Review protocol for diagnostic prediction models to predict carrier probability for pathogenic variants or likely pathogenic variants in breast cancer predisposition genes

ID	Field	Content
0.	PROSPERO registration number	Not applicable
1.	Review title	Diagnostic prediction models to predict the presence of pathogenic or likely pathogenic variants in breast cancer predisposition genes.
2.	Review question	In people with breast cancer or suspected heritable predisposition to breast cancer, which models demonstrate the best: • predictive performance for estimating the probability of carrying pathogenic or likely pathogenic variants in breast cancer predisposition genes; and • diagnostic performance at specific thresholds for identifying carriers of these variants compared with genetic testing?
3.	Objective	To evaluate and compare the ability of diagnostic prediction models to estimate the probability of carrying pathogenic variants or likely pathogenic variants in breast cancer predisposition genes and identify carriers of these variants at specific thresholds compared with genetic testing in people with breast cancer or suspected predisposition to breast cancer.
4.	Search approach	The following bibliographic databases will be searched: • Medline ALL (Ovid platform) • Embase (Ovid platform) • Cochrane Database of Systematic Reviews (Wiley platform) • Epistemonikos (for systematic reviews-only)

		Searching for systematic reviews will be limited to Epistemonikos and the Cochrane Database of Systematic Reviews-only. References to studies included in the previous NICE guideline (NG241, 2024) will also be included in the present review, along with any other relevant studies NICE has already identified during the guidance surveillance and prioritisation process. Reference lists for any relevant systematic reviews identified will be checked for additional primary studies. The guideline committee or other stakeholders will be asked for details of any additional, relevant studies they may be aware of. The full search strategies for all databases will be published as an appendix to the final evidence review. Database functionality will be used, where available, to exclude: • Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Registry entries for ongoing clinical trials or those that contain no results • Theses and dissertations • Papers not published in the English language. • Preprints • Studies published before January 2023
5.	Condition or domain being studied	Heritable breast cancer
6.	Population	Inclusion: • Adults with a personal history of breast cancer [this refers to the person having or having had high-grade ductal carcinoma in situ (DCIS), invasive breast

		cancer or both, but does not include low or intermediate grade DCIS or B3 lesions of intermediate nature]
		• Adults with no personal history of breast cancer or ovarian cancer who may have a heritable predisposition to breast cancer due to one or more factors such as:
		  ○ A family history of breast, ovarian or a related cancer
		  ○ Ancestry with a high prevalence of breast cancer predisposition genes, for example, Jewish, Greenlander, Westray (Orkney) or Whalsay (Shetland)
		
		Exclusion:
		• People who have been diagnosed with ovarian cancer without breast cancer (studies where greater than 20% of participants have been diagnosed with ovarian cancer without breast cancer will be excluded unless results are stratified by breast and ovarian cancer)
		• People who have been selected for inclusion in the study based on a previously calculated carrier probability or lifetime risk of developing breast cancer

7.	Diagnostic prediction model	• *BRCA1* and *BRCA2* risk assessment tools:
		  ○ BRCAPRO
		  ○ Manchester scoring system
		  ○ Tyrer-Cuzick (International Breast Cancer Intervention Study [IBIS]) including use of this tool through Family History Risk Assessment Software (FaHRAS)
		• *BRCA1*, *BRCA2, PALB2*, *CHEK2*, *ATM*, *RAD51D*, *RAD51C*, and *BARD1* risk assessment tools:
		  ○ CanRisk (BOADICEA)

		All versions of these risk assessment tools will be extracted.
8.	Reference standard	Germline pathogenic analysis
9.	Types of study to be included	Diagnostic prediction model studies and systematic reviews of such studies. • Single-gate, cross-sectional studies Only studies that evaluated performance of the model in an external validation cohort will be included (analysis types F and G in Collins [2024]).
10.	Other exclusion criteria	• Editorials, letters, items and commentaries • Conference abstracts and posters • Theses and dissertations • Papers not published in the English language • Preprints

11.	Context	There are several available tools for calculating the probability of whether a person has a pathogenic variant or likely pathogenic variant associated with heritable breast cancer. This is important as it informs whether a person should be offered germline testing to confirm whether they have gene variants that increase their risk of developing breast cancer.
		
		Although there is variation in practice across the UK, people generally undergo carrier probability testing for suspected heritable breast cancer in the following settings:
		• Specialist clinical genetics services where people have either:
		  ○ A previous diagnosis of breast cancer with either features of heritable breast cancer or a family history of breast, ovarian or related cancers OR
		  ○ No personal history of breast cancer with a family history of breast, ovarian or related cancers

		• Oncology multidisciplinary teams where people are currently being treated for breast cancer and have either features of heritable breast cancer or a family history of breast, ovarian or related cancers according to the criteria in the National genomic test directory. NICE's guidance on Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer [CG164] currently recommends that a carrier probability method with demonstrated acceptable performance should be used to assess the probability of whether a person has pathogenic variants in *BRCA1* or *BRCA2* genes. The guidance does not recommend a specific tool and instead lists BOADICEA and the Manchester scoring system as acceptable methods. This recommendation was published in 2013, and since then associations have been identified between a person's risk of developing breast cancer and pathogenic variants in several other genes. There may also be new evidence that could help determine the optimal tools for calculating a person's probability of carrying a pathogenic variant in breast cancer predisposition genes.

12.	Primary outcomes	Evaluation of model performance for diagnosing or predicting whether people do or do not have pathogenic variants or likely pathogenic variants in breast cancer predisposition genes:
		• Diagnostic performance:
		  ○ Area under the ROC curve (AUC)/c-statistics
		  ○ Sensitivity and specificity at a threshold of 10% or lower as reported by the study
		• Predictive performance:
		  ○ Observed and expected values (or frequencies) for different risks, from which ratios can be calculated (observed/expected ratio if observed and expected values are not reported)
		  ○ Calibration slopes and intercepts

		○ Calibration plots (observed compared to expected; for scanning and reanalysis) if observed and expected values or slopes and intercepts are not reported • Model fit for the validation dataset: ○ Adjusted R^2 statistic of overall model fit This statistic will be extracted and reported descriptively. Ideally, studies will report outcome measures pooled across breast cancer predisposition genes and these will be extracted (for example the combined probability of having a pathogenic variant/likely pathogenic variant in *BRCA1, BRCA2, PALB2, CHEK2, ATM, RAD51D, RAD51C*, and *BARD1).* Where pooled carrier probability outcomes are not available, we will extract the outcome measures for individual breast cancer predisposition genes.
13.	Secondary outcomes	• None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 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. 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 (age, sex and gender, ethnicity, previous cancer history, family history of cancer, ancestry), inclusion and exclusion criteria, details of the diagnostic prediction model and reference standard, 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	Quality assessment of individual studies will be performed using PROBAST. 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. **For AUC data:** Where appropriate, meta-analysis of AUC will be performed. AUC data will be synthesised on logit scale. **For sensitivity and specificity data:** Sensitivity and specificity will be jointly synthesised using a bivariate random effects meta-analysis model, following the NICE DSU TSD25. Results will be summarised in coupled forest plots of sensitivity and specificity, and summary receiver operating curves (SROC) plots, and leaf plots of post-test probability given a positive or negative test result, against prevalence. Data will only be pooled at a specific threshold if there are sufficient studies (>5) reporting sensitivity and specificity at that threshold.

		For calibration data:
		
		Observed/expected ratios will be calculated up to a 10% threshold and synthesised on the natural log scale. Results will also be provided for total observed/expected ratios calculated over the full range of predicted risk.
		
		Calibration slopes and intercepts will be synthesised by fitting a meta-regression for logit observed risk against logit expected risk (Debray et al 2019)
		
		R^2 will be reported descriptively.
		
		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 prediction test accuracy data
		Thresholds from Evidence Based Emergency Medicine; Part 5 Receiver Operating Curve and Area under the Curve:
		• AUC 90 to 100 = excellent
		• AUC 80 to 90 = good
		• AUC 70 to 80 = fair
		• AUC 60 to 70 = poor
		• AUC 50 to 60 = fail

		Decision making thresholds for observed/expected data: • O:E ratio <0.9 = model overpredicts • O:E ratio 0.9 to <0.96 = model slightly overpredicts • O:E ratio 0.96 to <1.05 = model shows accurate prediction • O:E ratio 1.05 to <1.1= model slightly underpredicts • O:E ratio >1.1 = model underpredicts **GRADE for binary accuracy data and prediction test accuracy data** 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: • Personal history of breast cancer Evidence will be subgrouped by the following only if there is significant heterogeneity in outcomes and there are at least two validation studies in each subgroup to detect a difference between subgroups: • Setting (primary care, family history clinics, specialist genetics clinics, oncology multidisciplinary teams) • Ethnicity • Diagnostic prediction model versions (case by case) Where evidence is 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	January 2026			
22.	Anticipated completion date	22nd April 2027			
23.	Stage of review at time of this submission	**Review stage**		**Started**	**Completed**
		Preliminary searches		☐	X
		Piloting of the study selection process		☐	X

		Formal screening of search results against eligibility criteria	X	☐
		Data extraction	X	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** NICE **5b Named contact e-mail** familialbreastcancer@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
25.	Review team members	• Sarah Boyce [NICE Senior technical analyst] • Lina Ford [NICE Technical Analyst] • Yolanda Martinez [NICE Technical Analyst] • Sarah Matthews [NICE Technical Analyst • Eric Slade [NICE Health economics adviser] • Tzujung Lai [NICE Health economist] • Daniel Tuvey [NICE Senior information specialist]		

		• Marie Harrisingh [NICE Topic Lead]
26.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.
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	Support for the methods used and analyses performed in this review will be provided by: Beatrice Downing, Nicky J. Welton and Hayley Jones from the Guidelines Technical Support Unit at the University of Bristol. 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: https://www.nice.org.uk/guidance/indevelopment/gid-ng10438.
29.	Other registration details	None
30.	Reference/URL for published protocol	Not applicable
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 model	
33.	Details of existing review of same topic by same authors	Not applicable	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	