Review protocol for detecting distant metastases in people with suspected advanced breast cancer using PET-CT and CT

Field	Content
Review title	Diagnostic accuracy and cost effectiveness of PET-CT and CT with or without bone scintigraphy for detecting distant metastases in people who have suspected advanced breast cancer.
Review question	In adults with suspected advanced breast cancer, what is the diagnostic accuracy and cost effectiveness of: - FDG PET-CT - CT (with or without bone scintigraphy) for detecting distant metastases? *This review will only be completed if there are no test and treat RCTs identified for the intervention review on PET-CT for diagnosing distant metastasis and subsequent outcomes.
Objective	To evaluate and compare the accuracy and cost effectiveness of FDG PET-CT and CT with or without bone scintigraphy for diagnosing distant metastases in adults with suspected advanced breast cancer.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Searches will be limited to exclude: • papers published before 2005 • Papers not published in the English language

	• Animal studies • Conference abstracts and posters • Editorials, letters, news items and commentaries • Theses and dissertations • Clinical trial registry records For the economics review the following databases will be searched: • Embase • MEDLINE ALL • INAHTA International HTA Database The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published in the final review.
Condition or domain being studied	Suspected advanced breast cancer Advanced is defined as people with a distant metastasis (M1 using the TNM staging system).
Population	Inclusion: Adults (18 and over) with invasive adenocarcinoma of the breast who have suspected distant metastases (M1).
Index Tests	• Fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) [FDG PET-CT] • Contrast-enhanced Computed Tomography (CECT) scan • Contrast-enhanced Computed Tomography (CECT) scan, with bone scintigraphy

	Exclusion • PET-CT used for screening • Imaging analysed using artificial intelligence (AI) • Imaging covering less than chest (or neck or thorax), abdomen and pelvis.
Reference standard	• Histopathology from surgery or biopsy confirming metastasis • Clinical follow-up involving expert decision making with support of imaging (other than the index tests alone) and / or histological data.
Types of study to be included	• Diagnostic accuracy cross-sectional studies and cohort studies. • Systematic reviews of diagnostic accuracy cross-sectional or cohort studies. • Where there are no cross-sectional or cohort studies identified, case-control studies will be included.
Other exclusion criteria	• Diagnostic accuracy studies that do not report sufficient information to allow a 2*2 table (TP, FP, TN, FN) to be constructed will be excluded • Diagnostic case-control studies that separately recruit diseased and non-diseased groups
Context	This guideline will update the NICE guideline on advanced breast cancer: diagnosis and treatment (CG81). New evidence that could affect recommendations was identified through the surveillance process. The surveillance review appendix noted increasing use of PET-CT scans in practice, and stakeholders identified this area for update. A timely and accurate diagnosis of metastatic breast cancer is important for guiding treatment and improving patient outcomes. PET-CT will be assessed alongside contrast-enhanced CT with or without bone scintigraphy, which is current practice for diagnosing metastatic breast cancer, to determine accuracy.
Outcomes	Target condition is presence of any distant metastasis, including non-axillary lymph node, bone, liver, brain and lung metastases, where the primary cancer is breast cancer. These may be reported by site or combined. Diagnostic accuracy outcomes: • Sensitivity and specificity

	• Positive and negative likelihood ratios
	
	Thresholds
	• Sensitivity
	  ○ Upper threshold = 90%
	  ○ Lower threshold = 70%
	• Specificity
	  ○ Upper threshold = 80%
	  ○ Lower threshold = 60%

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. 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, inclusion and exclusion criteria, details of the index and reference standard tests, 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. This review may make use of the priority screening functionality within the EPPI-reviewer software. If priority screening is used, the following rules will be adopted to determine when to stop screening: • at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) will be screened • After this point, screening is only terminated if a threshold of 750 is met for a number of abstracts being screened without a single new include being identified. • if sifting is terminated before the full database has been looked at additional checks will be carried out to ensure that relevant studies have not been missed.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • QUADAS-2 for diagnostic accuracy studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Diagnostic test accuracy (DTA) data will be used to generate a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not). Separate analysis will be undertaken according to whether data were reported per person included in the study or per lesion. 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 metaDTA app (https://crsu.shinyapps.io/MetaDTA/) and likelihood ratio plots obtained from the glmer package in R. Cochrane Review Manager software may be used to help with visually displaying information. Where sufficient data are not available for meta-analysis, separate independent pooling will be performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using R and the Cochrane Review Manager software. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (Deeks 2010). Sensitivity, specificity, and positive and negative likelihood ratios with 95% CIs will be used as outcomes for diagnostic test accuracy. These diagnostic accuracy parameters will be obtained from the studies or calculated by the technical team using data from the studies. 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/ Random-effects models (der Simonian and Laird) will be fit for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). Evidence from diagnostic accuracy studies will be initially rated as high-quality and then downgraded according to the standard GRADE criteria. GRADE will be carried out on the LR results, but the results for sensitivity and specificity will also be presented. Where data can be disambiguated it will be separated into the subgroups identified in section 16 (below). In all cases, the downstream effects of diagnostic accuracy on patient-important outcomes will be considered based on the evidence. If there is no or limited evidence for downstream effects of diagnostic accuracy,

	considerations for this will be explicitly discussed during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results.
Analysis of sub-groups	Evidence will be subgrouped by the following: • Location of metastases (bone or visceral) • Receptor types (HER2-positive, triple negative, ER+/HER2-) • Invasive lobular carcinoma vs all other types. • Inflammatory breast cancer vs all other types • Size of primary tumour (T1 to T2 vs T3+) • Nodal status (N0 vs N1 to N3) 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.
Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery

	☐ Other (please specify)		
Language	English		
Country	England		
Anticipated or actual start date	June 2025		
Anticipated completion date	December 2025		
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	☐	☐
	Data extraction	☐	☐
	Risk of bias (quality) assessment	☐	☐
	Data analysis	☐	☐
Named contact	**5a. Named contact** Centre for Guidelines, NICE **5b Named contact e-mail** breastcancerupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		

Review team members	From the Guideline Development Team • Marie Harrisingh, Topic lead • Olivia Crane, Senior technical analyst • Adefisayo Abba-Abba, Technical analyst • Yolanda Martinez, Technical analyst • James Hawkins, Health economist adviser • Tzujung Lai, Health economist analyst • Andrea Heath, Information specialist
Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
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.
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: Advanced breast cancer: diagnosis and treatment.
Other registration details	Not applicable

Reference/URL for published protocol	Not applicable	
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.	
Keywords	Advanced breast cancer, FDG PET-CT, distant metastasis, Stage 4 breast cancer	
Details of existing review of same topic by same authors	none	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued

Additional information	none
Details of final publication	www.nice.org.uk