Review protocol for carrier probability at which genetic testing should be offered to people without breast cancer who are suspected to have a heritable predisposition to breast cancer

ID	Field	Content
1.	Review title	Carrier probability at which genetic testing should be offered to people without breast cancer who are suspected to have a heritable predisposition to breast cancer.
2.	Review question	How does the pre-test carrier probability threshold at which germline genetic testing is offered affect the proportion of pathogenic variants identified in people with no personal history of breast cancer?
3.	Objective	To identify at what carrier probability threshold people without breast cancer, who have a suspected heritable predisposition to breast cancer, should receive genetic testing to confirm whether they have a pathogenic variant in breast cancer predisposition genes. The downstream effects of genetic testing can impact on future risk-reducing treatment and surveillance uptake. In this review, carrier probability is defined as the likelihood that an individual has a specific pathogenic variant in breast predisposition genes
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 without a personal history of breast cancer who have any of the following:
		  ○ a family history of breast and/or ovarian or related cancer
		  ○ ancestry with a high prevalence of pathogenic variants associated with breast cancer, for example, Jewish, Greenlander, Westray (Orkney) or Whalsay (Shetland)
		
		Exclusion:
		• People with breast cancer (this population will be covered by RQ2 when they have breast cancer that is suspected to be heritable)
		• People who have ovarian cancer (studies where greater than 20% of participants have been diagnosed with ovarian cancer will be excluded unless results are stratified by ovarian cancer status)

7.	Intervention	Germline pathogenic variant analysis only if a carrier probability threshold exceeds a certain threshold. We will review thresholds up to 10% carrier probability as this is the current threshold in practice. Genes tested for include: *BRCA1, BRCA2, PALB2, CHEK2, ATM, RAD51D, RAD51C,* and *BARD1* Models predicting carrier probability thresholds will be limited to those listed in RQ1: • BRCAPRO • Manchester scoring system Tyrer Cuzick/IBIS

		• CanRisk/BOADICEA Participants who undergo genetic testing and receive a pathogenic or likely pathogenic result are offered: • Enhanced surveillance (MRI or mammography) • Risk-reducing mastectomy • Chemoprevention
8.	Comparator	• Different threshold values (up to 10%)
9.	Types of study to be included	Include published full-text papers: • RCTs • Systematic reviews of RCTs [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.]
10.	Other exclusion criteria	• 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
11.	Context	NICE's guideline on Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer [CG164] currently states that people with no personal history of breast cancer and no available affected relative to test should only receive BRCA1 and BRCA2 genetic testing if they have a carrier probability of 10% or more. This recommendation was made in 2013; since then, additional pathogenic variants associated with breast cancer (such as those in PALB2, CHEK2, ATM, RAD51D, RAD51C and BARD1) have been identified, and there has been an increase in genetic testing capacity in the NHS, meaning that the recommendation may now be out of date. This recommendation is also not aligned with recommendations in NICE's guideline on Ovarian cancer: identifying and managing familial and genetic risk [NG241], where the carrier probability threshold for genetic testing ranges from 2% to 10% and is dependent upon the person's age and sex.
12.	Primary outcomes	• Proportion of people carrying pathogenic mutations in breast cancer predisposition genes

13.	Secondary outcomes	• Genetic testing uptake in relatives
		• Dissemination of the genetic information within family
		• Uptake of risk reducing treatments (timepoint as reported in studies):
		  ○ surgery (risk-reducing mastectomy)
		  ○ chemoprevention
		• Uptake of surveillance (mammography or MRI) timepoint as reported in studies)
		• Primary breast cancer incidence (10 years of latest follow up)

		• Incidence of related cancer (ovarian) (10 years of latest follow up
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, presence of bilateral breast cancer and presence of triple negative breast cancer), inclusion and exclusion criteria, details of the interventions and comparators, 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 the following checklists:

		• ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort 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 possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, the following criteria will be used to assess heterogeneity: no serious I^2 = <40%; serious I^2 = 40-60%; very serious I^2 = >60%. Where I^2 is 80% or above, the data will not be pooled. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. Publication bias will be investigated using a funnel plot when there are 10 or more studies in an analysis. 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/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). MIDs for each outcome are detailed in the methods supplement for this guideline.
17.	Analysis of sub-groups	Evidence will be stratified by: • Age < 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 years and older Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Ethnicity 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	April 2026		
22.	Anticipated completion date	22nd April 2027		
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** 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 Manounah Ford [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	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/documents
29.	Other registration details	None
30.	Reference/URL for published protocol	
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	Genetic testing, carrier probability, heritable 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