With Breast Cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 38(13): 1409-1418	- Outcomes in study do not match those specified in this review protocol

Excluded economic studies

No economic evidence was identified for this review. See supplementary material 2 for further information.

Appendix K Research recommendations – full details

Research recommendations for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

K.1.1 Research recommendation

What are the optimal tools to assess mutation carrier probability for a wider range of ovarian cancer susceptibility genes, not limited to *BRCA1* and *BRCA2*.

K.1.2 Why this is important

Those who carry ovarian cancer susceptibility genes are at an increased lifetime risk of developing ovarian cancer; this cancer has a poor prognosis, and its treatment is resource intensive. Those found to be carriers of ovarian cancer susceptibility genes can be offered risk reduction strategies, such as prophylactic surgery, which greatly reduces their risk of developing ovarian cancer. Therefore, there is innate benefit to identifying carriers before they develop ovarian cancer for both the individuals and health care systems.

Probability tools are one such way to identify a population so that it contains a high number of women who are ovarian cancer susceptibility gene carriers. Their use reduces the chance of detecting variants of unknown significance. Therefore, their use decreases the number of women who undergo testing which enables a more judicious use of resources. In addition, they help reduce non-beneficial interventions. To date, many validated probability tools exist however the majority of these are only designed to identify those at high risk of carrying a damaging change in the *BRCA* genes. As our understanding of other genes that can cause a susceptibility to ovarian cancer increases, research is needed to incorporate these genes into probability tools and refine the currently available ones.

K.1.3 Rationale for research recommendation

Table 33: Research recommendation rationale

Importance to 'patients' or the population	Importance to patients is through the more accurate identification of those women at an inherited risk of ovarian cancer. This would enable these women to make informed decisions about how they could reduce their personal cancer risk. Importance to the population is through a reduction in the number of genetic tests that would need to be performed which would free up genomic medicine resources.
Relevance to NICE guidance	The relative absence of evidence regarding this topic currently restricts NICE guidance from making recommendations regarding the use of probability tools that are not restricted to *BRCA1* and *BRCA2*. The outcome of this research would allow such recommendations to be developed and become part of NICE guidance.
Relevance to the NHS	The use of reliable and accurate probability tools would enable the targeted use of limited genomics resources and increase the yield of positive results. In addition, the incorporation of these tools into clinical practice would fit more broadly with the NHS Long Term Plan ambitions for cancer.
National priorities	Cancer survival is a key priority for patients and the government, as stated in documents such as the NHS long term plan for cancer and NHS Clinically-led review of NHS cancer standards: models of care and management.

Current evidence base	Current evidence is limited regarding the utility and accuracy of probability tools in identifying high risk populations for carrying ovarian cancer susceptibility genes; this is most marked when looking to find those who carry such gene changes that are not in either *BRCA1 or BRCA2*.
Equality considerations	Different ovarian cancer susceptibility genes will be seen more commonly in certain populations of women. Therefore, including lesser studied genes in probability tools will ensure a greater degree of benefit across a wider range of women.

K.1.4 Modified PICO table

Table 34: Research recommendation modified PICO table

Population	Women at risk of ovarian cancer The committee agreed that research would be particularly welcome in groups of people with characteristics under the Equality 2010 Act (for example trans and non-binary people or people from different ethnic backgrounds).
Intervention	Mutation carrier probability tools for estimating the risk of pathogenic variants associated with ovarian cancer (other than *BRCA*)
Comparator	Genetic testing for germline pathogenic variants
Outcome	The accurate prediction of carrier probability, including • Discrimination • Calibration
Study design	Cross-sectional studies
Timeframe	3 years
Additional information	Retrospective studies are also possible with the use of the large established biobanks with linked clinical information

Appendix L Outcome data and calibration analysis

Outcome data for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

Table 35: AUC data

Key to variables

- study: study identifier
- source: source of data (*FBC* = NICE familial breast cancer guideline; *new* = the literature searches conducted for this review)
- testname: carrier prediction model
- condition: mutation tested for
- AUC: area under the ROC curve
- 95%CI_lower, 95%CI_upper: 95% confidence intervals of AUC

study	source	testname	condition	AUC	95%CI_lower	95%CI_upper
Antoniou 2006	FBC	BOADICEA	BRCA1/2	0.83	0.75	0.91
Antoniou 2006	FBC	BRCAPRO	BRCA1/2	0.81	0.73	0.9
Antoniou 2008	FBC	BOADICEA	BRCA1/2	0.77	0.74	0.9
Antoniou 2008	FBC	BRCAPRO	BRCA1/2	0.76	0.73	0.79
Antoniou 2008	FBC	MSS1	BRCA1/2	0.75	0.72	0.77
Antoniou 2008	FBC	IBIS	BRCA1/2	0.74	0.71	0.77
Antoniou 2008	FBC	MYRIAD	BRCA1/2	0.72	0.69	0.75
Barcenas 2006	FBC	BOADICEA	BRCA1/2	0.788	0.676	0.901
Barcenas 2006	FBC	BRCAPRO	BRCA1/2	0.671	0.537	0.805
Barcenas 2006	FBC	MYRIAD II	BRCA1/2	0.75	0.624	0.876
Barcenas 2006	FBC	BOADICEA	BRCA1/2	0.781	0.717	0.845
Barcenas 2006	FBC	BRCAPRO	BRCA1/2	0.804	0.746	0.862
Barcenas 2006	FBC	MYRIAD II	BRCA1/2	0.781	0.724	0.838
de la Hoya 2003	FBC	HCSC	BRCA1/2	0.82	0.73	0.88
de la Hoya 2003	FBC	LUMC	BRCA1/2	0.8	0.72	0.88
de la Hoya 2003	FBC	PENN	BRCA1/2	0.77	0.68	0.85
de la Hoya 2003	FBC	Finnish	BRCA1/2	0.77	0.69	0.84
de la Hoya 2003	FBC	MYRIAD	BRCA1/2	0.82	0.73	0.89
de la Hoya 2003	FBC	Counsellor	BRCA1/2	0.69	0.6	0.78
Evans 2004	FBC	BRCAPRO	BRCA1/2	0.596	0.457	0.735
Evans 2004	FBC	MSS1	BRCA1/2	0.772	0.67	0.875
Evans 2004	FBC	MYRIAD	BRCA1/2	0.714	0.599	0.829
Evans 2009	FBC	MSS2	BRCA1/2	0.726	0.702	0.749
James 2006	FBC	BRCAPRO	BRCA1/2	0.78	0.72	0.85
James 2006	FBC	MSS1	BRCA1/2	0.7	0.62	0.77
James 2006	FBC	MYRIAD	BRCA1/2	0.74	0.67	0.81
James 2006	FBC	PENN	BRCA1/2	0.73	0.67	0.8
James 2006	FBC	FHAT	BRCA1/2	0.74	0.62	0.77
Kang 2006	FBC	BRCAPRO	BRCA1/2	0.743	0.672	0.814
Kang 2006	FBC	MSS1	BRCA1/2	0.759	0.688	0.831
Kang 2006	FBC	MYRIAD	BRCA1/2	0.753	0.68	0.827
Kang 2006	FBC	PENN	BRCA1/2	0.757	0.686	0.827
Kurian 2009	FBC	BRCAPRO	BRCA1/2	0.731	0.547	0.859
Kurian 2009	FBC	BOADICEA	BRCA1/2	0.739	0.542	0.871
Kurian 2009	FBC	BRCAPRO	BRCA1/2	0.689	0.563	0.792

study	source	testname	condition	AUC	95%CI_lower	95%CI_upper
Kurian 2009	FBC	BOADICEA	BRCA1/2	0.685	0.546	0.798
Kurian 2009	FBC	BRCAPRO	BRCA1/2	0.823	0.717	0.895
Kurian 2009	FBC	BOADICEA	BRCA1/2	0.818	0.706	0.894
Lindor 2010	FBC	LAMBDA	BRCA1/2	0.73	0.66	0.79
Lindor 2010	FBC	BRCAPRO	BRCA1/2	0.76	0.7	0.82
Lindor 2010	FBC	PENN II	BRCA1/2	0.72	0.64	0.78
Lindor 2010	FBC	MYRIAD II	BRCA1/2	0.71	0.64	0.77
Lindor 2010	FBC	PENN II	BRCA1/2	0.79	0.72	0.84
Oros 2006	FBC	MSS1	BRCA1/2	0.81	0.75	0.86
Panchal 2008	FBC	BRCAPRO	BRCA1/2	0.76	0.7	0.82
Panchal 2008	FBC	BOADICEA	BRCA1/2	0.74	0.67	0.8
Panchal 2008	FBC	MSS1	BRCA1/2	0.68	0.6	0.76
Panchal 2008	FBC	PENN II	BRCA1/2	0.74	0.67	0.8
Panchal 2008	FBC	MYRIAD II	BRCA1/2	0.76	0.71	0.82
Panchal 2008	FBC	FHAT	BRCA1/2	0.74	0.66	0.8
Panchal 2008	FBC	IBIS	BRCA1/2	0.47	0.28	0.69
Parmigiani 2007	FBC	BRCAPRO	BRCA1/2	0.75	0.7	0.81
Parmigiani 2007	FBC	MYRIAD	BRCA1/2	0.68	0.62	0.73
Parmigiani 2007	FBC	FHAT	BRCA1/2	0.69	0.64	0.75
Parmigiani 2007	FBC	YALE	BRCA1/2	0.65	0.59	0.71
Parmigiani 2007	FBC	PENN	BRCA1/2	0.69	0.63	0.74
Parmigiani 2007	FBC	Finnish	BRCA1/2	0.69	0.64	0.75
Parmigiani 2007	FBC	BRCAPRO	BRCA1/2	0.66	0.49	0.72
Parmigiani 2007	FBC	MYRIAD	BRCA1/2	0.66	0.49	0.82
Parmigiani 2007	FBC	FHAT	BRCA1/2	0.66	0.49	0.82
Parmigiani 2007	FBC	YALE	BRCA1/2	0.61	0.46	0.77
Parmigiani 2007	FBC	PENN	BRCA1/2	0.76	0.61	0.92
Parmigiani 2007	FBC	Finnish	BRCA1/2	0.78	0.6	0.95
Rao 2009a	FBC	BRCAPRO	BRCA1/2	0.725	0.64	0.81
Rao 2009a	FBC	MYRIAD II	BRCA1/2	0.744	0.65	0.84
Roudgari 2008	FBC	MSS1	BRCA1/2	0.76	0.704	0.82
Roudgari 2008	FBC	Tyrer-Cuzick	BRCA1/2	0.73	0.67	0.791
Roudgari 2008	FBC	COS	BRCA1/2	0.78	0.726	0.84
Simard 2007	FBC	MSS1	BRCA1/2	0.89	0.84	0.95
Simard 2007	FBC	MYRIAD	BRCA1/2	0.75	0.66	0.83
Vogel 2007	FBC	BRCAPRO	BRCA1/2	0.774	0.63	0.9
Vogel 2007	FBC	BRCAPRO	BRCA1/2	0.77	0.65	0.89
Zanna 2010	FBC	IC model	BRCA1/2	0.79	0.66	0.93
Zanna 2010	FBC	BRCAPRO	BRCA1/2	0.82	0.67	0.97
Zanna 2010	FBC	FHAT	BRCA1/2	0.72	0.53	0.91
Zanna 2010	FBC	MYRIAD	BRCA1/2	0.61	0.4	0.82
Ang 2022	new	ARiCA	BRCA1/2	0.8	0.75	0.84
Ang 2022	new	PENN II	BRCA1/2	0.74	0.69	0.8
Ang 2022	new	BOADICEA	BRCA1/2	0.73	0.68	0.78
Ang 2022	new	KOHCal	BRCA1/2	0.71	0.65	0.76
Antonucci 2017	new	BRCAPRO	BRCA1/2	0.852	0.751	0.953
Antonucci 2017	new	BRCAPRO	BRCA1/2	0.879	0.797	0.962
Berrino 2015	new	BOADICEA	BRCA1/2	0.783	0.674	0.892
Berrino 2015	new	BRCAPRO	BRCA1/2	0.801	0.707	0.895
Berrino 2015	new	BRCAPRO	BRCA1/2	0.845	0.771	0.918
Berrino 2015	new	COS	BRCA1/2	0.844	0.764	0.924
Biswas 2012	new	BRCAPRO	BRCA1/2	0.79	0.753	0.825
Biswas 2013	new	BRCAPRO	BRCA1/2	0.783	0.762	0.805
Biswas 2013	new	BRCAPROLYTE	BRCA1/2	0.772	0.75	0.795

study	source	testname	condition	AUC	95%CI_lower	95%CI_upper
Biswas 2013	new	BRCAPROLYTE-Plus	BRCA1/2	0.763	0.74	0.785
Biswas 2013	new	BRCAPROLYTE-Simple	BRCA1/2	0.77	0.75	0.79
Biswas 2013	new	FHAT	BRCA1/2	0.745	0.722	0.768
Chew 2018	new	MSS1	BRCA1/2	0.819	0.746	0.892
Chew 2018	new	MSS2	BRCA1/2	0.832	0.768	0.896
Chew 2018	new	MSS3	BRCA1/2	0.844	0.783	0.905
Daniels 2014	new	BRCAPRO	BRCA1/2	0.81	0.77	0.85
Daniels 2014	new	BRCAPRO	BRCA1/2	0.83	0.79	0.87
Eoh 2017	new	BRCAPRO	BRCA1/2	0.7965	0.688	0.836
Eoh 2017	new	MYRIAD II	BRCA1/2	0.751	0.674	0.828
Evans 2017	new	MSS1	BRCA1/2	0.766	0.745	0.787
Evans 2017	new	MSS3	BRCA1/2	0.816	0.795	0.832
Fischer 2013	new	BOADICEA	BRCA1/2	0.787	0.771	0.802
Fischer 2013	new	BOADICEA-Path	BRCA1/2	0.811	0.796	0.825
Fischer 2013	new	BRCAPRO	BRCA1/2	0.796	0.784	0.808
Fischer 2013	new	IBIS	BRCA1/2	0.749	0.735	0.763
Fischer 2013	new	eCLAUS	BRCA1/2	0.745	0.732	0.759
Hung 2019	new	BOADICEA	BRCA1/2	0.75	0.67	0.83
Hung 2019	new	BRCAPRO	BRCA1/2	0.73	0.64	0.81
Hung 2019	new	MYRIAD	BRCA1/2	0.68	0.59	0.77
Hung 2019	new	PENN II	BRCA1/2	0.69	0.6	0.77
Huo 2009	new	BRCAPRO	BRCA1/2	0.679	0.56	0.799
Huo 2009	new	BRCAPRO	BRCA1/2	0.832	0.716	0.947
Kang 2012	new	BRCAPRO	BRCA1/2	0.668	0.591	0.745
Kang 2012	new	MYRIAD II	BRCA1/2	0.671	0.594	0.745
Kast 2014	new	MSS1	BRCA1/2	0.77	0.75	0.79
Kast 2014	new	MSS2	BRCA1/2	0.82	0.8	0.83
Kurian 2008	new	BRCAPRO	BRCA1/2	0.77	0.66	0.88
Kurian 2008	new	MYRIAD II	BRCA1/2	0.78	0.67	0.89
Kurian 2008	new	BRCAPRO	BRCA1/2	0.71	0.63	0.8
Kurian 2008	new	MYRIAD II	BRCA1/2	0.67	0.59	0.76
Lindor 2007	new	BRCAPRO	BRCA1/2	0.73	0.7	0.82
Lindor 2007	new	PENN	BRCA1/2	0.72	0.64	0.78
Lindor 2007	new	MYRIAD II	BRCA1/2	0.71	0.64	0.77
Liu 2022	new	DrABC	BRCA1/2	0.792	0.735	0.848
Liu 2022	new	BRCAPRO	BRCA1/2	0.699	0.635	0.763
Liu 2022	new	BOADICEA	BRCA1/2	0.586	0.521	0.651
Liu 2022	new	MYRIAD II	BRCA1/2	0.587	0.537	0.637
Liu 2022	new	PENN II	BRCA1/2	0.628	0.56	0.697
Liu 2022	new	DrABC	Any cancer genes	0.737	0.687	0.787
Liu 2022	new	BRCAPRO	Any cancer genes	0.65	0.589	0.711
Liu 2022	new	BOADICEA	Any cancer genes	0.571	0.51	0.631
Liu 2022	new	MYRIAD II	Any cancer genes	0.556	0.508	0.603
Liu 2022	new	PENN II	Any cancer genes	0.606	0.543	0.668
Mazzola 2014	new	BRCAPRO	BRCA1/2	0.7927	0.7661	0.8126
Mitri 2015	new	BRCAPRO	BRCA1/2	0.83	0.759	0.907
Moghadasi 2018	new	BOADICEA	BRCA1/2	0.776	0.708	0.845
Moghadasi 2018	new	BRCAPRO	BRCA1/2	0.798	0.726	0.871
Moghadasi 2018	new	MYRIAD	BRCA1/2	0.671	0.599	0.743

study	source	testname	condition	AUC	95%CI_lower	95%CI_upper
Rao 2009b	new	BRCAPRO	BRCA1/2	0.699	0.699	0.788
Rao 2009b	new	PENN	BRCA1/2	0.692	0.607	0.777
Rao 2009b	new	Sh-E	BRCA1/2	0.694	0.595	0.792
Senda 2021	new	Tyrer-Cuzick	BRCA1/2	0.75	0.69	0.81
Stahlbom 2012	new	BOADICEA	BRCA1/2	0.83	0.76	0.88
Teixeira 2017	new	BOADICEA	BRCA1/2	0.87	0.77	0.97
Teixeira 2017	new	BRCAPRO	BRCA1/2	0.77	0.63	0.9
Teixeira 2017	new	MYRIAD	BRCA1/2	0.73	0.6	0.87
Teixeira 2017	new	MSS1	BRCA1/2	0.79	0.67	0.91
Teixeira 2017	new	BOADICEA + age at menarche	BRCA1/2	0.89	0.8	0.99
Teixeira 2017	new	BRCAPRO + age at meanrche	BRCA1/2	0.83	0.73	0.93
Teixeira 2017	new	Myriad + age at meanrche	BRCA1/2	0.81	0.71	0.92
Teixeira 2017	new	MSS1	BRCA1/2	0.86	0.76	0.95
Terkelsen 2019	new	BOADICEA	BRCA1/2	0.81	0.74	0.86
Thirthagiri 2008	new	MSS1	BRCA1/2	0.8	0.72	0.86
Thirthagiri 2008	new	BOADICEA	BRCA1/2	0.73	0.65	0.8
Varesco 2013	new	BOADICEA	BRCA1/2	0.79	0.75	0.83
Varesco 2013	new	BRCAPRO	BRCA1/2	0.8	0.76	0.84

Table 36: Diagnostic accuracy data

Key to variables

- study: study identifier
- source: source of data (*FBC* = NICE familial breast cancer guideline; *new* = the literature searches conduced for this review)
- ancestry: ancestry of study population
- testname: carrier prediction model
- prob_threshold: carrier probability threshold
- condition: mutation tested for
- TP, FP, FN, TN: true positive. false positive, false negative, true negative

study	source	ancestry	testname	prob_thresh	condition	TP	FP	FN	TN
Antoniou 2006	FBC	French_Canadian	BOADICEA	16	BRCA1/2	27	48	6	107
Antoniou 2006	FBC	French_Canadian	BRCAPRO	25	BRCA1/2	23	56	10	99
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	BOADICEA	10	BRCA1/2	330	949	35	620
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	BRCAPRO	10	BRCA1/2	322	893	43	676
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	MSS1	15	BRCA1/2	337	1045	28	524
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	IBIS	10	BRCA1/2	285	757	72	775
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	MYRIAD	10	BRCA1/2	288	843	77	726
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	BOADICEA	20	BRCA1/2	295	651	70	918
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	BRCAPRO	20	BRCA1/2	296	680	69	889
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	MSS1	17	BRCA1/2	318	888	47	681

study	source	ancestry	testname	prob_thresh	condition	TP	FP	FN	TN
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	IBIS	20	BRCA1/2	242	519	115	1013
Antoniou 2008	FBC	UK_non_Ashkenazi_Jewish	MYRIAD	20	BRCA1/2	186	306	179	1263
Barcenas 2006	FBC	US_non_Ashkenazi_Jewish	BOADICEA	10	BRCA1/2	51	88	19	218
Barcenas 2006	FBC	US_non_Ashkenazi_Jewish	BRCAPRO	10	BRCA1/2	52	101	18	205
Barcenas 2006	FBC	US_non_Ashkenazi_Jewish	MYRIAD II	10	BRCA1/2	57	116	13	190
Barcenas 2006	FBC	Ashkenazi_Jewish	BOADICEA	10	BRCA1/2	21	47	3	26
Barcenas 2006	FBC	Ashkenazi_Jewish	BRCAPRO	10	BRCA1/2	19	55	5	18
Barcenas 2006	FBC	Ashkenazi_Jewish	MYRIAD II	10	BRCA1/2	21	47	3	26
Bodmer 2006	FBC	Netherlands_All	MYRIAD	15	BRCA1/2	41	110	8	104
Bodmer 2006	FBC	Netherlands_All	GILPIN	15	BRCA1/2	39	79	10	135
Bodmer 2006	FBC	Netherlands_All	MSS1	10	BRCA1/2	40	98	9	116
Berry 2002	FBC	US_non_Ashkenazi_Jewish	BRCAPRO	10	BRCA1/2	85	76	5	39
Berry 2002	FBC	Ashkenazi_Jewish	BRCAPRO	10	BRCA1/2	77	43	1	5
Capalbo 2006	FBC	Italian_All	BRCAPRO	10	BRCA1/2	18	31	9	41
Capalbo 2006	FBC	Italian_All	MYRIAD	10	BRCA1/2	23	42	4	30
Capalbo 2006	FBC	Italian_All	IC model	10	BRCA1/2	24	35	3	37
de la Hoya 2003	FBC	Spanish_All	HCSC	11.4	BRCA1/2	25	39	2	33
de la Hoya 2003	FBC	Spanish_All	LUMC	7.5	BRCA1/2	25	33	2	39
de la Hoya 2003	FBC	Spanish_All	PENN	3.2	BRCA1/2	25	46	2	26
de la Hoya 2003	FBC	Spanish_All	Finnish	5.4	BRCA1/2	25	48	2	24
de la Hoya 2003	FBC	Spanish_All	MYRIAD	17.5	BRCA1/2	25	43	2	29
de la Hoya 2003	FBC	Spanish_All	Risk counselor	30	BRCA1/2	25	53	2	19
Euhus 2002	FBC	Spanish_All	BRCAPRO	10	BRCA1/2	58	58	5	27
Euhus 2002	FBC	Spanish_All	Risk counselor	10	BRCA1/2	59	71	4	14
Evans 2004	FBC	UK_non_Ashkenazi_Jewish	BRCAPRO	10	BRCA1/2	14	131	9	104
Evans 2004	FBC	UK_non_Ashkenazi_Jewish	MSS1	10	BRCA1/2	4	74	2	178
Evans 2004	FBC	UK_non_Ashkenazi_Jewish	MYRIAD	10	BRCA1/2	20	154	3	75
Evans 2009	FBC	UK_non_Ashkenazi_Jewish	MSS1	10	BRCA1/2	361	924	28	843
Evans 2009	FBC	UK_non_Ashkenazi_Jewish	MSS2	10	BRCA1/2	365	853	24	914
Evans 2009	FBC	UK_non_Ashkenazi_Jewish	MSS1	20	BRCA1/2	319	556	70	1211
James 2006	FBC	Australian_All	BRCAPRO	10	BRCA1/2	53	70	14	109

study	source	ancestry	testname	prob_thresh	condition	TP	FP	FN	TN
James 2006	FBC	Australian_All	MSS1	10	BRCA1/2	48	64	19	115
James 2006	FBC	Australian_All	MYRIAD	10	BRCA1/2	61	134	6	45
James 2006	FBC	Australian_All	PENN	10	BRCA1/2	48	66	19	113
James 2006	FBC	Australian_All	FHAT	10	BRCA1/2	61	152	6	27
Kang 2006	FBC	Australian_non_AJ	BRCAPRO	15	BRCA1/2	40	150	12	178
Kang 2006	FBC	Australian_non_AJ	MSS1	15	BRCA1/2	46	215	6	113
Kang 2006	FBC	Australian_non_AJ	MYRIAD	15	BRCA1/2	44	160	8	168
Kang 2006	FBC	Australian_non_AJ	PENN	15	BRCA1/2	36	106	16	216
Oros 2006	FBC	French_Canadian	BRCAPRO	10	BRCA1/2	86	68	10	60
Oros 2006	FBC	French_Canadian	MSS1	24	BRCA1/2	86	67	10	61
Panchal 2008	FBC	Canadian_All	BRCAPRO	10	BRCA1/2	75	76	25	124
Panchal 2008	FBC	Canadian_All	BOADICEA	10	BRCA1/2	70	70	30	130
Panchal 2008	FBC	Canadian_All	MSS1	15	BRCA1/2	58	58	42	142
Panchal 2008	FBC	Canadian_All	PENN II	10	BRCA1/2	93	138	7	62
Panchal 2008	FBC	Canadian_All	MYRIAD II	10	BRCA1/2	71	74	29	126
Panchal 2008	FBC	Canadian_All	FHAT	10	BRCA1/2	70	74	30	126
Panchal 2008	FBC	Canadian_All	IBIS	10	BRCA1/2	20	52	80	148
Parmigiani 2007	FBC	US_All	BRCAPRO	10	BRCA1/2	352	522	75	579
Parmigiani 2007	FBC	US_All	MYRIAD	10	BRCA1/2	331	574	96	527
Parmigiani 2007	FBC	US_All	FHAT	10	BRCA1/2	378	803	49	298
Parmigiani 2007	FBC	US_All	YALE	10	BRCA1/2	273	469	154	632
Parmigiani 2007	FBC	US_All	NCI	10	BRCA1/2	75	101	45	192
Parmigiani 2007	FBC	US_All	Finnish	10	BRCA1/2	284	358	106	673
Rao 2009a	FBC	Chinese	BRCAPRO	15	BRCA1/2	22	57	11	123
Rao 2009a	FBC	Chinese	MYRIAD II	15	BRCA1/2	24	51	9	128
Roudgari 2008	FBC	UK_non_Ashkenazi_Jewish	BOADICEA	20	BRCA1/2	74	30	65	106
Roudgari 2008	FBC	UK_non_Ashkenazi_Jewish	MSS1	20	BRCA1/2	126	78	13	58
Roudgari 2008	FBC	UK_non_Ashkenazi_Jewish	Tyrer-Cuzick	20	BRCA1/2	86	34	53	102
Roudgari 2008	FBC	UK_non_Ashkenazi_Jewish	COS	20	BRCA1/2	128	78	11	58
Simard 2007	FBC	French_Canadian	MSS1	18	BRCA1/2	48	24	8	111
Teller 2010	FBC	US_All	PAT	8	BRCA1/2	139	299	7	75

study	source	ancestry	testname	prob_thresh	condition	TP	FP	FN	TN
Teller 2010	FBC	US_All	MYRIAD II	10	BRCA1/2	124	227	22	147
Teller 2010	FBC	US_All	PENN II	10	BRCA1/2	135	316	11	58
Zanna 2010	FBC	Italian_All	BRCAPRO	10	BRCA1/2	8	20	2	71
Zanna 2010	FBC	Italian_All	FHAT	10	BRCA1/2	7	18	3	74
Zanna 2010	FBC	Italian_All	IC	10	BRCA1/2	10	79	0	13
Ang 2022	new	Malaysian_All	BOADICEA	10	BRCA1/2	21	118	74	2235
Ang 2022	new	Malaysian_All	BOADICEA	20	BRCA1/2	7	24	88	2329
Ang 2022	new	Malaysian_All	PENN II	20	BRCA1/2	14	24	81	2329
Antonucci 2017	new	Italian_All	BRCAPRO	10	BRCA1/2	18	37	3	92
Berrino 2015	new	Italian_All	BOADICEA	10	BRCA1/2	79	97	27	233
Berrino 2015	new	Italian_All	BRCAPRO	10	BRCA1/2	94	118	12	212
Berrino 2015	new	Italian_All	COS	10	BRCA1/2	96	118	10	212
Berrino 2015	new	Italian_All	BOADICEA	5	BRCA1/2	86	149	20	181
Berrino 2015	new	Italian_All	BRCAPRO	5	BRCA1/2	99	177	7	153
Berrino 2015	new	Italian_All	COS	5	BRCA1/2	99	172	7	158
Biswas 2012	new	US_All	BRCAPRO	5	BRCA1/2	148	244	39	365
Biswas 2012	new	US_All	BRCAPRO	10	BRCA1/2	127	158	60	451
Biswas 2012	new	US_All	BRCAPRO	20	BRCA1/2	103	97	84	512
Biswas 2013	new	US_All	BRCAPRO	10	BRCA1/2	415	620	161	1517
Biswas 2013	new	US_All	BRCAPROLYTE	10	BRCA1/2	495	1133	81	1004
Biswas 2013	new	US_All	BRCAPROLYTE-Plus	10	BRCA1/2	380	513	196	1624
Biswas 2013	new	US_All	BRCAPROLYTE-Simple	10	BRCA1/2	426	748	150	1389
Biswas 2013	new	US_All	FHAT	10	BRCA1/2	490	1133	86	1004
Biswas 2013	new	US_All	BRCAPRO	5	BRCA1/2	455	898	121	1239
Biswas 2013	new	US_All	BRCAPROLYTE	5	BRCA1/2	530	1496	46	641
Biswas 2013	new	US_All	BRCAPROLYTE-Plus	5	BRCA1/2	438	812	138	1325
Biswas 2013	new	US_All	BRCAPROLYTE-Simple	5	BRCA1/2	484	1026	92	1111
Biswas 2013	new	US_All	BRCAPRO	3	BRCA1/2	495	1133	81	1004
Biswas 2013	new	US_All	BRCAPROLYTE	3	BRCA1/2	553	1710	23	427
Biswas 2013	new	US_All	BRCAPROLYTE-Plus	3	BRCA1/2	472	1004	104	1133
Biswas 2013	new	US_All	BRCAPROLYTE-Simple	3	BRCA1/2	513	1282	63	855

study	source	ancestry	testname	prob_thresh	condition	TP	FP	FN	TN
Biswas 2013	new	US_All	BRCAPRO	1	BRCA1/2	547	1517	29	620
Biswas 2013	new	US_All	BRCAPROLYTE	1	BRCA1/2	570	2009	6	128
Biswas 2013	new	US_All	BRCAPROLYTE-Plus	1	BRCA1/2	536	1475	40	662
Biswas 2013	new	US_All	BRCAPROLYTE-Simple	1	BRCA1/2	559	1752	17	385
Chew 2018	new	East_Asian	MSS3	10	BRCA1/2	43	99	4	184
Cropper 2017	new	US_All	NCCN	99	BRCA1/2	88	644	11	329
Daniels 2014	new	UK_All	BRCAPRO	5	BRCA1/2	144	160	36	249
Eoh 2017	new	Korean	BRCAPRO	10	BRCA1/2	32	21	25	154
Eoh 2017	new	Korean	MYRIAD	10	BRCA1/2	33	19	24	156
Evans 2017	new	UK_non_Ashkenazi_Jewish	BOADICEA	10	BRCA1/2	5	3	12	209
Evans 2017	new	UK_non_Ashkenazi_Jewish	MSS2	10	BRCA1/2	12	49	5	165
Evans 2017	new	UK_non_Ashkenazi_Jewish	MSS3	10	BRCA1/2	15	83	2	131
Fischer 2013	new	German_All	BOADICEA	5	BRCA1/2	1632	3819	142	1939
Fischer 2013	new	German_All	BRCAPRO	5	BRCA1/2	1604	3598	170	2160
Fischer 2013	new	German_All	IBIS	5	BRCA1/2	1539	3709	235	2049
Fischer 2013	new	German_All	eCLAUS	5	BRCA1/2	1769	5605	5	153
Fischer 2013	new	German_All	BOADICEA	10	BRCA1/2	989	1584	230	2125
Fischer 2013	new	German_All	BOADICEA-Path	10	BRCA1/2	1002	1484	217	2225
Fischer 2013	new	German_All	BRCAPRO	10	BRCA1/2	1490	2591	284	3167
Fischer 2013	new	German_All	IBIS	10	BRCA1/2	1366	2505	408	3253
Fischer 2013	new	German_All	eCLAUS	10	BRCA1/2	1739	5205	35	553
Fischer 2013	new	German_All	BOADICEA	20	BRCA1/2	1219	1434	555	4324
Fischer 2013	new	German_All	BRCAPRO	20	BRCA1/2	1318	1739	456	4019
Fischer 2013	new	German_All	IBIS	20	BRCA1/2	1135	1486	639	4272
Fischer 2013	new	German_All	eCLAUS	20	BRCA1/2	1650	4342	124	1416
Gerdes 2006	new	Danish_All	MSS1	10	BRCA1/2	64	108	12	83
Gerdes 2006	new	Danish_All	MYRIAD	10	BRCA1/2	60	109	16	82
Hung 2019	new	Chinese	BOADICEA	10	BRCA1/2	22	42	26	557
Hung 2019	new	Chinese	BRCAPRO	10	BRCA1/2	34	243	14	356
Hung 2019	new	Chinese	MYRIAD	10	BRCA1/2	23	98	25	501
Hung 2019	new	Chinese	PENN II	10	BRCA1/2	41	367	9	230

study	source	ancestry	testname	prob_thresh	condition	TP	FP	FN	TN
Hung 2019	new	Chinese	BOADICEA	20	BRCA1/2	16	19	32	580
Hung 2019	new	Chinese	BRCAPRO	20	BRCA1/2	29	144	19	455
Hung 2019	new	Chinese	MYRIAD	20	BRCA1/2	11	24	37	575
Hung 2019	new	Chinese	PENN II	20	BRCA1/2	12	51	36	548
Huo 2009	new	African_American	BRCAPRO	10	BRCA1/2	21	34	11	38
Huo 2009	new	Hispanic	BRCAPRO	10	BRCA1/2	13	36	3	78
Kang 2012	new	Korean	BRCAPRO	10	BRCA1/2	22	27	24	163
Kang 2012	new	Korean	MYRIAD II	10	BRCA1/2	23	30	23	160
Kast 2014	new	White	MSS1	10	BRCA1/2	1852	5727	129	1682
Kast 2014	new	White	MSS2	10	BRCA1/2	1791	3986	190	3423
Kenan 2018	new	Israeli_All	BOADICEA	10	BRCA1/2	54	295	10	280
Kenan 2018	new	Israeli_All	PENN II	10	BRCA1/2	49	300	15	275
Kenan 2018	new	Israeli_All	BRCAPRO	10	BRCA1/2	53	285	11	289
Kenan 2018	new	Israeli_All	MYRIAD	10	BRCA1/2	36	186	28	388
Kenan 2018	new	Israeli_All	BOADICEA	15	BRCA1/2	49	239	15	336
Kenan 2018	new	Israeli_All	PENN II	15	BRCA1/2	40	187	24	388
Kenan 2018	new	Israeli_All	BRCAPRO	15	BRCA1/2	48	227	16	347
Kenan 2018	new	Israeli_All	MYRIAD	15	BRCA1/2	26	89	38	485
Kwong 2012	new	Chinese	BRCAPRO	5	BRCA1/2	30	86	8	161
Kwong 2012	new	Chinese	MYRIAD II	5	BRCA1/2	37	202	1	45
Kwong 2012	new	Chinese	BOADICEA	5	BRCA1/2	30	84	8	163
Kwong 2012	new	Chinese	BRCAPRO	10	BRCA1/2	28	50	10	197
Kwong 2012	new	Chinese	MYRIAD II	10	BRCA1/2	24	54	14	193
Kwong 2012	new	Chinese	BOADICEA	10	BRCA1/2	26	52	12	195
Kwong 2012	new	Chinese	BRCAPRO	20	BRCA1/2	22	34	16	213
Kwong 2012	new	Chinese	MYRIAD II	20	BRCA1/2	13	19	25	228
Kwong 2012	new	Chinese	BOADICEA	20	BRCA1/2	16	21	22	226
Lindor 2007	new	US_All	BOADICEA	10	BRCA1/2	47	42	15	78
Lindor 2007	new	US_All	PENN	10	BRCA1/2	44	45	14	67
Lindor 2007	new	US_All	MYRIAD	10	BRCA1/2	49	52	17	82
Liu 2022	new	Chinese	BOADICEA	10	BRCA1/2	12	64	66	589

study	source	ancestry	testname	prob_thresh	condition	TP	FP	FN	TN
Liu 2022	new	Chinese	MYRIAD II	10	BRCA1/2	7	7	71	646
Liu 2022	new	Chinese	NCCN	99	BRCA1/2	65	448	13	205
Liu 2022	new	Chinese	PENN II	5	BRCA1/2	48	251	30	402
Moghadasi 2018	new	Netherlands_All	BOADICEA	5	BRCA1/2	52	152	6	97
Moghadasi 2018	new	Netherlands_All	BRCAPRO	5	BRCA1/2	47	101	11	148
Moghadasi 2018	new	Netherlands_All	BOADICEA	10	BRCA1/2	45	96	13	153
Moghadasi 2018	new	Netherlands_All	BRCAPRO	10	BRCA1/2	43	50	15	199
Moghadasi 2018	new	Netherlands_All	MYRIAD	10	BRCA1/2	32	56	26	193
Moghadasi 2018	new	Netherlands_All	BOADICEA	20	BRCA1/2	38	49	20	200
Moghadasi 2018	new	Netherlands_All	BRCAPRO	20	BRCA1/2	36	28	22	221
Moghadasi 2018	new	Netherlands_All	MYRIAD	20	BRCA1/2	13	12	45	237
Mitri 2015	new	US_All	BRCAPRO	30	BRCA1/2	37	18	13	78
Mitri 2015	new	US_All	BRCAPRO	10	BRCA1/2	43	39	7	57
Rao 2009b	new	Chinese	BRCAPRO	10	BRCA1/2	23	79	8	90
Rao 2009b	new	Chinese	PENN	10	BRCA1/2	14	39	17	130
Rao 2009b	new	Chinese	SH-E	10	BRCA1/2	10	15	21	154
Schneegans 2012	new	German_All	BRCAPRO	10	BRCA1/2	41	51	7	84
Schneegans 2012	new	German_All	BOADICEA	10	BRCA1/2	41	59	7	76
Schneegans 2012	new	German_All	MYRIAD	10	BRCA1/2	42	45	6	90
Schneegans 2012	new	German_All	BRCAPRO	20	BRCA1/2	39	38	9	97
Schneegans 2012	new	German_All	BOADICEA	20	BRCA1/2	39	40	9	95
Schneegans 2012	new	German_All	MYRIAD	20	BRCA1/2	23	8	25	127
Senda 2021	new	Japanese	Tyrer-Cuzick	0.16	BRCA1/2	50	445	26	1473
Stahlbom 2012	new	Swedish_All	BOADICEA	4	BRCA1/2	59	150	1	78
Stahlbom 2012	new	Swedish_All	BOADICEA	5	BRCA1/2	57	135	3	93
Stahlbom 2012	new	Swedish_All	BOADICEA	10	BRCA1/2	53	85	7	143
Stahlbom 2012	new	Swedish_All	BOADICEA	15	BRCA1/2	49	63	11	165
Terkelsen 2019	new	Danish_All	BOADICEA	5	BRCA1/2	14	45	6	108
Terkelsen 2019	new	Danish_All	BOADICEA	10	BRCA1/2	9	17	11	136
Terkelsen 2019	new	Danish_All	BOADICEA	15	BRCA1/2	6	10	14	143
Terkelsen 2019	new	Danish_All	BOADICEA	20	BRCA1/2	5	7	15	146

study	source	ancestry	testname	prob_thresh	condition	TP	FP	FN	TN
Teixeira 2017	new	Brazil_All	BOADICEA	10	BRCA1/2	14	10	5	71
Teixeira 2017	new	Brazil_All	BRCAPRO	10	BRCA1/2	8	4	11	77
Teixeira 2017	new	Brazil_All	MYRIAD	10	BRCA1/2	11	16	8	65
Teixeira 2017	new	Brazil_All	BOADICEA	15	BRCA1/2	13	3	6	78
Thirthagiri 2008	new	Malaysian_All	BOADICEA	10	BRCA1/2	6	24	8	136
Varesco 2013	new	Italian_All	BOADICEA	10	BRCA1/2	136	225	43	514
Varesco 2013	new	Italian_All	BRCAPRO	10	BRCA1/2	137	229	42	510
Varesco 2013	new	Italian_All	BOADICEA	5	BRCA1/2	147	347	32	392
Varesco 2013	new	Italian_All	BRCAPRO	5	BRCA1/2	151	331	28	408

Table 37: Calibration data

Key to variables

- study: study identifier
- mutations: mutation predicted by model
- testname: carrier prediction model
- prob_threshold: carrier probability threshold range
- n_obs: number of observed mutations
- N_obs: number of participants
- n_exp: number of expected mutations predicted by model
- N_exp: number of participants

study	mutations	testname	prob_thresh	n_obs	N_obs	n_exp	N_exp
Apicella 2007	BRCA1/2	BRCAPRO	0 to 3%	4	154	2	154
Apicella 2007	BRCA1/2	BRCAPRO	3 to 10%	15	321	20	321
Apicella 2007	BRCA1/2	BRCAPRO	10 to 25%	26	304	48	304
Apicella 2007	BRCA1/2	BRCAPRO	25 to 50%	47	235	86	235
Apicella 2007	BRCA1/2	BRCAPRO	50 to 75%	32	116	72	116
Apicella 2007	BRCA1/2	BRCAPRO	75 to 100%	73	156	138	156
Eoh 2017	BRCA1	BRCAPRO	0 to 100%	41	232	46	232
Eoh 2017	BRCA2	BRCAPRO	0 to 100%	16	232	20	232
Eoh 2017	BRCA1/2	BRCAPRO	0 to 100%	57	232	53	232
Eoh 2017	BRCA1/2	MYRIAD	0 to 100%	57	232	52	232
Antoniou 2008	BRCA1	BOADICEA	0 to 5%	7	349	2.4	349
Antoniou 2008	BRCA1	BOADICEA	5 to 10%	8	305	5.6	305
Antoniou 2008	BRCA1	BOADICEA	10 to 15%	14	180	5.7	180
Antoniou 2008	BRCA1	BOADICEA	15 to 20%	7	154	6.9	154
Antoniou 2008	BRCA1	BOADICEA	20 to 30%	20	217	15.6	217
Antoniou 2008	BRCA1	BOADICEA	30 to 40%	13	132	12.9	132
Antoniou 2008	BRCA1	BOADICEA	40 to 50%	12	118	14.5	118
Antoniou 2008	BRCA1	BOADICEA	50 to 100%	130	479	136.9	479
Antoniou 2008	BRCA2	BOADICEA	0 to 5%	6	349	3.4	349
Antoniou 2008	BRCA2	BOADICEA	5 to 10%	14	305	7.3	305
Antoniou 2008	BRCA2	BOADICEA	10 to 15%	6	180	7.7	180
Antoniou 2008	BRCA2	BOADICEA	15 to 20%	8	154	8.8	154

study	mutations	testname	prob_thresh	n_obs	N_obs	n_exp	N_exp
Antoniou 2008	BRCA2	BOADICEA	20 to 30%	21	217	16.6	217
Antoniou 2008	BRCA2	BOADICEA	30 to 40%	16	132	14.8	132
Antoniou 2008	BRCA2	BOADICEA	40 to 50%	11	118	16	118
Antoniou 2008	BRCA2	BOADICEA	50 to 100%	72	479	83.4	479
Antoniou 2008# (Based on UK BRCA1 mutation frequencies)	BRCA1	BRCAPRO	0 to 5%	8	648	4.2	648
Antoniou 2008# (Based on UK BRCA1 mutation frequencies)	BRCA1	BRCAPRO	5 to 10%	13	211	6.5	211
Antoniou 2008# (Based on UK BRCA1 mutation frequencies)	BRCA1	BRCAPRO	10 to 15%	1	148	8.2	148
Antoniou 2008# (Based on UK BRCA1 mutation frequencies)	BRCA1	BRCAPRO	15 to 20%	5	90	7.4	90
Antoniou 2008# (Based on UK BRCA1 mutation frequencies)	BRCA1	BRCAPRO	20 to 30%	17	167	19.5	167
Antoniou 2008# (Based on UK BRCA1 mutation frequencies)	BRCA1	BRCAPRO	30 to 40%	26	135	23.2	135
Antoniou 2008# (Based on UK BRCA1 mutation frequencies)	BRCA1	BRCAPRO	40 to 50%	15	105	21.3	105
Antoniou 2008# (Based on UK BRCA1 mutation frequencies)	BRCA1	BRCAPRO	50 to 100%	126	569	233.3	569
Antoniou 2008# (Based on UK BRCA2 mutation frequencies)	BRCA2	BRCAPRO	0 to 5%	14	648	1.9	648
Antoniou 2008# (Based on UK BRCA2 mutation frequencies)	BRCA2	BRCAPRO	5 to 10%	8	211	2.5	211
Antoniou 2008# (Based on UK BRCA2 mutation frequencies)	BRCA2	BRCAPRO	10 to 15%	11	148	3	148
Antoniou 2008# (Based on UK BRCA2 mutation frequencies)	BRCA2	BRCAPRO	15 to 20%	9	90	2	90
Antoniou 2008# (Based on UK BRCA2 mutation frequencies)	BRCA2	BRCAPRO	20 to 30%	11	167	5.2	167
Antoniou 2008# (Based on UK BRCA2 mutation frequencies)	BRCA2	BRCAPRO	30 to 40%	10	135	5.8	135
Antoniou 2008# (Based on UK BRCA2 mutation frequencies)	BRCA2	BRCAPRO	40 to 50%	8	105	7.4	105
Antoniou 2008# (Based on UK	BRCA2	BRCAPRO	50 to 100%	83	569	48	569

study	mutations	testname	prob_thresh	n_obs	N_obs	n_exp	N_exp
BRCA2 mutation frequencies)							
Antoniou 2008# (Based on BRCA1 mutation population frequency of 0.001)	BRCA1	BRCAPRO	0 to 5%	5	326	1.7	318
Antoniou 2008# (Based on BRCA1 mutation population frequency of 0.001)	BRCA1	BRCAPRO	5 to 10%	8	205	3.3	199
Antoniou 2008# (Based on BRCA1 mutation population frequency of 0.001)	BRCA1	BRCAPRO	10 to 15%	7	129	3.6	125
Antoniou 2008# (Based on BRCA1 mutation population frequency of 0.001)	BRCA1	BRCAPRO	15 to 20%	2	113	4.8	106
Antoniou 2008# (Based on BRCA1 mutation population frequency of 0.001)	BRCA1	BRCAPRO	20 to 30%	11	195	13.6	179
Antoniou 2008# (Based on BRCA1 mutation population frequency of 0.001)	BRCA1	BRCAPRO	30 to 40%	14	137	13.7	125
Antoniou 2008# (Based on BRCA1 mutation population frequency of 0.001)	BRCA1	BRCAPRO	40 to 50%	23	127	17.5	119
Antoniou 2008# (Based on BRCA1 mutation population frequency of 0.001)	BRCA1	BRCAPRO	50 to 100%	141	702	190.4	609
Antoniou 2008# (Based on BRCA2 mutation population frequency of 0.001)	BRCA2	BRCAPRO	0 to 5%	8	326	3.1	326
Antoniou 2008# (Based on BRCA2 mutation population frequency of 0.001)	BRCA2	BRCAPRO	5 to 10%	6	205	5.2	205
Antoniou 2008# (Based on BRCA2 mutation population frequency of 0.001)	BRCA2	BRCAPRO	10 to 15%	4	129	5.6	129
Antoniou 2008# (Based on	BRCA2	BRCAPRO	15 to 20%	7	113	6.8	113

study	mutations	testname	prob_thresh	n_obs	N_obs	n_exp	N_exp
BRCA2 mutation population frequency of 0.001)							
Antoniou 2008# (Based on BRCA2 mutation population frequency of 0.001)	BRCA2	BRCAPRO	20 to 30%	16	195	15.4	195
Antoniou 2008# (Based on BRCA2 mutation population frequency of 0.001)	BRCA2	BRCAPRO	30 to 40%	12	137	13.8	137
Antoniou 2008# (Based on BRCA2 mutation population frequency of 0.001)	BRCA2	BRCAPRO	40 to 50%	8	127	17	127
Antoniou 2008# (Based on BRCA2 mutation population frequency of 0.001)	BRCA2	BRCAPRO	50 to 100%	93	702	153.1	702
Antoniou 2008	BRCA1	IBIS	0 to 5%	17	557	3.3	557
Antoniou 2008	BRCA1	IBIS	5 to 10%	18	290	5.9	290
Antoniou 2008	BRCA1	IBIS	10 to 15%	12	159	6.2	159
Antoniou 2008	BRCA1	IBIS	15 to 20%	9	121	6.1	121
Antoniou 2008	BRCA1	IBIS	20 to 30%	11	166	12.4	166
Antoniou 2008	BRCA1	IBIS	30 to 40%	18	116	13.6	116
Antoniou 2008	BRCA1	IBIS	40 to 50%	12	93	14.5	93
Antoniou 2008	BRCA1	IBIS	50 to 100%	113	387	122	387
Antoniou 2008	BRCA2	IBIS	0 to 5%	24	557	4.5	557
Antoniou 2008	BRCA2	IBIS	5 to 10%	13	290	6.4	290
Antoniou 2008	BRCA2	IBIS	10 to 15%	13	159	5.4	159
Antoniou 2008	BRCA2	IBIS	15 to 20%	9	121	6	121
Antoniou 2008	BRCA2	IBIS	20 to 30%	12	166	12.5	166
Antoniou 2008	BRCA2	IBIS	30 to 40%	9	116	10.1	116
Antoniou 2008	BRCA2	IBIS	40 to 50%	5	93	10.7	93
Antoniou 2008	BRCA2	IBIS	50 to 100%	62	387	61.7	387
Berry 2002 (Total)	BRCA1/2	BRCAPRO	0 to 11%	6	50	1.7	50
Berry 2002 (Total)	BRCA1/2	BRCAPRO	11 to 43%	16	50	13.1	50
Berry 2002 (Total)	BRCA1/2	BRCAPRO	43 to 73.1%	27	50	27.9	50
Berry 2002 (Total)	BRCA1/2	BRCAPRO	73.1 to 94.9%	36	50	43.3	50
Berry 2002 (Total)	BRCA1/2	BRCAPRO	94.9 to 98.88%	38	50	48	50
Berry 2002 (Total)	BRCA1/2	BRCAPRO	98.88 to 100%	45	51	50.7	51
Berry 2002 (Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	0 to 11%	1	6	0.2	6
Berry 2002 (Ashkenazi	BRCA1/2	BRCAPRO	11 to 43.5%	5	19	5.7	19

study	mutations	testname	prob_thresh	n_obs	N_obs	n_exp	N_exp
Jewish subgroup)							
Berry 2002 (Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	43.5 to 78%	15	28	15.1	28
Berry 2002 (Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	78 to 94.9%	15	19	16.4	19
Berry 2002 (Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	94.9 to 98.88%	13	22	21.2	22
Berry 2002 (Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	98.88 to 100%	29	32	31.8	32
Berry 2002 (Non-Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	0 to 11%	5	44	1.5	44
Berry 2002 (Non-Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	11 to 43.5%	11	31	7.4	31
Berry 2002 (Non-Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	43.5 to 78%	12	22	12.8	22
Berry 2002 (Non-Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	78 to 94.9%	21	31	26.9	31
Berry 2002 (Non-Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	94.9 to 98.88%	25	28	26.8	28
Berry 2002 (Non-Ashkenazi Jewish subgroup)	BRCA1/2	BRCAPRO	98.88 to 100%	16	19	18.9	19
Daniels 2014	BRCA1/2	BRCAPRO	0 to 1%	8	122	0.55	122
Daniels 2014	BRCA1/2	BRCAPRO	1 to 3%	17	107	1.9	107
Daniels 2014	BRCA1/2	BRCAPRO	3 to 10%	26	126	7.28	126
Daniels 2014	BRCA1/2	BRCAPRO	10 to 40%	42	117	24.4	117
Daniels 2014	BRCA1/2	BRCAPRO	40 to 100%	87	117	90.72	117
Evans 2004	BRCA1	MSS1	8 to 9%	2	53	4	104
Evans 2004	BRCA1	MSS1	10 to 11%	5	39	9	76
Evans 2004	BRCA1	MSS1	15 to 19%	11	23	36	99
Evans 2004	BRCA2	MSS1	8 to 9%	1	15	10	64
Evans 2004	BRCA2	MSS1	10 to 11%	7	21	20	61
Evans 2004	BRCA2	MSS1	15 to 19%	20	61	20	61
Fischer 2013	BRCA1	BOADICEA	0 to 5%	79	2081	23.1	2081
Fischer 2013	BRCA1	BOADICEA	5 to 10%	100	1405	40.6	1405
Fischer 2013	BRCA1	BOADICEA	10 to 15%	80	753	39.8	753
Fischer 2013	BRCA1	BOADICEA	15 to 20%	66	504	37.4	504
Fischer 2013	BRCA1	BOADICEA	20 to 30%	94	616	68.8	616
Fischer 2013	BRCA1	BOADICEA	30 to 40%	104	429	72.8	429
Fischer 2013	BRCA1	BOADICEA	40 to 50%	93	316	78.9	316
Fischer 2013	BRCA1	BOADICEA	50 to 100%	627	1248	616.5	1248
Fischer 2013	BRCA1	BRCAPRO	0 to 5%	92	2330	24.5	2330

study	mutations	testname	prob_thresh	n_obs	N_obs	n_exp	N_exp
Fischer 2013	BRCA1	BRCAPRO	5 to 10%	59	1016	33.4	1016
Fischer 2013	BRCA1	BRCAPRO	10 to 15%	50	588	35.9	588
Fischer 2013	BRCA1	BRCAPRO	15 to 20%	62	417	38	417
Fischer 2013	BRCA1	BRCAPRO	20 to 30%	82	581	74.7	581
Fischer 2013	BRCA1	BRCAPRO	30 to 40%	83	401	78.5	401
Fischer 2013	BRCA1	BRCAPRO	40 to 50%	85	351	92.1	351
Fischer 2013	BRCA1	BRCAPRO	50 to 100%	730	1668	907.2	1668
Fischer 2013	BRCA1	IBIS	0 to 5%	131	2284	25.5	2284
Fischer 2013	BRCA1	IBIS	5 to 10%	106	1276	41.1	1276
Fischer 2013	BRCA1	IBIS	10 to 15%	80	760	43.2	760
Fischer 2013	BRCA1	IBIS	15 to 20%	70	458	38.9	458
Fischer 2013	BRCA1	IBIS	20 to 30%	99	588	75	588
Fischer 2013	BRCA1	IBIS	30 to 40%	97	411	76.8	411
Fischer 2013	BRCA1	IBIS	40 to 50%	80	296	72.9	296
Fischer 2013	BRCA1	IBIS	50 to 100%	565	1191	602.9	1191
Fischer 2013	BRCA2	BOADICEA	0 to 5%	63	2081	38.2	2081
Fischer 2013	BRCA2	BOADICEA	5 to 10%	75	1405	59.6	1405
Fischer 2013	BRCA2	BOADICEA	10 to 15%	52	753	53.3	753
Fischer 2013	BRCA2	BOADICEA	15 to 20%	41	504	49.8	504
Fischer 2013	BRCA2	BOADICEA	20 to 30%	50	616	82.8	616
Fischer 2013	BRCA2	BOADICEA	30 to 40%	38	429	76.1	429
Fischer 2013	BRCA2	BOADICEA	40 to 50%	40	316	62.7	316
Fischer 2013	BRCA2	BOADICEA	50 to 100%	172	1248	343.8	1248
Fischer 2013	BRCA2	BRCAPRO	0 to 5%	78	2330	31.6	2330
Fischer 2013	BRCA2	BRCAPRO	5 to 10%	49	1016	38.8	1016
Fischer 2013	BRCA2	BRCAPRO	10 to 15%	26	588	36.8	588
Fischer 2013	BRCA2	BRCAPRO	15 to 20%	40	417	35.1	417
Fischer 2013	BRCA2	BRCAPRO	20 to 30%	43	581	68.3	581
Fischer 2013	BRCA2	BRCAPRO	30 to 40%	37	401	61.6	401
Fischer 2013	BRCA2	BRCAPRO	40 to 50%	36	351	65.1	351
Fischer 2013	BRCA2	BRCAPRO	50 to 100%	222	1668	429.2	1668
Fischer 2013	BRCA2	IBIS	0 to 5%	104	2284	29.7	2284
Fischer 2013	BRCA2	IBIS	5 to 10%	67	1276	50.3	1276
Fischer 2013	BRCA2	IBIS	10 to 15%	43	760	50	760
Fischer 2013	BRCA2	IBIS	15 to 20%	37	458	41	458
Fischer 2013	BRCA2	IBIS	20 to 30%	42	588	69.9	588
Fischer 2013	BRCA2	IBIS	30 to 40%	38	411	65.3	411
Fischer 2013	BRCA2	IBIS	40 to 50%	32	296	60.2	296
Fischer 2013	BRCA2	IBIS	50 to 100%	153	1191	317.5	1191
Fischer 2013	BRCA1/2	BOADICEA	0 to 5%	142	2081	61.3	2081
Fischer 2013	BRCA1/2	BOADICEA	5 to 10%	175	1405	100.2	1405
Fischer 2013	BRCA1/2	BOADICEA	10 to 15%	132	753	93.2	753
Fischer 2013	BRCA1/2	BOADICEA	15 to 20%	107	504	87.2	504
Fischer 2013	BRCA1/2	BOADICEA	20 to 30%	144	616	151.5	616
Fischer 2013	BRCA1/2	BOADICEA	30 to 40%	142	429	148.9	429
Fischer 2013	BRCA1/2	BOADICEA	40 to 50%	133	316	141.7	316
Fischer 2013	BRCA1/2	BOADICEA	50 to 100%	799	1248	960.3	1248
Fischer 2013	BRCA1/2	BRCAPRO	0 to 5%	170	2330	56.3	2330
Fischer 2013	BRCA1/2	BRCAPRO	5 to 10%	108	1016	72.2	1016
Fischer 2013	BRCA1/2	BRCAPRO	10 to 15%	76	588	72.7	588
Fischer 2013	BRCA1/2	BRCAPRO	15 to 20%	102	417	73.1	417
Fischer 2013	BRCA1/2	BRCAPRO	20 to 30%	125	581	143	581
Fischer 2013	BRCA1/2	BRCAPRO	30 to 40%	120	401	140.1	401

study	mutations	testname	prob_thresh	n_obs	N_obs	n_exp	N_exp
Fischer 2013	BRCA1/2	BRCAPRO	40 to 50%	121	351	157.2	351
Fischer 2013	BRCA1/2	BRCAPRO	50 to 100%	952	1668	1336.4	1668
Fischer 2013	BRCA1/2	IBIS	0 to 5%	235	2284	55.2	2284
Fischer 2013	BRCA1/2	IBIS	5 to 10%	173	1276	91.4	1276
Fischer 2013	BRCA1/2	IBIS	10 to 15%	123	760	93.3	760
Fischer 2013	BRCA1/2	IBIS	15 to 20%	107	458	79.9	458
Fischer 2013	BRCA1/2	IBIS	20 to 30%	141	588	144.9	588
Fischer 2013	BRCA1/2	IBIS	30 to 40%	135	411	142.1	411
Fischer 2013	BRCA1/2	IBIS	40 to 50%	112	296	133.1	296
Fischer 2013	BRCA1/2	IBIS	50 to 100%	718	1191	920.4	1191
Fischer 2013	BRCA1/2	eCLAUS	0 to 5%	5	158	5.3	158
Fischer 2013	BRCA1/2	eCLAUS	5 to 10%	30	410	31.1	410
Fischer 2013	BRCA1/2	eCLAUS	10 to 15%	47	510	63.4	510
Fischer 2013	BRCA1/2	eCLAUS	15 to 20%	43	420	73.4	420
Fischer 2013	BRCA1/2	eCLAUS	20 to 30%	84	727	179.7	727
Fischer 2013	BRCA1/2	eCLAUS	30 to 40%	96	636	222.4	636
Fischer 2013	BRCA1/2	eCLAUS	40 to 50%	102	635	284	635
Fischer 2013	BRCA1/2	eCLAUS	50 to 100%	1346	3798	3079.5	3798
Hung 2019	BRCA1/2	BOADICEA	0 to 100%	48	647	32.2	647
Hung 2019	BRCA1/2	BRCAPRO	0 to 100%	48	647	112.5	647
Hung 2019	BRCA1/2	MYRIAD	0 to 100%	48	647	39.6	647
Hung 2019	BRCA1/2	PENN II	0 to 100%	48	647	82.3	647
Huo 2009 (African-American subgroup)	BRCA1/2	BRCAPRO	0 to 100%	32	104	24	104
Huo 2009 (Hispanic subgroup)	BRCA1/2	BRCAPRO	0 to 100%	16	130	21	130
Huo 2009 (Total)	BRCA1/2	BRCAPRO	0 to 100%	58	292	56	292
Kang 2012	BRCA1	BRCAPRO	0 to 100%	8.9	21	5.8	21
Kang 2012	BRCA2	BRCAPRO	0 to 100%	11	26	3.1	26
Kang 2012	BRCA1/2	BRCAPRO	0 to 100%	19.5	46	9	46
Kang 2012	BRCA1/2	MYRIAD II	0 to 100%	19.5	46	5.6	46
Kurian 2009 (African-American subgroup)	BRCA1/2	BRCAPRO	0 to 100%	12	398	17	398
Kurian 2009 (African-American subgroup)	BRCA1/2	BOADICEA	0 to 100%	12	398	20	398
Kurian 2009 (Hispanic subgroup)	BRCA1/2	BRCAPRO	0 to 100%	27	425	16	425
Kurian 2009 (Hispanic subgroup)	BRCA1/2	BOADICEA	0 to 100%	27	425	18	425
Kurian 2009 (Non-Hispanic white subgroup)	BRCA1/2	BRCAPRO	0 to 100%	27	542	26	542
Kurian 2009 (Non-Hispanic white subgroup)	BRCA1/2	BOADICEA	0 to 100%	27	542	30	542
Kwong 2012	BRCA1	BRCAPRO	0 to 5%	1	169	0.3	169
Kwong 2012	BRCA1	BRCAPRO	5 to 10%	0	38	0	38
Kwong 2012	BRCA1	BRCAPRO	10 to 20%	2	21	1	21
Kwong 2012	BRCA1	BRCAPRO	20 to 40%	1	17	2.4	17

study	mutations	testname	prob_thresh	n_obs	N_obs	n_exp	N_exp
Kwong 2012	BRCA1	BRCAPRO	40 to 100%	11	40	15.6	40
Kwong 2012	BRCA2	BRCAPRO	0 to 5%	7	169	2.4	169
Kwong 2012	BRCA2	BRCAPRO	5 to 10%	2	38	2.7	38
Kwong 2012	BRCA2	BRCAPRO	10 to 20%	4	21	2	21
Kwong 2012	BRCA2	BRCAPRO	20 to 40%	1	17	2.4	17
Kwong 2012	BRCA2	BRCAPRO	40 to 100%	9	40	12.8	40
Kwong 2012	BRCA1/2	MYRIAD II	0 to 5%	1	46	1.3	46
Kwong 2012	BRCA1/2	MYRIAD II	5 to 10%	13	161	10.8	161
Kwong 2012	BRCA1/2	MYRIAD II	10 to 20%	10	45	7.1	45
Kwong 2012	BRCA1/2	MYRIAD II	20 to 40%	11	27	9.1	27
Kwong 2012	BRCA1/2	MYRIAD II	40 to 100%	3	6	3.5	6
Kwong 2012	BRCA1	MYRIAD II	0 to 5%	2	171	0.9	171
Kwong 2012	BRCA1	MYRIAD II	5 to 10%	1	35	0.6	35
Kwong 2012	BRCA1	MYRIAD II	10 to 20%	4	42	2.4	42
Kwong 2012	BRCA1	MYRIAD II	20 to 40%	2	14	1.5	14
Kwong 2012	BRCA1	MYRIAD II	40 to 100%	6	23	8.8	23
Kwong 2012	BRCA2	MYRIAD II	0 to 5%	6	171	2.7	171
Kwong 2012	BRCA2	MYRIAD II	5 to 10%	3	35	1.8	35
Kwong 2012	BRCA2	MYRIAD II	10 to 20%	6	42	3.5	42
Kwong 2012	BRCA2	MYRIAD II	20 to 40%	3	14	2.3	14
Kwong 2012	BRCA2	MYRIAD II	40 to 100%	5	23	7.3	23
Kwong 2012	BRCA2	MYRIAD II	5 to 10%	2	11	0.9	11
Lindor 2007	BRCA1/2	BRCAPRO	0 to 10%	15	93	2.2	93
Lindor 2007	BRCA1/2	BRCAPRO	10 to 25%	6	19	2.9	19
Lindor 2007	BRCA1/2	BRCAPRO	25 to 50%	13	28	10.2	28
Lindor 2007	BRCA1/2	BRCAPRO	50 to 100%	28	42	36.8	42
Lindor 2007	BRCA1/2	COUCH	0 to 10%	14	67	3.1	67
Lindor 2007	BRCA1/2	COUCH	10 to 25%	13	45	7.5	45
Lindor 2007	BRCA1/2	COUCH	25 to 50%	10	26	9.5	26
Lindor 2007	BRCA1/2	COUCH	50 to 100%	21	32	26.7	32
Lindor 2007	BRCA1/2	MYRIAD II	0 to 10%	17	82	4.9	82
Lindor 2007	BRCA1/2	MYRIAD II	10 to 25%	24	84	13.9	84
Lindor 2007	BRCA1/2	MYRIAD II	25 to 50%	20	28	10.9	28
Lindor 2007	BRCA1/2	MYRIAD II	50 to 100%	5	6	4.4	6
Rao 2009	BRCA1/2	BRCAPRO	0 to 10%	7	101	4.6	101
Rao 2009	BRCA1/2	BRCAPRO	10 to 20%	5	44	6	44
Rao 2009	BRCA1/2	BRCAPRO	20 to 40%	12	35	10.3	35
Rao 2009	BRCA1/2	BRCAPRO	40 to 60%	2	15	7.2	15
Rao 2009	BRCA1/2	BRCAPRO	60 to 80%	2	7	4.9	7
Rao 2009	BRCA1/2	BRCAPRO	80 to 100%	5	10	9.3	10
Rao 2009	BRCA1/2	MYRIAD II	0 to 10%	9	135	6.8	135
Rao 2009	BRCA1/2	MYRIAD II	10 to 20%	18	64	10.1	64
Rao 2009	BRCA1/2	MYRIAD II	20 to 40%	5	12	3.8	12
Rao 2009	BRCA1/2	MYRIAD II	40 to 60%	0	0	0	0
Rao 2009	BRCA1/2	MYRIAD II	60 to 80%	1	1	0.67	1
Rao 2009	BRCA1/2	MYRIAD II	80 to 100%	0	0	0	0
Stahlbom 2012	BRCA1	BOADICEA	0 to 100%	47	263	33	263
Stahlbom 2012	BRCA2	BOADICEA	0 to 100%	13	263	21	263
Stahlbom 2012	BRCA1/2	BOADICEA	0 to 100%	60	263	54	263
Terkelsen 2019	BRCA2	BOADICEA	30 to 40%	1	3	0.22	3
Terkelsen 2019	BRCA2	BOADICEA	40 to 50%	0	1	0.41	1

study	mutations	testname	prob_thresh	n_obs	N_obs	n_exp	N_exp
Terkelsen 2019	BRCA2	BOADICEA	50 to 100%	1	1	0.01	1
Varesco 2013	BRCA1/2	BOADICEA	0 to 5%	32	424	9.3	424
Varesco 2013	BRCA1/2	BOADICEA	5 to 10%	11	133	9.7	133
Varesco 2013	BRCA1/2	BOADICEA	10 to 15%	15	70	8.4	70
Varesco 2013	BRCA1/2	BOADICEA	15 to 20%	4	42	7.2	42
Varesco 2013	BRCA1/2	BOADICEA	20 to 30%	13	52	12.6	52
Varesco 2013	BRCA1/2	BOADICEA	30 to 40%	14	45	15.8	45
Varesco 2013	BRCA1/2	BOADICEA	40 to 50%	14	26	11.6	26
Varesco 2013	BRCA1/2	BOADICEA	50 to 100%	76	126	95.8	126
Varesco 2013	BRCA1/2	BRCAPRO	0 to 5%	28	436	7.8	436
Varesco 2013	BRCA1/2	BRCAPRO	5 to 10%	14	116	8.3	116
Varesco 2013	BRCA1/2	BRCAPRO	10 to 15%	10	59	7.2	59
Varesco 2013	BRCA1/2	BRCAPRO	15 to 20%	11	44	7.6	44
Varesco 2013	BRCA1/2	BRCAPRO	20 to 30%	11	54	13.7	54
Varesco 2013	BRCA1/2	BRCAPRO	30 to 40%	9	40	14.1	40
Varesco 2013	BRCA1/2	BRCAPRO	40 to 50%	9	31	14.1	31
Varesco 2013	BRCA1/2	BRCAPRO	50 to 100%	87	138	112.2	138
Terkelsen 2019	BRCA1	BOADICEA	0 to 5%	4	114	1.02	114
Terkelsen 2019	BRCA1	BOADICEA	5 to 10%	5	33	1.32	33
Terkelsen 2019	BRCA1	BOADICEA	10 to 15%	3	10	0.63	10
Terkelsen 2019	BRCA1	BOADICEA	15 to 20%	1	4	0.37	4
Terkelsen 2019	BRCA1	BOADICEA	20 to 30%	3	7	0.97	7
Terkelsen 2019	BRCA1	BOADICEA	30 to 40%	0	3	0.79	3
Terkelsen 2019	BRCA1	BOADICEA	40 to 50%	0	1	0	1
Terkelsen 2019	BRCA1	BOADICEA	50 to 100%	0	1	0.95	1
Terkelsen 2019	BRCA2	BOADICEA	0 to 5%	2	114	1.55	114
Terkelsen 2019	BRCA2	BOADICEA	5 to 10%	0	33	1.02	33
Terkelsen 2019	BRCA2	BOADICEA	10 to 15%	0	10	0.61	10
Terkelsen 2019	BRCA2	BOADICEA	15 to 20%	0	4	0.3	4
Terkelsen 2019	BRCA2	BOADICEA	20 to 30%	0	7	0.75	7

[#] Data reported in the text of the article and in Table 3 contradict, therefore data reported here are based on the information provided in the text rather than the table

Appendix M Calibration analysis

Calibration analysis for review question: What are the optimal methods of assessing the probability of having a pathogenic variant associated with familial ovarian cancer?

Summary of dataset

This analysis was conducted on a subset of the data appearing in Table 37.

Fit statistics were calculated for prediction models where studies reported observed and expected values where the study population was larger than 5 and where the mutation was given as type BRCA1/2. Where results were reported for both the full population and subpopulations within the same study, summaries from the subpopulations were excluded from the generation of calibration statistics. The analysis dataset included 104 observations of 8 prediction models from 14 studies.

Cox Model: regression of expected probability on observed probability

For each prediction model, a linear regression was fitted to the logit probability of expected cases given logit probability of observed cases. In this test of calibration, an intercept of zero and slope for the regression line of one represents perfect calibration since in these circumstances the observed values perfectly predict the expected values (Yingxiang 2020). These parameters give a better indication of calibration, and of at which probabilities the models tend to over/underpredict, than a single summary statistic such as R^2 or the Hosmer-Lemeshow statistic.

Studies suggest that most tests show overall overestimation, with intercepts greater than zero. The eCLAUS and IBIS tests appear to overestimate the number of expected cases at all but the lowest probabilities (Figure 60). MYRIAD II was the only test found to show an overall underestimation of cases, with an intercept less than zero. Regression slopes greater than one are seen where the direction of effect is to underestimate the number of expected cases at low probabilities and overestimate the number of expected cases at high probabilities of BRCA1/2 mutation. Effects in this direction were observed for the BRCAPRO, COUCH, eCLAUS and IBIS tests. The MYRIAD II test may show the opposite directional effect, with underestimation increasing at higher probabilities, but there was considerable uncertainty around the estimation of this trend effect. The BOADICEA test met the standard of adequate calibration, with an intercept close to zero and a slope close to one. p-values for the intercept and slope indicate the strength of evidence against the null hypotheses that the intercept is zero and that the slope is one.

Summary statistics for each prediction model were estimated without a study effect for consistency with Figure 59. When observing the relationship between observed and expected cases, estimating a separate intercept and slope for each study suggests that prediction models may produce more or less informative estimates when applied to specific populations (Figure). This highlights the importance of considering the generalisablity of the prediction tool and the similarity of the target population to the population on which the tool was developed.

Uncertainty in relationship between logit probability(Observed) and logit probability(Expected)

The R^2 statistic indicates the proportion of variation in logit(probability(Expected)) that is explained by the logit(probability(Observed)). In a perfectly calibrated model this would be equal to 1. The R^2 statistic indicates that the models are not very well calibrated for BOADICEA, BRCAPRO and MYRIAD II. R^2 statistics for COUCH, eCLAUS and IBIS tests

should be interpreted in context of the number of individual studies since these regressions were informed by only a single study.

Table 38. Calibration statistics for eight prediction models of the BRCA1/2 mutation. Standard errors (SE), confidence intervals (CI) and p values were not estimable for MYRIAD and PENN II prediction models.

Test Name	N Observations (N studies)	R^2	Intercept (SE) [95% CI]	P value Hypothesis: intercept = 0	Slope (SE) [95% CI]	P value Hypothesis: slope = 1
BOADICEA	21 (5)	0.88	0.12 (0.19) [-0.27, 0.51]	0.538	1.16 (0.10) [0.95, 1.37]	0.127
BRCAPRO	47 (11)	0.76	0.70 (0.21) [0.28, 1.12]	0.002	1.55 (0.13) [1.29, 1.81]	<0.001
COUCH	4 (1)	0.98	0.28 (0.18) [-0.50, 1.06]	0.261	2.28 (0.20) [1.42, 3.15]	0.024
eCLAUS	8 (1)	0.97	2.49 (0.29) [1.79, 3.19]	<0.001	1.81 (0.13) [1.49, 2.13]	<0.001
IBIS	8 (1)	0.97	0.65 (0.17) [0.23, 1.07]	0.009	1.79 (0.13) [1.48, 2.10]	<0.001
MYRIAD	2 (2)	-	-0.05 (-) [not estimable]	Not estimable	1.06 (-) [not estimable]	Not estimable
MYRIAD II	13 (4)	0.83	-0.73 (0.19) [-1.16, -0.31]	0.003	0.83 (0.12) [0.58, 1.09]	0.173
PENN II	1 (1)	-	Not estimable	Not estimable	Not estimable	Not estimable

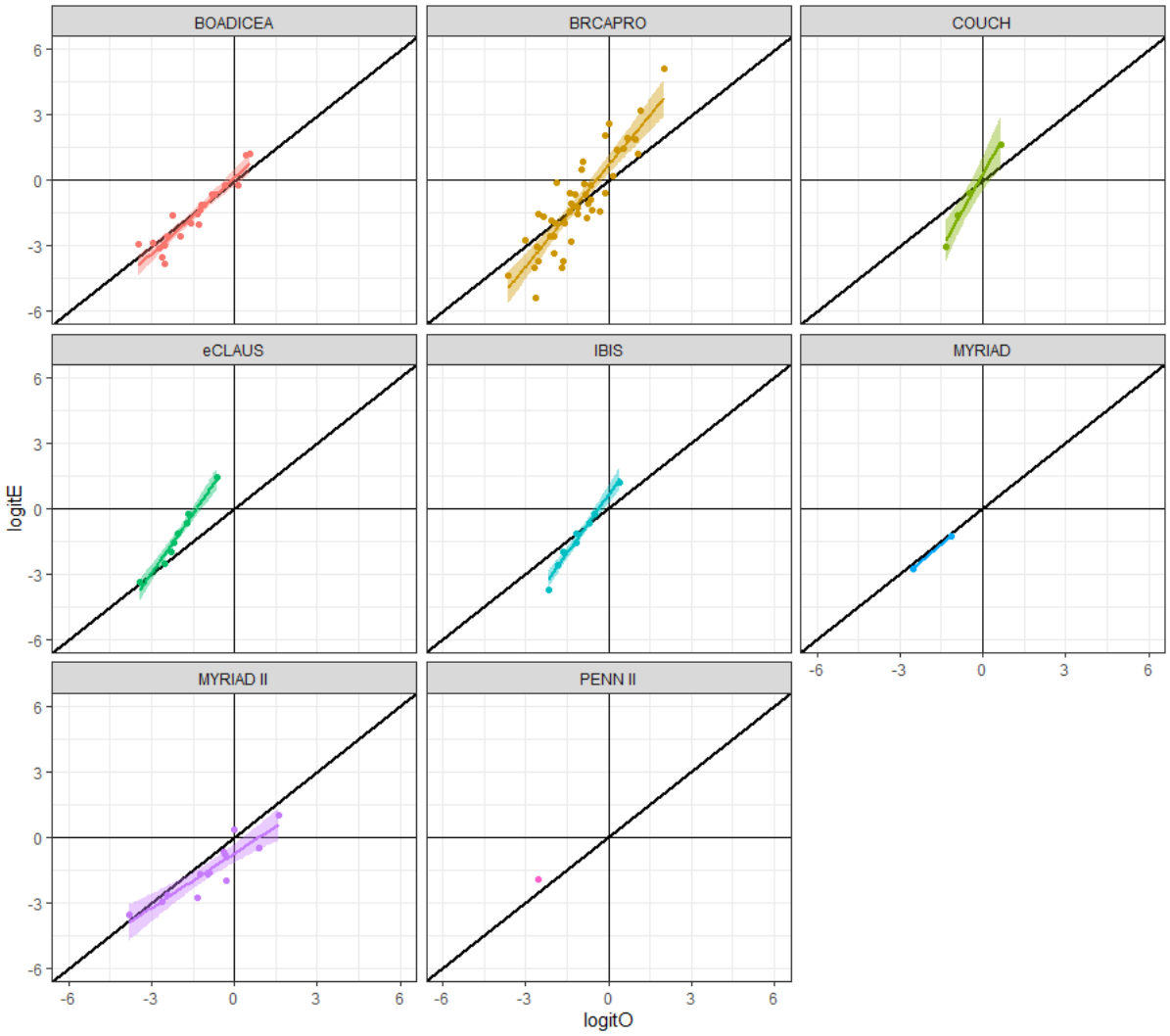

BOADICEA
BRCAPRO
COUCH
eCLAUS
IBIS
MYRIAD
MYRIAD II
PENN II
logitE
logitO
6
3
0
-3
-6

Figure 60. Regression of logit p(Exp) on logit p(Obs) by prediction model. Solid black lines are reference lines with intercept = 0 and slope = 1. Solid coloured lines are predictions from the linear model, shown with uncertainty as a shaded area.

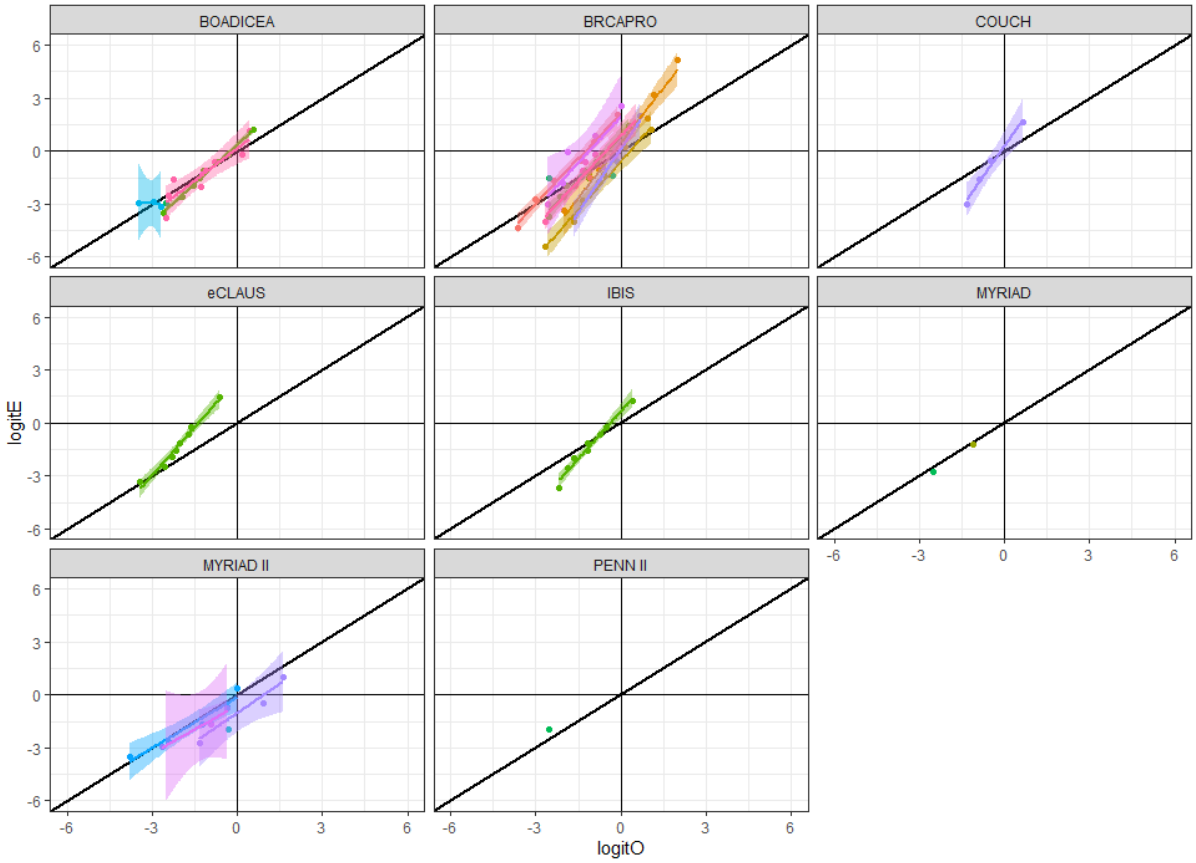


Figure 61. Regression of logit p(Exp) on logit p(Obs) by prediction model. Solid black lines are reference lines with intercept = 0 and slope = 1. Solid coloured lines are predictions from the linear model for individual studies.

Hosmer-Lemeshow

The Hosmer-Lemeshow (HL) statistic, a measure of goodness of fit related to a X^2 test, which quantifies fit by comparing observed and expected cases is often used to establish goodness of fit. The HL statistic was calculated for each predictive test, with aggregation following the probability threshold column of Table 37. Where the predictive model has good predictive properties, the number of expected cases would closely match the number of observed cases, resulting in a small contribution to the HL statistic. However, since the HL statistic is affected by the degree of information at each data point, models that were investigated in larger datasets using larger counts of observed cases are likely to result in larger contributions to the HL statistic. Therefore, the HL test and the resulting p-value is likely to suggest poorer fit in models investigated on more cases. This is why the HL test is often recommended against as a measure of calibration. We report it here for completeness.

Comparing the summary HL statistic for each test against the X^2 statistic for the relevant degrees of freedom suggests that none of the models can be considered to be a “good” fit to the data across the full range of probabilities (whilst acknowledging the caveat mentioned above; Table 39).

Table 39. Hosmer-Lemeshow statistics for the eight prediction models, shown with the reference Chi² value for the appropriate degrees of freedom. Where the test shows good predictive properties, the HL statistic would be smaller than the Chi² value.

Test Name	Observations (N studies)	HL statistic	Chi² stat for comparison (n obs-2)	p-value
BOADICEA	21 (5)	413.07	10.12	<0.001
BRCAPRO	47 (11)	1987.96	30.61	<0.001
COUCH	4 (1)	52.41	0.10	<0.001
Eclaus	8 (1)	5567.50	1.64	<0.001
IBIS	8 (1)	903.20	1.64	<0.001
MYRIAD	2 (2)	2.52	0.00	<0.001
MYRIAD II	13 (4)	103.97	4.57	<0.001
PENN II	1 (1)	16.38	-	

References

Yingxiang Huang, Wentao Li, Fima Macheret, Rodney A Gabriel, Lucila Ohno-Machado, A tutorial on calibration measurements and calibration models for clinical prediction models, Journal of the American Medical Informatics Association, Volume 27, Issue 4, April 2020, Pages 621–633, https://doi.org/10.1093/jamia/ocz228