Review protocol for risk prediction tools for developing new primary invasive breast cancer

ID	Field	Content
1.	Review title	Prognostic risk prediction tools for future invasive breast cancer in adults at increased heritable risk
2.	Review question	What validated prognostic tools perform best at predicting the risk of future invasive breast cancer in adults with: • a personal history of breast cancer that is suspected or known to be heritable • with no personal history of breast cancer but with a family history of breast, ovarian or a related cancer, or a confirmed pathogenic variant that predisposes them to developing breast cancer?
3.	Objective	To evaluate the ability of validated prognostic tools to predict the risk of developing a new primary invasive breast cancer in adults with or without a personal history of breast cancer.
4.	Searches	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
5.	Condition or domain being studied	Heritable breast cancer
6.	Population	Inclusion: Adults born with female reproductive organs, trans women and non-binary people born with male reproductive organs who have been on female gender affirming hormone therapy for 5 years or more (18 years or over) who: • have a personal history of breast cancer (diagnosis of breast cancer) that is suspected or known to be heritable or • have no personal history of breast cancer but with: ○ a family history of breast, ovarian or a related cancer, or ○ a confirmed pathogenic variant that predisposes them to developing breast cancer. 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)

7.	Predictor (Prognostic tool)	Validated multivariable prognostic models from the list below for predicting the risk of breast cancer. Prognostic tool for people with or without a personal history: • BOADICEA/CanRisk (for assessing contralateral risk) Prognostic tool for people without a personal history only: • IBIS/Tyler-Cuzick All versions of prognostic models will be extracted. Prognostic models should include the following factors linked to breast cancer: • Family cancer history • Age • Pathogenic variants in any breast cancer predisposition genes (e.g. BRCA1 and BRCA2)
9.	Types of study to be included	The following types of external model validation studies will be included in the review: • Prospective and retrospective cohort studies (specifically those that include validation of the model in an independent cohort) • Systematic reviews of these studies [For a systematic review (SR) to be included it must be conducted in line with the methodological processes described in the NICE manual. If sufficient details are provided, the SR will be fully included, or it will be

		used as the basis for further analyses where possible. If sufficient details are not provided to include a relevant SR, the review will only be used for citation searching.] Only studies that evaluated performance of the model in an external validation cohort will be included (analysis type F and G in Collins [2024]).
10.	Other exclusion criteria	• Abstracts, conference presentations and theses • Non-human studies • Non-English language studies • Model derivation studies that do not contain any validation data. • Editorials, letters, news items and commentaries • Registry entry for ongoing clinical trials or those that contain no results • Preprints • Case-control studies
11.	Context	Available risk prediction tools such as CanRisk (BOADICEA) can now take more breast cancer risk factors into account than family history alone. The recommendations in the current familial breast guideline (CG164) do not specify which tool should be used to assess risk of developing breast cancer. As there is more than one tool available for predicting risk, it is important to identify which tools can be used, taking into account their prognostic ability and resource use.
12.	Primary outcomes	Evaluation of model performance for predicting risk of developing breast cancer. **Outcome measures**

		<u>Discrimination:</u> • C-statistics for time to event outcomes accounting for censoring • Time dependent AUC at fixed time horizons, 5 and 10 years C-statistics will be prioritised over time dependent AUC. Where c-statistics are not reported, time dependent AUC will be extracted. Risk horizons for which data will be extracted for time to event discrimination measures: • 5-year risk • 10-year risk • Lifetime risk (for no personal history of breast cancer only) • Remaining lifetime risk (for those with or without personal history of BC) <u>Calibration:</u> • 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: o Adjusted R^2 statistic of overall model fit This statistic will be extracted and reported descriptively.

		Where required for calibration, risk stratifications from NICE (modified to include very high risk) for calibration defined as: Lifetime/remaining risk until age 80: • Less than 17% (near population risk) • Greater than 17% but less than 30% (Moderate risk) • 30% or greater (high risk) • 40% or greater (very high risk) Or 10-year risk • Less than 3% (near population risk) • 3 to <8% (moderate risk) • ≥8% from age 40 (high risk) • ≥8% from age 30 (very high risk) • ≥12% from age 40 (very high risk) 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 and 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, ethnicity, previous breast cancer history, gender), inclusion and exclusion criteria, details of the prognostic model, 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: PROBAST checklist will be performed for individual prognostic model studies ROBIS checklist will be performed for systematic reviews 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/C-statistics will be performed. **For calibration data:** Observed/expected ratios will be synthesised on the natural log scale. 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 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 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 vs no previous breast cancer diagnosis • Confirmed pathological variant vs no confirmed pathological variant

		Evidence will be sub-grouped by the following only if there is significant heterogeneity in outcomes and there are at least two validation studies in each subgroup to detect the differences between subgroups: • Setting (primary care, family history clinics, specialist genetics clinics, oncology multidisciplinary teams) • Age (29 and under, 30-40 and over 40 years) • Ethnicity • Diagnostic prediction model versions (case by case) Where evidence is stratified or sub-grouped 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	April 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	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		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: Project documents | Familial Breast Cancer: initial assessment and genetic testing (update) | Guidance | NICE
29.	Other registration details	Not applicable
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	Prognostic, risk model, breast cancer

33.	Details of existing review of same topic by same authors	None
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