National Institute for Health and Care Excellence

# Advanced breast cancer: diagnosis and treatment

## [B] Evidence reviews for FDG PET-CT and contrast-enhanced CT for diagnosing and monitoring distant metastases

NICE guideline CG81

Evidence reviews underpinning recommendations 1.1.2, 1.1.3, 1.2.2, 1.3.1 to 1.3.5, 1.5.1, 1.5.2 and recommendations for research in the NICE guideline

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# Contents

# B1: FDG PET-CT and contrast-enhanced CT for diagnosing distant metastases

## 1.1 Review questions

**Review question 1**

What is the clinical and cost effectiveness of FDG PET-CT compared to contrast-enhanced CT (with or without bone scintigraphy) for diagnosing distant metastases and determining subsequent management in people with suspected advanced breast cancer? (test and treat review).

**Review question 2**

In adults with suspected advanced breast cancer, what is the diagnostic accuracy and cost effectiveness of (1) FDG PET-CT and (2) contrast-enhanced CT (with or without bone scintigraphy) for diagnosing/detecting distant metastases? (Diagnostic Test Accuracy [DTA] review).

### 1.1.1 Introduction

A timely and accurate diagnosis of metastatic breast cancer is important for guiding management decisions and improving patient outcomes by mitigating the risks associated with a false negative (missed diagnosis) or a false positive diagnosis (diagnosed as having metastatic breast cancer when a person does not have it). The 2009 NICE guideline on advanced breast cancer recommends a combination of imaging tests to assess the presence and extent of visceral metastases, which include plain radiography, ultrasound, computed tomography (CT) scans, and magnetic resonance imaging (MRI), or bone windows on a CT or MRI, or bone scintigraphy when bone metastasis is suspected. The use of fluorodeoxyglucose positron emission tomography computed tomography (FDG PET-CT) is only recommended for people with breast cancer where there is suspicion of metastatic disease on other imaging.

New evidence that could affect the recommendations was identified by the NICE surveillance review (2023), and there has been an increasing use of FDG PET-CT scans in practice. Contrast-enhanced CT (CECT) with or without bone scintigraphy is thought to be the most commonly used modality in practice for detecting metastatic breast cancer.

This review aims to investigate the effectiveness and cost effectiveness of using FDG PET-CT to diagnose distant metastases (test and treat question), or the diagnostic accuracy of FDG PET-CT for detecting metastases in people who are suspected of having metastatic breast cancer. The diagnostic accuracy question was to be completed only if no test and treat evidence was identified. The clinical and cost effectiveness of the same tests for monitoring response to treatment is covered in review B2.

### 1.1.2 Summary of the protocol

**Table 1: PICOS inclusion criteria (test and treat review question)**

| | |
|---|---|
| **Population** | Adults (18 and over) with invasive adenocarcinoma of the breast who have suspected distant metastases (M1). |

| | |
|---|---|
| **Index Test** | • Fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) [FDG PET-CT] followed by management of the metastases based on the results of the test<br><br>Exclusion:<br>• FDG PET-CT used for screening<br>• Imaging analysed using artificial intelligence (AI)<br>• Imaging covering less than chest (or neck or thorax), abdomen and pelvis. |
| **Comparator** | • Contrast-enhanced Computed Tomography (CECT) scan<br>• Contrast-enhanced Computed Tomography (CECT) scan, with bone scintigraphy<br>Both comparators will be followed by management of the metastases based on the results of the test.<br><br>Exclusion:<br>• CECT used for screening<br>• Imaging analysed using artificial intelligence (AI)<br>• Imaging covering less than chest (or neck or thorax), abdomen and pelvis. |
| **Outcomes** | Critical outcomes:<br>• Overall survival (time to event data)<br>• Breast cancer-specific survival (time to event data or event data if time to event not available) – breast cancer mortality will be accepted if breast cancer-specific survival is not reported<br>Important outcomes:<br>• Quality of life (all validated measures including EQ-5D)<br>• Changes to management or treatment (event data), for example:<br>  ○ People who avoided treatments aimed at non-metastatic disease<br>  ○ People who started treatment for metastatic disease |
| **Study type** | • Test and treat RCTs<br>• Systematic reviews of test and treat RCTs |

AI: artificial intelligence; CECT: contrast enhanced computed tomography; CT: computed tomography; FDG: fluorodeoxyglucose; PET: positron emission tomography; RCT: randomised controlled trial

## Table 2: PICTOS inclusion criteria (Diagnostic Test accuracy [DTA] review question)

| | |
|---|---|
| **Population** | 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]<br>• Contrast-enhanced Computed Tomography (CECT) scan<br>• Contrast-enhanced Computed Tomography (CECT) scan, with bone scintigraphy |

| | |
|---|---|
| | Exclusion:<br>• FDG PET-CT used for screening<br>• Imaging analysed using artificial intelligence (AI)<br>• Imaging covering less than chest (or neck or thorax), abdomen and pelvis. |
| **Comparator (reference standard)** | • Histopathology from surgery or biopsy confirming metastasis<br>• Clinical follow-up involving expert decision making with support of imaging (other than the index tests alone) and / or histological data. |
| **Target condition** | Presence of any distant metastases, 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. |
| **Outcomes** | • Sensitivity and specificity<br>• Positive and negative likelihood ratios |
| **Study type** | • Diagnostic accuracy cross-sectional studies and cohort studies.<br>• Systematic reviews of diagnostic accuracy cross-sectional or cohort studies.<br>• Where there are no cross-sectional or cohort studies identified, case-control studies will be included. |

AI: artificial intelligence; CECT: contrast enhanced computed tomography; CT: computed tomography; FDG: fluorodeoxyglucose; PET: positron emission tomography

For the full protocols see appendix A.

### 1.1.3 Methods and process

These evidence reviews were developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to the review questions are described in the review protocols in appendix A, in the methods chapter, and below.

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

**Review question 2 additional methods**

The following methods were specific to the DTA review question:

1. Completing review question 2 was contingent on no studies being identified for inclusion in review question 1. No studies were identified for review question 1.
2. Two systematic reviews (Shen et al., 2025, Xia et al., 2023) were used as sources of evidence for this evidence review. Both systematic reviews were assessed as high risk of bias using the ROBIS tool. Usually, only systematic reviews rated low or moderate risk of bias are considered for use as a source of data. However, the main reasons for the high-risk judgements related to the reviews reporting insufficient information to fully assess the appropriateness of included studies or the screening process, and not reporting risk of bias separately for each study included. Both reviews had published protocols on PROSPERO, which did not include full protocol details. These sources of bias were largely mitigated by independently assessing the individual included studies for inclusion in the NICE review, and conducting risk of bias assessment for each of the studies taken from the systematic reviews. The results were also re-analysed for this review.

3. Fifteen of the studies included by Shen et al., 2025 reporting on the diagnostic accuracy of FDG PET-CT in detecting distant metastases in people with breast cancer met our inclusion criteria. Seven of the studies included by Xia et al., 2023 reporting on the diagnostic accuracy of FDG PET-CT in detecting bone metastasis in people with breast cancer met our inclusion criteria. Two of these studies were already included in Shen et al., 2025 and therefore, 5 additional studies were included from Xia et al., 2023 in this review (see Table 1 and Table 2 for our inclusion criteria and Table 3 and Table 4 for the included studies in our review).
4. Primary studies published after the search date of the systematic reviews, and studies reporting on the accuracy of contrast-enhanced CT (CECT) which were not included in either of the systematic reviews (Shen et al., 2025 and Xia et al., 2023), were included in this review. Primary studies included in the systematic reviews (Shen et al., 2025 and Xia et al., 2023) were checked for index tests and target conditions relevant to this review that were not reported in the respective systematic reviews, and any additional relevant data was extracted.
5. Risk of bias assessment in the included systematic reviews was not reported separately for each study. Therefore, risk of bias assessment was conducted by NICE both for studies included in the systematic reviews, and for all additional studies identified.
6. Data for 'distant metastases' was used in analysis where reported. For studies not reporting distant metastases, all site-specific metastasis reported within the study, such as bone or lung metastasis, were included in the analysis of 'any distant metastases' as separate target conditions. Where a study reported on both 'distant metastases' and site-specific metastasis, only the 'distant metastases' data was included in the analysis for 'any distant metastases' and the site-specific metastases data reported was included in the subgroup analysis for the respective sites. Visceral metastases include metastases to all non-bone sites, including lung, liver, lymph nodes and pleura.
7. Sensitivity analysis was conducted for studies reporting on 'distant metastases' only, in order to see if removing data for site-specific metastases changed the results. This sensitivity analysis was reported as whole-body distant metastases.
8. Two clinical decision thresholds were set a priori for sensitivity and specificity individually. The upper threshold is the value above which a test would be recommended, and the lower threshold is the value below which a test would be considered of no clinical use. The upper and lower thresholds for sensitivity were set at 90% and 70% respectively. The upper and lower thresholds for specificity were set at 80% and 60% respectively. These values were used to judge imprecision in GRADE, and also as an indicator of the usefulness of the test for the population of interest, and at this particular point in the pathway. Confidence intervals were downgraded once if one clinical decision-making threshold was crossed or twice if both thresholds were crossed.
9. Subgroup analyses were not carried out (apart from location of metastasis) because the included studies did not report data in a format that could be used to carry out these analyses. One study included participants with inflammatory breast cancer, but it is not possible to carry out a subgroup analysis of a single study. This study has been highlighted as a note in the forest plots in appendix E.

#### 1.1.3.1 Search methods

The searches for clinical effectiveness evidence were run on 21st May 2025. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL)

(Wiley); Cochrane Database of Systematic Reviews (CDSR); Embase (Ovid); Epistemonikos (web platform); Medline ALL (Ovid).

Limits were applied to remove: animal studies; editorials; letters; news items; commentaries; conference abstracts; conference posters; clinical trial registry records; theses; dissertations; non-English language publications and references published before 2005.

The searches for the cost effectiveness evidence were run between 22nd May 2025 and 28th May 2025. The following databases were searched: Embase (Ovid); International Health Technology Assessment Database (INAHTA) and Medline ALL (Ovid).

Limits were applied to remove: animal studies; editorials; letters; news items; commentaries; conference abstracts; conference posters; clinical trial registry records; theses; dissertations; non-English language publications and references published before 2005. A range of previously validated search filters were used to narrow the searches down to cost effectiveness-related studies.

Reference lists of included studies and relevant systematic reviews were also checked, and any additional, relevant papers were added to the respective reviews.

A NICE senior information specialist (SIS) conducted the database searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in appendix B.

#### 1.1.3.2 Protocol deviations

Subgroup analysis was planned to separate results for people with lobular breast cancer from all other results. There was insufficient data in the lobular breast cancer category to conduct a subgroup analysis as there was only one study included. The committee agreed that seeing the overall results was not useful and preferred to see data for lobular breast cancer separately to aid decision making. Therefore, the analyses were stratified to separate out results for lobular breast cancer from results for mixed population (‘mixed population’ includes studies which did not limit to specific types of breast cancer, and studies which limited to specific types of breast cancer other than lobular breast cancer).

### 1.1.4 Effectiveness and diagnostic evidence

#### 1.1.4.1 Included studies

A single search was carried out for both review questions. A systematic search carried out to identify potentially relevant studies found 6,955 references (see appendix B for the literature search strategy).

These 6,955 references were screened at title and abstract level against the review protocol, with 6,847 excluded at this level. 10% of references were screened separately by two reviewers with 99.6% agreement. Discrepancies were resolved by discussion.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

**Review question 1**

The full text of 1 randomised controlled trial was ordered for closer inspection. No studies were identified that met the criteria specified in the review protocol for the test and treat review (appendix A).

**Review question 2**

The full texts of 16 systematic reviews and 91 other articles (107 articles in total) were ordered for closer inspection. Two systematic reviews (Shen et al., 2025, Xia et al., 2023) and 8 cohort studies (2 prospective and 6 retrospective) met the criteria specified in the review protocol for the DTA review (appendix A). Fifteen studies from Shen et al., (2025) and 5 unique studies from Xia et al. (2023) were also included, totalling 28 cohort studies.

All studies assessing accuracy of FDG PET-CT looked at 18F FDG PET-CT. Twenty-seven studies presented results about PET-CT, one of which included only people with lobular breast cancer (Usmani et al., 2024). Five studies presented results about contrast-enhanced CT, none of which limited to people with lobular breast cancer.

For a summary of the included studies see Table 3 and Table 4.

The study selection process is presented as a PRISMA in appendix C.

See section 1.1.13 References – included studies for the full references of the included studies.

### 1.1.4.2 Excluded studies

Details of studies excluded at full text for both review questions, along with reasons for exclusion are given in appendix J.

### 1.1.5 Summary of studies included in the diagnostic evidence

**Review question 1**

No evidence was identified that met the inclusion criteria for this review.

**Review question 2**

### Table 3 Summary of the systematic reviews included in the diagnostic evidence

| Author (year) | Primary studies from the systematic review included in the NICE review | Population covered by the systematic review | Index test assessed in systematic review that is of interest in the NICE review | Reference Standard | Target condition | Risk of bias/ Applicability of the systematic review |
|---|---|---|---|---|---|---|
| Shen et al., 2025 | • Abo-Sheisha et al., 2014<br>• Aukema et al., 2010<br>• Carkaci et al., 2009<br>• Choi et al., 2012<br>• Gajjala et al., 2018<br>• Garg et al., 2016<br>• Goktas et al., 2018<br>• Ko et al., 2020<br>• Koolen et al., 2012<br>• Krammer et al., 2015<br>• Manohar et al., 2013<br>• Melsaether et al., 2016*<br>• Niikura et al., 2011* | **Inclusion criteria**<br>• Studies assessing the diagnostic efficacy of [18F] FDG PET-CT and/or [18F] FDG PET-MRI in detecting distant metastases in breast cancer patients<br>• Studies including over 10 participants<br><br>**Exclusion criteria** | • [18F] FDG PET-CT | • Pathology<br>• Imaging follow-up | Any distant metastases | High<br><br>Fully applicable |

| Author (year) | Primary studies from the systematic review included in the NICE review | Population covered by the systematic review | Index test assessed in systematic review that is of interest in the NICE review | Reference Standard | Target condition | Risk of bias/ Applicability of the systematic review |
|---|---|---|---|---|---|---|
| | • Reigger et al., 2012<br>• Vogsen et al., 2021b | • Studies using other different radiotracers, or PET without CT or MRI | | | | |
| Xia et al., 2023 | • Melsaether et al., 2016*<br>• Niikura et al., 2011*<br>• Catalano et al., 2015<br>• Balci et al., 2012<br>• Manohar et al., 2012<br>• Rager et al., 2018<br>• Shawky et al., 2020 | **Inclusion criteria**<br>• Studies evaluating the diagnostic performance of [18F] FDG PET-CT and/or [18F] FDG PET-MRI in detecting bone metastases in breast cancer patients<br>• Studies including over 10 participants<br><br>**Exclusion criteria**<br>• Studies using other different radiotracers, or PET without CT or MRI | • [18F] FDG PET-CT | • Pathology<br>• Imaging follow-up | Bone metastasis | High<br><br>Partially applicable |

[18F] FDG PET-CT: 18F-Fluorodeoxyglucosepositron emission tomography computed tomography; CT: computed tomography PET: positron emission tomography; MRI: magnetic resonance imaging

*Note: These studies were included in both systematic reviews using the same data. Data from these studies were only extracted and analysed once.

Study characteristics were extracted from the primary studies included in the systematic reviews except the reference standard for Yilmaz et al., 2019 which was not clearly stated in the primary study and was taken from the systematic review (Shen et al., 2025). Table 4 displays study characteristics for all 29 included cohort studies.

**Table 4 Summary of studies included in the diagnostic evidence**

| Study details | Location/Funding | Population | Index test | Reference standard | Target condition | Risk of bias |
|---|---|---|---|---|---|---|
| Abd-Elkader et al., 2020<br><br>Retrospective study<br><br>N = 71 | Egypt<br><br>Not financially supported by any institute | Women with pathologically proved breast cancer referred for FDG PET-CT examination | • FDG PET-CT (brain to mid-thigh)<br>• CECT (brain to mid-thigh) | • Combination of clinical and radiological follow-up | • Bone metastasis<br>• Hepatic metastasis | High |
| Abo-Sheisha et al., 2014<br><br>Retrospective study<br><br>N = 50 | Egypt<br><br>Funding not reported | Women with a history of breast cancer with high clinical suspicion (sign or symptoms) of recurrence or distant metastases | • FDG -PET-CT (from the skull base to pelvis) | • Histopathology results from biopsy<br>• Clinical and imaging follow-up (regular history, physical examination and mammography) | Distant metastases or recurrence | Moderate |
| Aukema et al., 2010<br><br>Retrospective study<br><br>N = 56 | Netherlands<br><br>Funding not reported | Patients with a confirmed locoregional breast cancer recurrence | • FDG PET-CT (whole body) | • Histopathological findings from biopsy (fine needle aspiration or core needle biopsy)<br>• Imaging and/or clinical follow-up | Distant metastases | Moderate |

| Study details | Location/Funding | Population | Index test | Reference standard | Target condition | Risk of bias |
|---|---|---|---|---|---|---|
| Balci et al., 2012<br><br>Retrospective cohort<br><br>N = 162 | Turkey<br><br>Funding not reported | Breast cancer patients | • FDG PET-CT (skull to mid-thigh) | • Clinical or imaging follow-up (no additional information reported) | Bone metastasis | Moderate |
| Bruckmann et al., 2021<br><br>Prospective study<br><br>N = 154 | Germany<br><br>The study was funded by Deutsche Forschungsgemeinschaft, the German Research Foundation (BU3075/2-1) | Women with newly diagnosed, treatment-naïve T2 or higher tumour, triple-negative tumour of every size or tumour with molecular high risk | • CECT (thoraco-abdominal; pelvic bones metastasis also reported) | • Histopathology or imaging follow-up | Bone metastasis | High |
| Carkaci et al., 2009<br><br>Retrospective study<br><br>N = 41 | USA<br><br>Funding not reported | Women who had been diagnosed with inflammatory breast cancer | • FDG PET-CT (from skull base to midthigh) | • Histopathological findings from biopsy<br>• Concurrent or subsequent imaging findings (CECT, CEMRI, sonography, or follow-up FDG PET-CT)<br>• Clinical follow-up | Distant metastases | High |
| Catalano et al., 2015<br><br>Retrospective cohort<br><br>N = 109 | Italy<br><br>No funding received but authors were consultants for Siemens Healthcare who had access to data and control of the information | Women with treated or untreated invasive breast cancer who had contrast enhanced FDG PET-CT and contrast enhanced FDG-PET-MRI on the same day | • FDG PET-CT (cranial vault to mid-thighs) | • Correlations with prior imaging and follow-up studies | Bone metastasis | Moderate |

| Study details | Location/Funding | Population | Index test | Reference standard | Target condition | Risk of bias |
|---|---|---|---|---|---|---|
| Choi et al., 2012<br><br>Retrospective study<br><br>N = 154 | Korea<br><br>Funding not reported | Consecutive patients with newly diagnosed invasive breast cancer | • FDG PET-CT (whole body) | • Histopathological findings from biopsy (core needle)<br>• Imaging and/or clinical follow-up | Distant metastases | Moderate |
| Dirisamer et al., 2010<br><br>Retrospective study<br><br>N = 52 | Austria<br><br>Funding not reported | Patients with suspected breast cancer recurrence free of metastases after first line of treatment | • FDG PET-CT (skull base to the femur)<br>• CECT (head to the symphysis) | • Combination of histological verification from biopsy and follow-up examinations | • Distant metastases<br>• Pulmonary metastasis | High |
| Evangelista et al., 2012<br><br>Retrospective study<br><br>N = 29 | Italy<br><br>Funding not reported | Consecutive breast cancer patients referred to perform FDG PET-CT for the evaluation of indeterminate solid lung nodules detected on previous CECT scans | • FDG PET-CT (whole body) | • Histopathology<br>• Imaging follow-up | Lung metastasis | Moderate |
| Gajjala et al., 2018<br><br>Prospective cohort<br><br>N = 61 | India<br><br>Funding not reported | Consecutive female patients with biopsy-proved newly diagnosed Locally advanced breast cancer, presenting to surgical, medical | • FDG PET-CT (whole body) | • Histopathological findings from biopsy<br>• MRI of the spine | • Distant metastases<br>• Site-specific metastasis (lung, | Moderate |

| Study details | Location/Funding | Population | Index test | Reference standard | Target condition | Risk of bias |
|---|---|---|---|---|---|---|
| | | or radiation oncology departments | | | bone, liver, brain) | |
| Garg et al., 2016<br><br>Prospective cohort<br><br>N = 79 | India<br><br>Funding not reported | Consecutive female patients with locally advanced invasive breast cancer | • FDG PET-CT (whole body) | • Histopathological findings from biopsy<br>• MRI for confirmation on skeletal metastasis | Distant metastases | Moderate |
| Göktas et al., 2018<br><br>Retrospective cohort<br><br>N = 77 | Turkey<br><br>Funding not reported | Patients followed up for breast cancer with suspicion of recurrence based on elevated serum levels | • FDG PET-CT (from skull base to midthigh) | • Histopathological findings from biopsy<br>• Radiological follow-up (mammography, US, CT or MRI within 6 months of FDG PET-CT scan) | Distant recurrence | Moderate |
| Groheux et al., 2014<br><br>Retrospective study<br><br>N = 14 | France<br><br>No funding received | Male patients with breast cancer referred for 18F-FDG PET-CT imaging | • FDG PET-CT (mid-thigh level to the base of the skull) | • Histopathology<br>• Clinical follow-up | • Distant metastases<br>• Bone metastasis<br>• Visceral metastasis | Moderate |
| Ko et al., 2020<br><br>Retrospective cohort<br><br>N = 195 | USA<br><br>Funding not reported | Women with newly diagnosed breast cancer who underwent FDG PET-CT within 4 months of their diagnosis | • FDG PET-CT (from skull base to midthigh) | • Histopathological findings from biopsy<br>• Imaging follow-up (MRI or CT) | Distant metastases | Moderate |

| Study details | Location/Funding | Population | Index test | Reference standard | Target condition | Risk of bias |
|---|---|---|---|---|---|---|
| Koolen et al., 2011<br><br>Prospective cohort<br><br>N = 167 | Netherlands<br><br>Funding not reported | Women with invasive breast cancer >3 cm in diameter and/or at least one tumour-positive axillary lymph node | • FDG PET-CT (whole body) | • Cytology or histological findings<br>• Additional imaging<br>• Prolonged follow-up | Distant metastases | High |
| Krammer et al., 2015<br><br>Prospective study<br><br>N = 101 | Germany<br><br>No funding was received | Women with clinical tumour stage ≥T2 or positive lymph nodes were included preoperatively. Clinical node negative patients with stage T1 tumours were included postoperatively, if following SLNB, they were positive for malignant cells. | • FDG PET-CT (whole body) | • Follow-up (medical records were checked after 1 year for occurrence of distant metastases) | Distant metastases | Moderate |
| Lee et al., 2015<br><br>Retrospective study<br><br>N = 64 | Korea<br><br>Funding not reported | Patients with breast cancer who had undergone surgery | • FDG PET-CT (skull vertex to the knee level) | • Pathological confirmation from biopsy | Supraclavicular lymph node metastasis | High |

| Study details | Location/Funding | Population | Index test | Reference standard | Target condition | Risk of bias |
|---|---|---|---|---|---|---|
| Manohar et al., 2012<br><br>Retrospective cohort<br><br>N = 111 | India<br><br>Funding not reported | Women suspected of recurrent breast carcinoma and underwent F-18 FDG PET-CT | • FDG PET-CT (skull base to mid-thigh) | • Histopathological analysis (40 patients)<br>• Correlative imaging (10 patients)<br>• Clinical follow-up (21 patients)<br>• Imaging follow-up (40 patients) | • Distant metastases<br>• Bone metastasis | Moderate |
| Manohar et al., 2013<br><br>Prospective study<br><br>N = 43 | India<br><br>Funding not reported | Women with biopsy-proven locally advanced breast cancer who were negative for distant metastases on conventional imaging | • FDG PET-CT (vertex to mid-thigh) | • Histopathology or clinical or imaging follow-up at 6 months | Distant metastases | Moderate |
| Melsaether et al., 2016<br><br>Prospective study<br><br>N = 242 | USA<br><br>Funding not reported | Patients with a breast cancer diagnosis who were scheduled for clinical FDG PET-CT | • FDG PET-CT (vertex to the thighs or skull base to the thighs) | • Imaging and clinical follow-up | • Distant metastases<br>• Site-specific metastasis (liver, lung, pleura, distant lymph node, bone) | Moderate |
| Niikura et al., 2011 | USA | Patients with breast cancer for whom reports of FDG | • FDG PET-CT (vertex or base of the | • Histopathologic findings or subsequent imaging findings | Distant metastases | Low |

| Study details | Location/Funding | Population | Index test | Reference standard | Target condition | Risk of bias |
|---|---|---|---|---|---|---|
| Retrospective study<br><br>N = 225 | Research supported by the National Institutes of Health and by the Nellie B. Connally Breast Cancer Research Fund | PET-CT scans ordered for staging of primary breast cancer were available | skull to the midthigh, calf, or toes) | or clinical follow-up at 2 years | | |
| Rager et al., 2018<br><br>Retrospective cohort<br><br>N = 25 | Switzerland<br><br>Funding not reported | Women with biopsy-proven breast cancer referred for routine clinical work-up with whole-body SPECT-CT and FDG PET-CT within 90 days | • FDG PET-CT (vertex to proximal thigh) | • Follow-up imaging (including CT, MRI and a subsequent PET or subsequent scintigraphy with or without SPECT-CT) | Bone metastasis | Moderate |
| Riegger et al., 2012<br><br>Retrospective study<br><br>N = 106 | Germany<br><br>Funding not reported | Women with newly diagnosed breast cancer referred for whole-body FDG PET-CT staging | • FDG PET-CT (whole body) | • Histopathology, cross-sectional imaging follow-up, or clinical follow-up | Distant metastases | Low |
| Shawky et al., 2020<br><br>Prospective cohort<br><br>N = 30 | Egypt<br><br>No funding received | Women with pathologically proven breast cancer who had started treatment and underwent PET-CT and CECT to assess for metastasis or recurrence | • FDG PET-CT (skull base to mid-thigh)<br>• CECT (skull base to mid-thigh) | • Histopathological analysis<br>• Clinical and imaging follow-up | • Distant metastases<br>• Bone metastasis | Moderate |

| Study details | Location/Funding | Population | Index test | Reference standard | Target condition | Risk of bias |
|---|---|---|---|---|---|---|
| Usmani et al., 2024<br><br>Retrospective cohort<br><br>N = 21 | Oman<br><br>Funding not reported | Patients with histopathological diagnosis of invasive lobular carcinoma which underwent 18F-FDG PET-CT imaging | • FDG PET-CT (whole body) | • Clinical follow-up | Bone metastasis | Moderate |
| Vogsen et al., 2021a<br><br>Prospective study<br><br>N = 225 | Denmark<br><br>Study was funded by independent and university grants | Women 18 years or older who had a prior diagnosis of early-stage breast cancer | • FDG PET-CT (top skull to mid-thigh)<br>• CECT (scan field-of-view of 70 cm) | • Histopathology or imaging follow-up | Distant metastases | Moderate for FDG PET-CT<br>High for CECT |
| Vogsen et al., 2021b<br><br>Prospective study<br><br>N = 103 | Denmark<br><br>Work was supported by grants to authors, The Independent Research Fund Denmark, University of Southern Denmark, Odense University Hospital, and the Centre for Personalised Response Monitoring in Oncology | Women older than 18 years with biopsy-verified primary breast cancer at high risk of metastatic spread | • FDG PET-CT (top skull to mid-thigh) | • Biopsy or 6 months of follow-up | Distant metastases | Moderate |

FDG PET-CT: 18F-Fluorodeoxyglucose positron emission tomography computed tomography; CECT: contrast enhanced computer tomography; CEMRI: contrast enhanced magnetic resonance imaging; MRI: magnetic resonance imaging; PET: position-emission tomography; SLNB: sentinel lymph node biopsy; SPECT: single-photon emission computed tomography; US: ultrasonography

### 1.1.6 Summary of the diagnostic evidence

**Review question 1**

No studies were identified that met the inclusion criteria for this review.

**Review question 2**

The interpretation for the diagnostic ability of each index test was based on the agreed clinical decision making thresholds for sensitivity (70% and 90%) and specificity (60% and 80%). Sensitivity and specificity were rated as high, moderate or low based on the following:

- High: Point estimate is greater than or equal to the upper clinical decision making threshold (≥90% for sensitivity and ≥80% for specificity).
- Moderate: Point estimate greater than or equal to the lower clinical decision making threshold but lower than the upper clinical decision making threshold (≥70% to <90% for sensitivity and ≥60% to <80% for specificity).
- Low: Point estimate is less than the lower clinical decision making threshold (<70% for sensitivity and <60% for specificity).

Sensitivity is the proportion of those with the target condition who test positive, Specificity is the proportion of those without the target condition who test negative. A test with high sensitivity will classify more people as having the disease, thereby being good at ruling out the condition in people with a negative test result. A test with high specificity will classify fewer people as having the disease, thereby being good at ruling in the condition in people with a positive test result.

Where an analysis only contained 2 studies, regardless of whether the data converged in MetaDTA, meta-analysis was not completed because a minimum of 3 studies is needed to estimate the parameters needed for bivariate meta-analysis.

### Summary of diagnostic evidence for FDG PET-CT (mixed population)

Mixed population analyses include all studies other than those which include only participants with lobular breast cancer.

### Table 5: Summary of findings for diagnostic accuracy of FDG PET-CT for detecting any distant metastases (mixed population)

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 26* | Diagnostic accuracy (presence of any distant metastases or not) | 4923 (2513 counting multiple interpretation studies only once) | Sensitivity 0.95 (0.93, 0.97) | VERY LOW | High sensitivity. Test will rule out 5% of people who have the condition |
| | | | Specificity 0.98 (0.97, 0.99) | LOW | High specificity. Test will rule in 2% of people who do not have the condition |

CI: confidence interval; FDG PET-CT: Fluorodeoxyglucose positron emission tomography computed tomography

*Note: 26 studies were included in this analysis. This analysis includes whole-body distant metastases or any site-specific distant metastases where whole-body distant metastases was not reported. Of these 26 studies, some contributed multiple results: 1 study reported on 3 metastatic sites, 1 study reported on 4 metastatic sites and 1 study reported on 5 metastatic sites from 2 different interpreters.

Reasons for downgrading can be found in the full GRADE tables in appendix F.

### Table 6: Summary of findings for diagnostic accuracy of FDG PET-CT for detecting whole-body distant metastases only (mixed population) (sensitivity analysis)

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|
| 18 | Diagnostic accuracy (presence of whole-body distant metastases or not) | 1789 | Sensitivity 0.97 (0.94, 0.99) | MODERATE | High sensitivity. Test will rule out 3% of people who have the condition |
| | | | Specificity 0.95 (0.93, 0.97) | MODERATE | High specificity. Test will rule in 5% of people who do not have the condition |

CI: confidence interval; FDG PET-CT: Fluorodeoxyglucose positron emission tomography computed tomography

Reasons for downgrading can be found in the full GRADE tables in appendix F.

### Table 7: Summary of findings for diagnostic accuracy of FDG PET-CT for detecting any distant metastases in studies assessing both PET-CT and CECT (mixed population) (sensitivity analysis)

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 4 | Diagnostic accuracy (presence of any distant metastases or not) | 488 (256 counting multiple interpretation studies only once) | Sensitivity 0.96 (0.91, 0.99) | VERY LOW | High sensitivity. Test will rule out 4% of people who have the condition |
| | | | Specificity 1.00 (0.24, 1.00) | VERY LOW | High specificity. Test will rule in 0% of people who do not have the condition |

CI: confidence interval; FDG PET-CT: Fluorodeoxyglucose positron emission tomography computed tomography

Reasons for downgrading can be found in the full GRADE tables in appendix F.

*Note: 4 studies were included in this analysis. This analysis includes whole-body distant metastases or any site-specific distant metastases where whole-body distant metastases was not reported. Of these 4 studies, some contributed multiple results: 1 study reported on 3 metastatic sites and 1 study reported on 4 metastatic sites.

### Table 8: Summary of findings for diagnostic accuracy of FDG PET-CT for detecting bone metastasis (mixed population)

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|
| 8* | Diagnostic accuracy (presence of bone metastasis or not) | 1001 | Sensitivity 0.93 (0.88, 0.96) | VERY LOW | High sensitivity. Test will rule out 7% of people who have the condition |
| | | | Specificity 1.00 (0.97, 1.00) | LOW | High specificity. Test will rule in 0% of people who do not have the condition |

CI: confidence interval; FDG PET-CT: Fluorodeoxyglucose positron emission tomography computed tomography

Reasons for downgrading can be found in the full GRADE tables in appendix F.

*Note: 8 studies were included in this analysis. Of these 8 studies: 1 reported sclerotic bone metastasis and lytic bone metastasis separately, and 1 study reported results from 2 interpreters.

### Table 9: Summary of findings for diagnostic accuracy of FDG PET-CT for detecting visceral metastasis (mixed population)

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 7* | Diagnostic accuracy (presence of any visceral metastasis or not) | 2248 | Sensitivity 0.91 (0.83, 0.96) | VERY LOW | High sensitivity. Test will rule out 9% of people who have the condition |
| | | | Specificity 1.00 (0.95, 1.00) | LOW | High specificity. Test will rule in 0% of people who do not have the condition |

CI: confidence interval; FDG PET-CT: Fluorodeoxyglucose positron emission tomography computed tomography

Reasons for downgrading can be found in the full GRADE tables in appendix F.

*Note: 7 studies were included in this analysis. Of these 7 studies: 1 reported on 3 metastatic sites, and 1 reported on 4 metastatic sites from 2 different interpreters.

### Summary of diagnostic evidence for FDG PET-CT (lobular breast cancer only)

### Table 10: Summary of findings for diagnostic accuracy of FDG PET-CT for detecting bone metastases (lobular breast cancer only)

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|
| 1 | Diagnostic accuracy (presence of bone metastases) | 21 | Sensitivity 0.33 (0.10, 0.70) | VERY LOW | Low sensitivity. Test will rule out 67% of people who have the condition |
| | | | Specificity 0.93 (0.70, 0.99) | VERY LOW | High specificity. Test will rule in 7% of people who do not have the condition |

CI: confidence interval; FDG PET-CT: Fluorodeoxyglucose positron emission tomography computed tomography

Reasons for downgrading can be found in the full GRADE tables in appendix F.

### Summary of diagnostic evidence for CECT

All studies and analyses for CECT are mixed population. Mixed population analyses include all studies other than those which include only participants with lobular breast cancer.

### Table 11: Summary of findings for diagnostic accuracy of CECT for detecting any distant metastases

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|
| 5* | Diagnostic accuracy (presence of any distant metastases or not) | 532 | Sensitivity 0.80 (0.65, 0.89) | VERY LOW | Moderate sensitivity. Test will rule out 20% of people who have the condition |
| | | | Specificity 0.96 (0.89, 0.98) | LOW | High specificity. Test will rule in 4% of people who do not have the condition |

CECT: contrast enhanced computer tomography; CI: confidence interval

Reasons for downgrading can be found in the full GRADE tables in appendix F.

*Note: 5 studies were included in this analysis. Of these 5 studies: 1 reported 3 metastatic sites, and 1 reported 4 metastatic sites.

### Table 12: Summary of findings for diagnostic accuracy of CECT for detecting whole-body distant metastases only (sensitivity analysis)

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|
| 2* | Diagnostic accuracy (presence of whole-body distant metastases or not) | 277 | Sensitivity 0.67 to 0.96 [0.67 (0.52, 0.79) and 0.96 (0.87, 0.99)] | VERY LOW | Low to high sensitivity. Test will rule out 4% to 33% of people who have the condition |
| | | | Specificity 0.88 to 1.00 [1.00 (0.72, 1.00) and 0.88 (0.82, 0.92)] | VERY LOW | High specificity. Test will rule in 0% to 12% of people who do not have the condition |

CECT: contrast enhanced computer tomography; CI: confidence interval

Reasons for downgrading can be found in the full GRADE tables in appendix F.

*Note: A bivariate meta-analysis could not be conducted due to the low number of studies, so the range has been presented for the effect estimates.

### Table 13: Summary of findings for diagnostic accuracy of CECT for detecting whole-body distant metastases in studies that assessed both PET-CT and CECT (sensitivity analysis)

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|
| 4 | Diagnostic accuracy (presence of any distant metastases or not) | 488 (256 counting multiple interpretation studies only once) | Sensitivity 0.81 (0.64, 0.91) | VERY LOW | Moderate sensitivity. Test will rule out 19% of people who have the condition |
| | | | Specificity 0.95 (0.87, 0.99) | LOW | High specificity. Test will rule in 5% of people who do not have the condition |

CECT: contrast enhanced computer tomography; CI: confidence interval

Reasons for downgrading can be found in the full GRADE tables in appendix F.

*Note: 4 studies were included in this analysis. This analysis includes whole-body distant metastases or any site-specific distant metastases where whole-body distant metastases was not reported. Of these 4 studies, some contributed multiple results: 1 study reported on 3 metastatic sites and 1 study reported on 4 metastatic sites.

### Table 14: Summary of findings for diagnostic accuracy of CECT in detecting bone metastasis

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|
| 3* | Diagnostic accuracy (presence of bone metastasis or not) | 255 | Sensitivity 0.83 (0.63, 0.93) | VERY LOW | Moderate sensitivity. Test will rule out 17% of people who have the condition |
| | | | Specificity 0.99 (0.95, 0.99) | VERY LOW | High specificity. Test will rule in 1% of people who do not have the condition |

CECT: contrast enhanced computer tomography; CI: confidence interval

Reasons for downgrading can be found in the full GRADE tables in appendix F.

*Note: Includes 1 study that reported sclerotic bone metastasis and lytic bone metastasis separately.

**Table 15: Summary of findings for diagnostic accuracy of CECT in detecting visceral metastasis**

| Number of studies | Outcome | Sample size | Effect estimate (95% CI) | Certainty | Interpretation of diagnostic ability using the point estimate |
|---|---|---|---|---|---|
| 3* | Diagnostic accuracy (presence of any visceral metastasis or not) | 153 | Sensitivity 0.76 (0.44, 0.92) | VERY LOW | Moderate sensitivity. Test will rule out 24% of people who have the condition |
| | | | Specificity 0.93 (0.80, 0.98) | VERY LOW | High specificity. Test will rule in 7% of people who do not have the condition |

CECT: contrast enhanced computer tomography; CI: confidence interval

Reasons for downgrading can be found in the full GRADE tables in appendix F.

*Note: Includes 1 study reporting on 3 metastatic sites.

See appendix F for full GRADE tables.

### 1.1.7 Economic evidence

#### 1.1.7.1 Included studies

A separate search was performed for each review question to identify published economic evaluations of relevance to the review questions. See the literature search strategy in appendix B.

One economic study was identified which was applicable to this review question B1. (see economic study selection flow chart in appendix G).

One UK study compared conventional work-up (i.e. diagnostic package comprising ultrasound, radiography, CT, bone scintigraphy and measurement of serum tumour markers), PET, PET-CT and PET-CT as an adjunct to conventional work-up in people who had completed a course of treatment for primary breast cancer and were suspected of having a recurrence (Auguste 2011)

Characteristics of included economic studies are provided in the economic evidence study extraction tables in appendix H.

#### 1.1.7.2 Excluded studies

See appendix J for a list of excluded economic studies, with reason for exclusion.

### 1.1.8 Summary of included economic evidence

**Table 16: Summary of characteristics of included economic studies**

| Study details | Study design and type of analysis | Population | Interventions and comparators | Perspective | Primary outcome | Time horizon |
|---|---|---|---|---|---|---|
| Auguste 2011<br><br>UK | Cost-utility analysis<br><br>Decision tree model | People who had completed a course of treatment for primary breast cancer and undergoing diagnosis for distant recurrence. | Conventional work-up (i.e. diagnostic package comprising ultrasound, radiography, CECT, bone scintigraphy and measurement of serum tumour markers)<br><br>PET<br><br>PET-CT<br><br>PET-CT as an adjunct to conventional work-up. | UK NHS+PSS | QALY<br><br>Cost per case of recurrent cancer appropriately diagnosed and treated<br><br>Cost per diagnostic error avoided | 1 year |

Abbreviations: CECT: Contrast-enhanced computed tomography; ICER: Incremental cost-effectiveness ratio PET-CT: 2-deoxy-2-[$^{18}$F]fluoro-D-glucose PET/CT positron emission tomography with integrated computed tomography; Vs: Versus

See Table 17 for a summary of the economic evidence and appendix H for the economic evidence study extraction tables.

**Table 17: Economic evidence summary table: PET-CT versus conventional work-up, PET and PET-CT as an adjunct to conventional work-up in people with who had completed a course of treatment for primary breast cancer and were suspected of having a recurrence**

| Study | Applicability and limitations | Incremental cost[1] | Incremental effects | Cost effectiveness[1] | Uncertainty[1] | Economic evidence statement |
|---|---|---|---|---|---|---|
| Auguste 2011 | Directly applicable2<br>Potentially serious limitations3 | PET-CT + conventional work-up £1013 more costly than PET-CT alone.<br><br>PET £1942 more costly than conventional work-up.<br><br>PET-CT £747 more costly than PET alone. | PET-CT + conventional work-up gained of 0.0241 compared with PET-CT alone.<br><br>PET QALY gained of 0.0663 compared with conventional work-up.<br><br>PET-CT QALY gained of 0.0241 compared with PET alone. | ICERs<br><br>PET-CT + conventional work-up vs PET-CT<br><br>£42,100 per QALY<br><br>PET vs compared with conventional work-up:<br>£29,300 per QALY<br><br>PET-CT vs PET alone:<br>£31,000 per QALY | Deterministic analysis:<br>When the sensitivity of PET-CT was increased to a value of 97%, the ICER for PET-CT versus PET fell to £27,800 per QALY.<br><br>The specificity of PET-CT was increased to a value of 100%, and the ICER for PET-CT versus PET was estimated at £30,800 per QALY.<br><br>The cost of PET-CT with a reduction of £26, which had the effect of reducing the ICER for PET-CT versus PET to an estimated ICER of £29,900 per QALY.<br><br>The ICER for PET-CT versus conventional work-up of £29,700 per QALY.<br><br>Probabilistic analysis:<br>Under WTP £20k per QALY, conventional work-up has the | Compared to conventional work-up, PET was not cost-effective at £20,000 per QALY gained.<br>Compared to PET, PET-CT was not cost-effective at £20,000 per QALY gained<br>Compared to conventional work-up, PET-CT was not cost-effective at £20,000 per QALY gained.<br><br>For each additional diagnostic test that is added to PET, the more expensive the package becomes, but also the more effective it becomes in terms of QALYs gained. |

| Study | Applicability and limitations | Incremental cost[1] | Incremental effects | Cost effectiveness[1] | Uncertainty[1] | Economic evidence statement |
|---|---|---|---|---|---|---|
| | | | | | highest probability of being cost-effective.<br><br>When WTP >£40k per QALY, PET-CT + conventional work-up becomes the preferred strategy with a high probability of cost-effectiveness.<br><br>At WTP of £30k per QALY, there is considerable uncertainty regarding what would be considered the preferred strategy, and none of the strategies has over a 60% probability of being cost-effective.<br><br>Neither of the PET nor PET-CT strategies appear cost-effective at this threshold given the current model. | |

Abbreviations: CECT: Contrast-enhanced computed tomography; ICER: Incremental cost-effectiveness ratio PET-CT: 2-deoxy-2-[18F] fluoro-D-glucose PET-CT positron emission tomography with integrated computed tomography; QALY: Quality adjusted life-year; Vs: Versus; WTP: Willingness-to-pay

1. Other currencies were converted to pound sterling using IMF Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx.

2. Study takes a UK NHS and PSS perspective and reports outcomes in QALYs.

3. Time horizon for costs in the study too short to capture all differences in costs between interventions.

### 1.1.9 Economic model

The Economic model for the review questions 1 and 2 were informed by a combined economic model that reflects a realistic diagnostic and monitoring pathway used in clinical practice.

In the diagnostic phase, FDG PET-CT was consistently more costly than CECT in both cohorts (new diagnosis and previous diagnosis), but it delivered small QALY gains due to improved diagnostic accuracy and fewer misdiagnoses. The full details are provided in appendix I.

### 1.1.10 The committee's discussion and interpretation of the evidence

#### 1.1.10.1. The outcomes that matter most

**Review question 1**

The committee discussed the clinical outcomes from test and treat studies that would be particularly important for this review. These included overall survival, breast cancer-specific survival, quality of life and changes to management or treatment. These outcomes would provide information about the impact of FDG PET-CT compared with CECT on outcomes which are meaningful to people. The committee noted that an early and accurate diagnosis of metastasis will result in more appropriate treatment options that can control or slow the growth of the cancer and relieve symptoms. As a result, the committee agreed that the critical outcomes for this review were survival outcomes (overall survival and breast cancer specific survival). The other outcomes were considered important outcomes but were not considered critical to make decisions.

**Review question 2**

The committee agreed that diagnostic test accuracy outcome measures (sensitivity and specificity, and positive and negative likelihood ratios) were the relevant measures of the usefulness of the tests of interest for this review. Sensitivity and specificity as a paired measure were considered critical and provide information on how well the index test would accurately identify those with distant metastases and those without. Likelihood ratios were considered to be important, rather than critical, outcomes. Positive likelihood ratios provide information about how much more likely a positive test result is in someone with metastases, compared to someone without. Negative likelihood ratios provide information about how much less likely a negative test result is in someone with metastases, compared to someone without. Sensitivity and specificity were prioritised as the primary measure of interest for decision making.

The committee discussed the consequences of false positive and false negative results with imaging using FDG PET-CT and CECT. They noted that false positive results of the index test may lead to inappropriate management such as offering non-curative treatments to people with non-metastatic breast cancer and potentially missing the time when the cancer could be cured. False positive results will be reduced as a test increases in specificity.

A false negative result of the index test may mean that metastasis is overlooked, and that interventions for localised and locally advanced disease, such as surgery, are offered. The individual may also experience delays in accessing treatments for metastases, which could affect life expectancy. Unnecessary surgery, and potentially negative effects on a person's health from the side effects and consequences of the surgery, could be reduced with increased sensitivity for detecting metastases.

The committee agreed that, while both sensitivity and specificity were important, a high sensitivity would be required at this point in the pathway, and that reduction in false negatives was of particular importance.

#### 1.1.10.2 The certainty of the evidence

The evidence was rated as moderate to very low certainty for FDG PET-CT and low to very low for CECT, with most of the evidence being very low certainty. The evidence was assessed for risk of bias using the QUADAS-2 tool. The reasons for downgrading for risk of

bias were often due to insufficient information on how participants were selected into the study, and concerns around whether the interpreters of the reference standard test had knowledge of the index test results and vice versa. Evidence was downgraded for inconsistency if the point estimates for less than 80% of studies lay within the same range of test performance, determined by the pre-specified thresholds (less than 70%, 70% to less than 90% and 90% or more for sensitivity; less than 60%, 60% to less than 80% and 80% or more for specificity). The evidence was downgraded once if the point estimates were separated by 1 decision threshold and twice if the point estimates were separated by 2 decision thresholds. Downgrading for imprecision occurred when the confidence intervals crossed one or more decision making thresholds. For sensitivity, the thresholds were 0.70 and 0.90, for specificity, the thresholds were 0.60 and 0.80.

Some of the evidence was downgraded for indirectness because the participants in the included study did not fully represent the population in the protocol. The participants in 5 studies (Abd-Elkader et al., 2020, Gajjala et al., 2018, Garg et al., 2016, Melsaether et al., 2016, Rager et al., 2018) did not clearly state whether the participants were suspected of metastasis prior to the imaging test being completed.

Subgroup analysis was carried out for the location of distant metastases (bone or visceral) but was not possible for the other planned subgroups because the included studies did not report data for the subgroups of interest in a format that could be used to carry out these analyses. One study included participants with inflammatory breast cancer but it was not possible to carry out a subgroup analysis of a single study. This study has been highlighted as a note in the forest plots in appendix E. Sensitivity analysis was carried out where there was heterogeneity in the data to see if this changed the result, for example, excluding studies that reported site-specific metastases from the analysis of any distant metastases. Analysis was carried out separately for one study that had participants with lobular breast cancer only due to prior knowledge from the committee that from their experience, FDG PET-CT has poorer results in this population.

In current clinical practice, people who are offered FDG PET-CT may be different, on average, from people offered CECT. While CECT may be used as the first scan for detecting metastases, FDG PET-CT may be used as a secondary scan method if CECT is equivocal. If this practice was reflected in the included studies, FDG PET-CT might be disadvantaged by its use in more complex situations. The following was done to investigate whether this might be the case:

- Studies reporting results for both CECT and FDG PET-CT (n = 4) were assessed to see whether the same participants received each type of imaging at the same time (Table 18). Although there were some gaps in reporting, it appears that the same people were given both types of scan (meaning that the group who had PET-CT in these studies were not a separate, ‘difficult to diagnose’ group), and the scans are likely to have happened within the same period. However, this information does not necessarily apply to the rest of the included studies outside of these four.
- The results for studies reporting both CECT and FDG PET-CT (n = 4, see Figure 7, Figure 8 and Table 18) were presented separately for comparison with overall results. These results were consistent with the results of the main analyses pooling all the studies.
- When looking at the forest plots of the main analyses of all studies (see Figure 3 and Figure 4), and those for the 4 studies reporting results for both CECT and FDG PET-CT, the committee noted that there was very little difference in the results and the 4 studies

did not appear to be outliers, although they noted that this is not a statistical comparison and merely a 'sense check'.

- However, the studies which reported on PET-CT only (n = 23) may have represented a different group on average. The committee noted that if this was the case, the PET-CT studies were likely to represent people who were more difficult to diagnose (for whatever reason), which should bias against PET-CT results. Despite this, results of the analyses of all studies show, with moderate to very low certainty, that PET-CT may be more sensitive than, and have similar specificity to, CECT.

**Table 18: Comparison of the test timings in studies that assessed both FDG PET-CT and CECT**

| Study details | Population | Participant overlap | Relative timing of both scans |
|---|---|---|---|
| Abd-Elkader et al., 2020<br><br>N = 71 patients | Women with pathologically proved breast cancer referred for PET-CT examination | Same participants that underwent PET-CT had CECT (N = 71 for both tests) | CECT was carried out immediately after PET-CT |
| Dirisamer et al., 2010<br><br>N = 52 patients | Patients with suspected breast cancer recurrence free of metastases after first line of treatment. | Same participants that underwent PET-CT had CECT (N=52 for both tests) | Retrospective analysis of breast cancer patients' database. Insufficient information to determine when scans were performed in relation to each other. |
| Shawky et al., 2020<br><br>N = 30 women | Female patients with pathologically proven breast cancer who had started treatment and underwent PET-CT and CECT to assess for metastasis or recurrence | Same participants that underwent PET-CT had CECT (N = 30 for both tests) | PET-CT scans were immediately followed by volumetric contrast-enhanced CT scan using the same PET-CT machine. |
| Vogsen et al., 2021a<br><br>N = 225 women | Women 18 years or older who had a prior diagnosis of early-stage breast cancer | Same participants that underwent PET-CT had CECT (N = 225 for both tests) | PET-CT imaging was performed prospectively, while CECT scans were assessed retrospectively. Insufficient information to determine when scans were performed in relation to each other. |

### 1.1.10.3 Benefits and harms

The committee discussed the results of both review B1 and B2 together, and there is a single benefits and harms section to record this. See 2.1.10.3 Benefits and harms for the full discussion.

### 1.1.10.4 Cost effectiveness and resource use

One previous economic evaluation was identified for this review question. This was a cost-utility study comparing 4 strategies; conventional work-up (i.e. diagnostic package comprising ultrasound, radiography, CECT, bone scintigraphy and measurement of serum tumour markers), PET, PET-CT alone and PET-CT as an adjunct to conventional work-up in people who had completed a course of treatment for primary breast cancer and were suspected of having a recurrence.

The study concluded that FDG PET-CT either as an adjunct to conventional work-up or alone was not cost-effective at a threshold of £20k per QALY gained. This conclusion was robust to probabilistic and deterministic sensitivity analyses.

Although the study used a UK NHS perspective and reported outcomes in QALYs, its relevance to current practice was limited because the cost year was more than 15 years old and treatment for metastatic breast cancer has since changed substantially, with many more therapies now available.

The committee highlighted the short 1-year time horizon for costs which would exclude any costs or savings such as those from correct diagnosis in terms of optimisation of the treatment pathway. Although health outcomes in the model had a lifetime time horizon these only captured overall survival and did not capture any difference in quality of life from differences in treatment decisions. The committee also noted that the cost differential between CECT and PET-CT has reduced significantly. The published evaluation used a PET-CT cost of £1,236, whereas the NICE bespoke model applies the current NHS cost of £387. As the previous published study showed a substantial reduction in the ICER when PET-CT costs were lowered, this updated cost input is likely to influence the cost-effectiveness. It was also highlighted that the study also missed other important outcomes such as prevention of unnecessary surgery and anxiety from missed diagnoses.

Consequently, the committee gave little weight to this economic evaluation in coming to their recommendations.

A bespoke economic evaluation was undertaken by NICE considering FDG PET-CT and CECT as part of a longer pathway of diagnosis and monitoring consistent with the 2 review questions. This was a cost-utility study from the perspective of the UK NHS, reporting QALYs scored using the EQ-5D and took a lifetime horizon. Although the whole pathway was considered (taking account of the impact of initial diagnosis modality on modality decisions in monitoring) a separate analysis was undertaken looking at costs and QALYs up to the end of the diagnostic pathway. This was done because of the large amount of evidence around diagnosis and the limited evidence for monitoring. The diagnostic study included all imaging and biopsy costs and all costs associated with misdiagnosis (retesting, unnecessary treatment etc).

The model, based on the diagnostic test accuracy estimated in the accompanying clinical evidence review and using unit costs from NHS cost collection. The resource use was based on published clinical pathways within the NHS.

The base-case analysis showed that FDG PET-CT was above £20k per QALY for both de-novo and previously diagnosed populations. This result was sensitive to both the prevalence of advanced breast cancer in the imaged population and assumptions around anxiety related to misdiagnosis. Small increases in prevalence of the imaged population or higher disutilities

associated with misdiagnosis reduced the ICER to below £20k per additional QALY. The main driver of cost effectiveness for FDG PET-CT was the lower number of people having advanced breast cancer missed at diagnosis. This part of the model only covered diagnosis and did not capture additional benefits and costs over the lifetime of the populations considered.

PET-CT was cost increasing in all analyses and a wider recommendation for the use of PET-CT in imaging would likely lead to increased costs, however this could be justified by the additional QALYs gained.

The committee acknowledged that choice of diagnostic modality would likely impact upon monitoring modality. Recommending PET-CT means it is more likely that PET-CT will be used in monitoring for which the economic and clinical evidence is more uncertain. They also took into account variation nationally around the availability of PET-CT when recommending a choice between the two modalities. Based on these considerations the committee decided not to recommend one diagnostic imaging modality in preference to another.

### 1.1.11 Recommendations supported by this evidence review

This section applies to review B1. This evidence review supports recommendations 1.1.2, 1.1.3, 1.2.2, 1.3.1 to 1.3.5 and the research recommendation on imaging modalities to detect distant metastases in people with lobular breast cancer.

### 1.1.12 References – included studies

#### 1.1.12.1 Diagnostic

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# B2: PET-CT to monitor response to treatment

## 2.1 Review question

What is the clinical and cost effectiveness of FDG PET-CT compared to contrast-enhanced CT with or without bone scintigraphy for monitoring response to treatment in people who have been or are being treated for advanced breast cancer?

### 2.1.1 Introduction

Accurate assessment of response to treatment for metastases from breast cancer may allow for more effective management (i.e. earlier move to a further line treatment if there is progression on the current treatment). This in turn may result in improved clinical outcomes, including survival.

This review will update part of the NICE guideline on advanced breast cancer: diagnosis and treatment (CG81). The NICE surveillance review (January 2023) found system intelligence highlighting that PET-CT scans are being increasingly used for monitoring patients with advanced breast cancer in many settings. It was concluded that current recommendations may be out of line with practice indicating that evidence on the use of PET-CT scans for monitoring response to treatment should be reviewed. Contrast-enhanced CT with or without bone scintigraphy is currently the most commonly used modality in practice and was used as a comparator in this review.

The clinical and cost effectiveness and diagnostic accuracy of the same tests for diagnosing distant metastases is covered in review B1.

### 2.1.2 Summary of the protocol

**Table 19: PICOS inclusion criteria**

| | |
|---|---|
| **Population** | **Inclusion:** Adults (18 and over) who are being or have been treated for confirmed invasive adenocarcinoma of the breast with distant metastases (M1).<br><br>**Exclusion:**<br>• Adults who have not received treatment for invasive adenocarcinoma of the breast with distant metastases (M1)<br>• Adults (18 and over) with metastases to the breast from other primary tumours.<br>• Adults (18 and over) with non-epithelial breast tumours (for example, angiosarcoma, lymphoma). |
| **Interventions** | Fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET-CT) for monitoring (i.e. detecting treatment response and progression).<br><br>**Exclusions:**<br>• Other tracers that may be used with PET-CT. |

| | |
|---|---|
| | • Imaging analysed using artificial intelligence (AI). |
| **Comparator** | Contrast-enhanced CT with or without bone scintigraphy for monitoring (i.e. detecting treatment response and progression).<br><br>**Exclusions:**<br>• Imaging analysed using artificial intelligence (AI).<br>• Imaging covering less than chest (or neck or thorax), abdomen and pelvis. |
| **Outcomes** | **Primary outcomes**<br>• Overall survival (OS) (time to event data)<br>• Cancer-specific survival (time to event data) - equivalent to breast cancer mortality<br>  ○ Some studies may report cancer-specific survival as breast cancer mortality (dichotomous data). This will be extracted as a proxy outcome where cancer-specific survival data is not reported in the study.<br><br>**Secondary outcomes**<br>• Change to management or treatment (event data), for example:<br>  ○ People whose treatments were stopped as they were no longer working<br>  ○ People who moved to a further line of treatment.<br>• Quality of life (all validated measures including EQ-5D). |
| **Study type** | • Systematic reviews of RCTs<br>• RCTs. |

For the full protocol see appendix A.

### 2.1.3 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.

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

#### 2.1.3.1 Search methods

The searches for the effectiveness evidence were run on 9th July 2025. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR); Embase (Ovid); Epistemonikos; Medline ALL (Ovid).

Limits were applied to remove: animal studies; editorials; letters; news items; commentaries; conference abstracts; conference posters; clinical trial registry records; non-English language publications and references published before 2005. Standard NICE filters were used to limit to randomised controlled trials.

The searches for the cost effectiveness evidence were run on 9th July 2025. The following databases were searched: Embase (Ovid); International Health Technology Assessment Database (INAHTA) and Medline ALL (Ovid).

Limits were applied to remove animal papers, non-English language papers, conference abstracts, editorials and letters. The validated NICE Cost Utility Filter was used on MEDLINE ALL and Embase.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in appendix B.

### 2.1.4 Effectiveness evidence

#### 2.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 825 references (see appendix B for the literature search strategy).

These 825 references were screened at title and abstract level against the review protocol, with 824 excluded at this level. 10% of references were screened separately by two reviewers with 100% agreement.

The full text of 1 systematic review was ordered for closer inspection. The systematic review did not meet the criteria specified in the review protocol (appendix A), therefore there were no studies included in this evidence review.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

#### 2.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

### 2.1.5 Summary of studies included in the effectiveness evidence

No studies were included in this review.

### 2.1.6 Summary of the effectiveness evidence

No studies were included in this review.

### 2.1.7 Economic evidence

#### 2.1.7.1 Included studies

A separate search was performed for each review question to identify published economic evaluations of relevance to the review questions. See the literature search strategy in appendix B.

One economic study was identified which was applicable to this review question. (see economic study selection flow chart in appendix G).

One Danish study compared PET-CT to CECT in follow-up of people with biopsy-verified distant relapse or de novo metastatic breast cancer Naghavi-Behzad (2023).

Characteristics of included economic studies are provided in the economic evidence study extraction tables in appendix H.

#### 2.1.7.2 Excluded studies

See appendix J for a list of excluded economic studies, with reason for exclusion.

### 2.1.8 Summary of included economic evidence

**Table 20: Summary of characteristics of included economic studies**

| Study details | Study design and type of analysis | Population | Interventions and comparators | Perspective | Primary outcome | Time horizon |
|---|---|---|---|---|---|---|
| Naghavi-Behzad (2023)<br><br>Denmark | Cost-effectiveness analysis<br><br>Register-based comparative study. | Biopsy-verified distant relapse or de novo MBC patients (biopsy verification of primary tumour or distant metastases along with disseminated disease at baseline scan) | FDG PET-CT<br>vs<br>CECT<br>vs<br>Combination FDG PET-CT and CECT | Danish Healthcare perspective | Inpatient and outpatient visits, response monitoring scans, and treatments during the follow-up period.<br><br>Overall and oncology-specific costs.<br><br>Time-related costs<br><br>ICERs present the mean cost per patient over the median number of months of survival gained. | Median follow-up: 30 months<br><br>Range: 2-124 months |

Abbreviations: CECT: Contrast-enhanced computed tomography; ICER: Incremental cost-effectiveness ratio PET-CT: 2-deoxy-2-[$^{18}$F]fluoro-D-glucose PET/CT positron emission tomography with integrated computed tomography; Vs: Versus

See Table 21 for a summary of the economic evidence and appendix H for the economic evidence study extraction tables.

**Table 21: Economic evidence summary table: PET-CT versus CECT in people with biopsy-verified distant relapse or de novo metastatic breast cancer**

| Study | Applicability and limitations | Incremental cost[1] | Incremental effects | Cost effectiveness[1] | Uncertainty[1] | Economic evidence statement |
|---|---|---|---|---|---|---|
| Naghavi-Behzad (2023)<br>Denmark | Partially applicable[2]<br>Potentially serious limitations[3] | Vs CECT<br><br>FDG PET-CT:<br>-£6,552<br><br>Combined (FDG PET-CT and CT both used during follow-up): £70,716<br><br>Cost year:2019 | Vs CECT<br><br>FDG PET-CT:<br>1.19 Life Years<br>Combined:<br>2.00 Life years | Vs CECT<br><br>PET-CT:<br>Dominant<br><br>Combined:<br>£35,358 per life-year gained<br><br>Combined vs FDG PET-CT:<br>£95,589 per life-year gained | PET-CT was cost-saving with increased survival when the analysis was restricted to the following sub-groups:<br>• Patients not enrolled in clinical trials<br>• Diagnosed before 2009<br>• Oligometastatic disease<br>• ER+<br>• HER2 –<br>• De-novo metastatic breast cancer<br>• Performance status>2<br>• Performance status<2<br>ICERs for the following subgroups were: | • FDG PET-CT was both cost saving and had greater life-years gained compared to CECT<br>• Combined modality had an incremental cost of £35,358 per life-year gained compared to CECT<br>• FDG PET-CT remained cost-saving and associated with greater survival in nearly all sensitivity analyses. |

| Study | Applicability and limitations | Incremental cost[1] | Incremental effects | Cost effectiveness[1] | Uncertainty[1] | Economic evidence statement |
|---|---|---|---|---|---|---|
| | | | | | Liver/lung metastases :£2,523 per life-year gained<br>ER+, HER-, non-oligometastatic: £1,589<br><br>Sensitivity analysis matching CECT and PET-CT patients by performance status, age, years since diagnosis and number of involved organs:<br>All above groups PET-CT cost-saving and increase survival apart from:<br><br>Liver/lung metastases at baseline scan<br><br>ICER £6,732 per life year gained.<br><br>Sensitivity analyses not reported for combined modality | |

Abbreviations: CECT: Contrast-enhanced computed tomography; ER+: Estrogen receptor-positive, HER-: human epidermal growth factor receptor 2 negative; ICER: Incremental cost-effectiveness ratio PET-CT: 2-deoxy-2-[18F]fluoro-D-glucose PET-CT positron emission tomography with integrated computed tomography; Vs: Versus

1. Other currencies were converted to pound sterling using IMF Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx.
2. Study takes a Danish healthcare system perspective. QALYs not reported.
3. Probabilistic sensitivity analyses not reported. Effectiveness data not from randomised sources, likely to be a high level of confounding.

### 2.1.9 Economic model

The economic model for the review questions 1 and 2 were informed by a combined economic model that reflects a realistic diagnostic and monitoring pathway used in clinical practice.

In the monitoring phase, FDG PET-CT was slightly more costly than CECT, and it delivered small QALY gains due to improved diagnostic accuracy. The full details are provided in appendix I.

### 2.1.10 The committee's discussion and interpretation of the evidence

### 2.1.10.1. The outcomes that matter most

This section applies to review B2. Accurate scans can identify treatment response in people with advanced breast cancer. Treatment response can be used to make changes to management or treatment if necessary. Changes to management would be made with the aim of identifying a treatment which is effective and can provide oncological control, potentially improving survival. As a result, the committee agreed that the critical outcomes for this review were survival outcomes (overall survival and cancer-specific survival).

The committee agreed that change to management or treatment was an important outcome as it indicates detection of progression, and higher detection of progression is likely to indicate a more sensitive test. It is also a useful indicator of potential impact of the scans on practice more widely. The committee acknowledged the importance of quality of life and understanding how these imaging methods and subsequent management might impact on people's wellbeing and so included this as an important outcome.

### 2.1.10.2 The certainty of the evidence

This section applies to review B2. No evidence was identified for this review question.

### 2.1.10.3 Benefits and harms

The committee discussed reviews B1 and B2 together. This benefits and harms section records the combined discussion and covers FDG PET-CT and contrast-enhanced CT (CECT) for both diagnosis and monitoring.

Many of the committee's points apply to both diagnosing and monitoring advanced breast cancer, unless otherwise specified.

**Performance of FDG PET-CT and contrast-enhanced CT in different types of breast cancer**

The committee discussed the diagnostic performance of CECT and FDG PET-CT in detecting distant metastases in people with breast cancer. They noted that it may be harder to detect low volume metastases (than high volume) using CECT. While the committee noted that in their experience FDG PET-CT usually performs well in detecting metastases in inflammatory and triple-negative breast cancers, which

typically show higher FDG uptake, FDG PET-CT may be less reliable at detecting metastases in people with low grade cancer or lobular breast cancer due to low avidity. This was supported by very low certainty evidence from a small study of people with lobular breast cancer (Usmani et al., 2024; n = 21), which the committee considered clinically relevant despite its limited size. However, they noted that no studies were available on the diagnostic accuracy of CECT in the same population, and based on clinical experience, CECT may not perform better than PET-CT in these cases. The committee noted that current clinical practice might be to use either whole-body or targeted MRI in these situations, but that whole-body MRI was not widely available. Decisions about what type of imaging to use may also depend on the anatomical area being looked at.

Due to the small amount of evidence and the poor diagnostic accuracy of the tests examined in this review for people with lobular breast cancer compared with non-lobular breast cancer, the committee made a research recommendation for research about the diagnostic accuracy of different imaging modalities for detecting distant metastasis in people with lobular breast cancer (see appendix K). They included PET-CT imaging in this research recommendation because other tracers (FAPI and FES) are becoming available that might be more suitable for people with lobular breast cancer and more research is needed to investigate this.

**Harms and contraindications of FDG PET-CT and contrast-enhanced CT**

The committee discussed the potential harms and contraindications associated with FDG PET-CT and CECT. They noted that radiation exposure is broadly comparable between the two modalities. Although PET-CT may involve slightly higher doses due to the tracer, the difference is not considered clinically meaningful, and both are within acceptable limits for medical imaging. The committee acknowledged that radiation doses have been decreasing over time and that ongoing efforts aim to further reduce exposure. See the section on monitoring below for consideration of radiation during monitoring.

The clinical characteristics of the person having the scan would need to be considered when choosing the modality to use for either diagnosis or monitoring. The committee discussed the following as examples:

- Diabetes: as FDG is similar to glucose, PET-CTs using this tracer may require altering of insulin regimens in people with diabetes.
- Pregnancy: although pregnancy is not an absolute contraindication, the committee agreed that CECT and PET-CT in pregnancy should be approached with caution and other imaging types, such as MRI, would also be considered in order to reduce radiation. However, the committee noted that gadolinium-based contrast agent used in contrast-enhanced MRI would need extra consideration during pregnancy.
- Venous access: FDG for a PET-CT is administered via an intravenous injection, whereas the contrast agent for CECT is via an intravenous cannula (needed for the high volume of contrast agent given via pump injection at a specific rate). Due to the differences in approaches to administering PET-CT tracer and iodinated contrast for CECT, PET-CT may be preferable for individuals with difficult venous access. Committee members with lived experience explained how having had chemotherapy can make it difficult to have a cannula inserted, which might lead to multiple attempts – sometimes at different appointments – to conduct a CECT scan.

- Renal impairment: some people, including people with renal impairment, might be at increased risk of acute kidney injury associated with iodine-based contrast media used in CECT scans. The committee noted that there is existing NICE guidance in this area and linked to this in the recommendations. (NICE's diagnostics guidance on point-of-care creatinine devices to assess kidney function before CT imaging with intravenous contrast; recommendations on assessing risk factors for and preventing acute kidney injury in adults having iodine-based contrast media in NICE's guideline on acute kidney injury.)
- Allergies to contrast agents used in CECT.

When considering test failure rates, the committee discussed that for PET-CT, occasional shortage of tracers sometimes resulted in scan cancellations which might affect whole clinics rather than just individual scans. For CECT, being unable to cannulate was one of the more common causes of test failure at an individual level, and due to the issues discussed above about venous access, they noted that this was not uncommon (although difficult to accurately quantify).

**Availability and current usage of FDG PET-CT and contrast-enhanced CT**

The committee discussed the current use and accessibility of FDG PET-CT and CECT for diagnosing and monitoring distant metastases in breast cancer. They noted that CECT is widely available and remains the most commonly used imaging modality for this purpose across the UK. In contrast, the use of PET-CT varies considerably by region and is influenced by differences in scanner availability and local protocols for requesting PET-CT scans. The committee was aware of a planned national survey by the Royal College of Radiologists to better understand PET-CT usage patterns and access across the country, which is not yet published.

In terms of infrastructure and workforce, the committee highlighted that PET-CT availability is limited by the number of scanners and a shortfall in trained radiologists and nuclear medicine specialists. Although there is a drive to expand PET-CT training, particularly in trusts without current access, this remains a barrier to wider implementation. The committee also noted that PET-CT scans typically require longer preparation and scanning times compared with CECT. Overall, the committee agreed that while FDG PET-CT may offer a high level of accuracy, its broader use will depend on addressing current limitations in access and workforce capacity.

**FDG PET-CT and CECT (with/without bone scintigraphy) for diagnosing distant metastases**

When discussing the use of FDG PET-CT and CECT for diagnosis specifically, the committee agreed that reducing false positives and false negatives were both of great importance – people with a false negative test result may undergo inappropriate treatments, such as surgery, for presumed locoregional disease, and people with a false positive test result may receive systemic anti-cancer therapy aimed at treating metastases. However, they prioritised high sensitivity and reducing false negatives over high specificity, agreeing that people with metastases undergoing treatments for non-metastatic cancer would have the greater health burden. FDG PET-CT had high sensitivity in all analyses and CECT had lower sensitivity (predominantly moderate sensitivity), but the evidence for this was moderate to very low certainty.

The committee noted the diversity within the group of people receiving scans to diagnose distant metastases. Some people will have been diagnosed previously with

early breast cancer and therefore are likely to have had a biopsy and subsequent treatment. In these cases, features of the cancer which might affect choice of imaging modality may already be known. On the other hand, people may present with suspected cancer of unknown primary and have investigations to assess this further. In these situations, the grade of the cancer, the receptor subtype and whether it is ductal or lobular is unlikely to be known and choice of imaging will be based on other factors such as availability of the different imaging modalities, the individual's preference and other clinical characteristics.

**FDG PET-CT and CECT (with/without bone scintigraphy) for monitoring advanced breast cancer**

Monitoring advanced breast cancer can last for years. There may be multiple factors affecting the frequency of monitoring including the likelihood of changes in the tumour, toxicity of treatment, consequences of carrying on treatment, and aggressiveness of the disease. The individual may also have preferences about frequency of monitoring, and some people prefer more frequent monitoring to reduce anxiety. The type of imaging chosen for monitoring will not usually affect the frequency or scheduling of scans.

The committee reiterated their previous point (made during the discussion about diagnosis) that radiation levels are broadly comparable between the two modalities. (See the section on harms and contraindications of FDG PET-CT and CECT above for more details.) They also noted that cumulative radiation exposure may be a relevant consideration for monitoring, but they didn't think that even with repeated imaging one modality was clinically significantly worse than the other in terms of radiation dosage. However, they acknowledged that attempts are being made in clinical practice to reduce radiation exposure over time from both FDG PET-CT and CECT. They also highlighted that identifying treatment response or disease progression is likely to be a greater benefit compared to the harms of radiation exposure from these types of imaging.

Although there was no evidence for review B2 on monitoring response to treatment, the committee agreed that FDG PET-CT and CECT were likely to perform in a similar way for monitoring as they did for diagnosing as the aim – identifying number, size, location and, for FDG PET-CT, metabolic activity of metastases – is the same for both processes. This assumption was used as part of the health economic modelling.

The committee also noted that choice of imaging for monitoring would be heavily influenced by the imaging used at diagnosis. This is because comparability between baseline (diagnosis) and follow-up (monitoring) scan results is often important to observe how the metastases are responding to treatment. Radiologists may use standardised criteria or frameworks to decide response to treatment. These frameworks have set definitions for each of the possible results, and swapping scan method means swapping framework, losing continuity of assessment. However, the committee noted that RECIST for CECT and PERCIST for PET-CT are mainly used in research currently. Radiologists on the committee pointed out that even within scan type, variation (for example in machine or calibration) can affect interpretation and needs to be taken into account by radiologists, and that variation between scan types could make interpretation of response to treatment very difficult. However, they noted that there are some situations where a change in the scan method used may be required, for example in cases of indeterminate lesions in response assessment.

**Drafting the recommendations**

Diagnosis and assessment

The committee agreed that – after considering the moderate to very low certainty diagnostic evidence, health economics modelling, and their own experience – FDG PET-CT should be an option for diagnosing distant metastases. They agreed that the other option, and the imaging type that is used most commonly in current practice, is CECT, which includes the chest, abdomen and pelvis (CAP). They agreed that diagnostic accuracy evidence suggested with moderate to very low certainty that FDG PET-CT may have high sensitivity and high specificity, and that a lower volume of low to very low certainty evidence suggested that CECT may have moderate sensitivity and high specificity. Economic analysis suggested that FDG PET-CT is highly likely to be cost effective compared with CECT if test accuracy is similar in monitoring as for diagnosis. The committee considered that uncertainties in the evidence base, along with concerns around limited availability of FDG PET-CT, system capacity, and potential inequities in access justified positioning CECT and FDG PET-CT as equivalent first options for diagnosing distant metastases. They agreed that both imaging types were appropriate and therefore they recommended that CECT (CAP) or FDG PET-CT should be used to assess the presence and extent of distant metastases for diagnosis and staging. They explained that both the presence and the extent of metastases are important for staging – the presence is to assess whether there are metastases for diagnostic purposes, and the extent is to determine how widespread and sizeable the metastases are and their locations. They also noted the importance of including the supraclavicular fossae and the proximal femurs in the CECT used for diagnosing breast metastases because lymph nodes in the supraclavicular region and bone in the proximal femurs are common sites of breast metastases, and these regions may not be captured by a standard CAP CT.

The committee discussed several factors to take into account when deciding between FDG PET-CT and CECT in addition to the evidence that suggested that FDG PET-CT may have higher sensitivity than CECT. They noted that although evidence about the diagnostic accuracy of FDG PET-CT and CECT in different types of breast cancer was very limited, in their experience performance of FDG PET-CT is more variable in some cancer types (for example, lobular and low-grade cancers) than others. Due to the limited evidence and the fact that performance of FDG PET-CT (uptake of the tracer) can't be predicted with certainty even when there is information about the type of cancer, they decided not to recommend against use of FDG PET-CT or CECT in any particular type of cancers. Instead, they agreed that any available information about the person's cancer should be taken into account when choosing imaging modality – particularly subsequent imaging once there is information about how at least one scan type performed at initial imaging – and when interpreting the results of imaging. For example, where FDG PET-CT has been used for initial diagnosis and avidity is low, this could be due to poor uptake of the tracer (particularly in the context of lobular or low-grade cancer) and further imaging may be required. They noted that clinician judgement on the performance of the scan for specific clinical indications, as well as availability, would be important deciding factors in which scan is offered, and so agreed that these factors should be taken into account when deciding on the imaging modality to use. They also included the person's preference as this is also important. (See the section on other factors the committee took into account for more discussion about personal preference.)

The committee also considered the previous recommendations on diagnosis and assessment from the 2009 version of the guideline. They agreed that some of the recommendations were too prescriptive about when each of the possible imaging types (plain radiography, ultrasound, CT, PET-CT, MRI and bone scintigraphy) could be used and that the recommendations did not fully reflect the current range of scenarios or the complexity of the decision about how to approach them, and that they therefore were not useful for clinicians. The committee decided to collapse the recommendations into a single new recommendation listing the imaging options after either FDG PET-CT or CECT has been offered, and there is uncertainty around the presence and extent of distant metastases or further characterisation is needed (for example, to look for bone metastases using bone scintigraphy). They agreed that all the options previously present in the 2009 recommendations should still be in the new recommendation, along with the option to use FDG PET-CT after CECT based on the appropriateness of each option to answer the clinical question. They agreed that it was not likely that CECT would be used to resolve uncertainty when FDG PET-CT had been used as the initial imaging method, and so did not include CECT in this recommendation.

The committee also recommended that NICE's guideline on brain tumours (primary) and brain metastases in over 16s and NICE's guideline on spinal metastases and metastatic spinal cord compression, which provide more detail about specific imaging for brain metastases and spinal metastases, should be used where brain metastases or spinal cord or metastases are suspected because they have detailed recommendations covering their diagnosis.

Monitoring disease status

There was no evidence about FDG PET-CT or CECT for monitoring response to treatment for advanced breast cancer. Based on the diagnostic accuracy evidence of FDG PET-CT and CECT for diagnosing distant metastases and the results of the economic model, the committee recommended using either FDG PET-CT or CECT (whichever is the best in individual cases) for monitoring response to the treatment, but for consideration to be given to using the same imaging modality that was used for initial staging of distant metastases. They added that using the same imaging modality would be useful to identify changes over time because imaging would be comparable.

### 2.1.10.4 Cost effectiveness and resource use

One previous economic evaluation was identified comparing PET-CT to CECT in people with biopsy verified metastatic breast cancer. The study also included a cohort of people receiving both modalities during monitoring although this was outside of the scope of the review question. This study used Danish registry data to estimate costs and survival from the different modalities of imaging. The study took a Danish healthcare system perspective. Outcomes were reported in life-years and no analysis was presented that adjusted these for health-related quality-of-life (HRQoL). The committee did not believe that there would be large differences in HRQoL between the two groups.

The study reported that PET-CT led to both cost savings (through reduction in lines of treatment) and increases in life expectancy. Given the committee did not believe there would be large differences in HRQoL between the two groups it is very likely

that if QALY years had been used as an outcome PET-CT would have dominated (increased QALYs and reduced costs) CECT.

The main weakness that the committee highlighted with the analysis was that it was non-randomised evidence. Factors associated with the choice of imaging modality were also likely to impact on overall survival. The study did undertake a sensitivity analysis in which the cohorts were matched on a number of characteristics. This analysis produced similar results to the base-case analysis. The committee highlighted that there were a number of characteristics which had not been accounted for in the matching and it was likely there remained significant confounding in the analysis. The increased survival of 1.2 years did not match their own clinical and lived experience with the base-case in the NICE bespoke economic model (based on committee opinion) assuming no difference in survival between modalities.

Even though the study was published in 2023 it included people receiving monitoring as early as 2004. Treatment for metastatic breast cancer has changed significantly in that time reducing further the applicability of results.

Despite the strong conclusions of the study the committee placed little weight on it during their considerations of the recommendation given its methodological limitations and the low applicability to current UK practice.

The bespoke economic analysis undertaken for this review considered PET-CT and CECT in the monitoring of metastatic breast cancer. The analysis considered 3 interventions PET-CT for monitoring with CECT for diagnosis, CECT for both stages and PET-CT for both stages. CECT for monitoring with PET-CT for diagnosis was not considered in the analysis as the committee considered it unlikely that you would use CECT if the baseline image from diagnosis was from PET-CT.

The analysis took a UK NHS and PSS perspective and reported outcomes in terms of QALYs scored using the EQ-5D. The clinical evidence review for this topic found no evidence reporting diagnostic test accuracy for monitoring. The values for diagnostic accuracy were used instead and were identical to those used in the diagnosis sub-analysis. Overall survival was assumed to be identical between the CECT and PET-CT modalities based on committee opinion and in the absence of identified clinical evidence to the contrary although the model took a lifetime perspective.

The model found in the base-case that PET-CT for diagnosis and monitoring was below £20k per QALY compared to CECT for both stages. CECT for both stages was preferred to CECT for diagnosis followed by PET-CT for monitoring. The probabilistic sensitivity analysis showed that there was less than a 60% probability of PET-CT for both stages being the most cost-effective option. This was reinforced by the variable results during deterministic sensitivity analysis. Results were particularly sensitive to costs of the Markov health states, anxiety detriments and transitions between states especially to the best supportive care state. These were all variables for which limited evidence was identified.

CECT diagnosis followed by PET-CT for monitoring was the most cost-effective option in less than 2% of iterations of the PSA. This was most likely as a result of identical assumptions between the test accuracy for monitoring and diagnosis with favourable assumptions in the diagnosis portion of the model making the monitoring

portion also favourable. The committee did not think this supported a recommendation against having these mixed modalities.

The economic evidence weakly supported PET-CT for all stages of diagnosis and monitoring but with significant uncertainty. Despite a slightly stronger case for the cost-effectiveness of PET-CT in diagnosis and monitoring and the interrelationship between both portions of the pathway, given the uncertainty in estimates, the committee did not recommend one imaging modality in preference to another. The committee decided the choice of monitoring imaging modality should follow what was used for diagnosis unless clinical judgement, the person's preference or availability made the alternative imaging modality preferable.

### 2.1.10.5 Other factors the committee took into account

This section covers both review B1 and review B2.

The committee acknowledged that PET-CT scanners are currently only available at some centres. This means that many people would have to travel to be able to access them, and that current capacity may not be sufficient to meet potential demand in a timely manner to meet the 28-day faster diagnosis standard. The committee agreed that people for whom it is suitable should not be denied the opportunity to access FDG PET-CT imaging and specifically noted that a recommendation to give people information about relevant treatment options and services that they are entitled to, even if they are not provided locally already exists in the NICE guideline on patient experience in adult NHS services. However, they noted that scanner availability and workforce numbers may limit capacity to image large numbers of people without increasing their waiting time and potentially delaying diagnosis. The committee agreed that this constraint should be considered when implementing recommendations. While recognising these limitations, the committee noted that inclusion of PET-CT in the recommendations may help support future investment in imaging infrastructure, particularly in regions where availability is currently low. The committee considered this an important step towards improving equity of access and ensuring that more people can benefit from FDG PET-CT in the future.

The importance of accurate data collection about people who are diagnosed with metastatic breast cancer was discussed, and the committee noted that inconsistent coding can make it hard to estimate incidence and prevalence of the disease. Accurately recording which people have advanced disease and the treatments they receive will help with forward planning of resource allocation, may help identify under-represented groups within the care pathway which could help inform how to address inequalities in healthcare access, and support research and improvements in the quality of care. This is currently supported by The National Audit of Metastatic Breast Cancer (NAoMe), which aims to report on metastatic breast cancer in NHS hospitals in England and Wales. The committee agreed to make a consensus recommendation to support improved data collection.

The committee recognised that multidisciplinary team (MDT) processes and referral criteria can vary across organisations. Although many services already discuss all breast cancer cases within existing MDT meetings, the committee noted that this may not be routine practice for advanced disease in all centres. They agreed that it is good practice for people with breast cancer who develop metastatic disease to be referred to an MDT, as outlined in the NICE quality standard on breast cancer.

The committee agreed that people who have been diagnosed with advanced breast cancer need to be provided with information and support, including physical, psychological and social support. The guideline already has a recommendation for assessment and discussion of their needs. However, the committee noted the key role that clinical nurse specialists play in providing information and support throughout diagnosis, during management and palliative care for people with advanced breast cancer. The NICE guideline on early and locally advanced breast cancer has a recommendation about having a clinical nurse specialist and the committee agreed that this also applies to people with advanced breast cancer. They added it to the current guideline for consistency but made minor changes to reflect the differences between managing early or locally advanced breast cancer and advanced disease.

The committee were aware of the NICE guideline on depression in adults with a chronic physical health problem and noted that this has information about identifying, treating and managing depression in people aged 18 and over who also have a chronic physical health problem such as cancer. They added a cross reference to this guideline in the section on providing information and support. The committee were also aware of the NICE guidelines on Patient experience in adult NHS services and Shared decision making, which support sharing of information and decision making but did not include cross refences to these in the same section because they are already listed at the top of every NICE guideline.

The committee also discussed imaging during pregnancy and acknowledged that there are no universal rules (see discussion under benefits and harms section). Most studies of imaging types exclude pregnant women from participating, making it difficult to assess diagnostic accuracy in this group. Both PET-CT and CECT are usually avoided in practice during pregnancy in order to reduce radiation exposure to the baby, but can be offered based on an assessment of risk by the clinicians involved and in discussion with the individual. The committee noted that alternative scan methods would most likely be preferred, for example MRI, but that this should be discussed between the individual and the clinical team providing their care, particularly with regard to administration of gadolinium-based contrast agents.

The committee were aware of a number of health inequalities experienced by people with advanced breast cancer and considered these when making recommendations about diagnosing distant metastases and monitoring response to treatment. The health inequalities assessment that accompanies this update outlines relevant issues – however, the committee noted that many of these are societal and not within the committee's ability to address. They discussed that many people, for example people with caring or work responsibilities especially women, who are on low income, who are frail, may find it difficult to attend regular appointments for monitoring, particularly if this involves travelling in order to access scan types that aren't available locally. The committee retained CECT as an option for both diagnosis and monitoring as it is more widely available and may be a preferred option for people who do not have access to FDG PET-CT locally, are unable or unwilling to travel to other centres for imaging.

The committee also discussed the fact that people with lower health literacy or who don't have English as a first language may find it difficult to fully take part in decisions about diagnosis and monitoring. Undergoing scans to potentially diagnose metastatic cancer will also be overwhelming for many people, and extra support may be helpful. The committee agreed that it was not necessary for them to make recommendations to address the issues discussed above around communication and shared decision

making because they are already covered by other NICE guidelines. They noted that the following sections are particularly relevant:

- enabling patients to actively participate in their care (covering communication and information), knowing the patient as an individual in the NICE guideline on patient experience in adult NHS services
- putting shared decision making into practice and communicating risks, benefits and consequences in the NICE guideline on shared decision making.

### 2.1.11 Recommendations supported by this evidence review

This section applies to review B2. This evidence review supports recommendation 1.5.1 and 1.5.2.

### 2.1.12 References – included studies

#### 2.1.12.1 Effectiveness

No studies were identified that met the inclusion criteria for this review.

#### 2.1.12.2 Economic

Naghavi-Behzad, M., Gerke, O., Kodahl, A. R., Vogsen, M., Asmussen, J. T., Weber, W., ... & Kidholm, K. (2023). Cost-effectiveness of 2-[18F] FDG-PET/CT versus CE-CT for response monitoring in patients with metastatic breast cancer: a register-based comparative study. Scientific Reports, 13(1), 16315.

# Appendices

## Appendix A – Review protocols

### B1: Review protocols for FDG PET-CT and contrast-enhanced CT for diagnosing distant metastases

### Test and Treat review protocol (review question 1)

| ID | Field | Content |
|---|---|---|
| 1. | Review title | The effectiveness and cost effectiveness of PET-CT compared to contrast-enhanced CT with or without bone scintigraphy for detection, and for informing subsequent management, of distant metastases in people who have suspected advanced breast cancer. |
| 2. | Review question | What is the clinical and cost effectiveness of FDG PET-CT compared to contrast-enhanced CT (with or without bone scintigraphy) for diagnosing distant metastases and determining subsequent management in people with suspected advanced breast cancer? |
| 3. | Objective | To evaluate and compare the clinical effectiveness and cost effectiveness of FDG PET-CT and contrast-enhanced CT with or without bone scintigraphy for diagnosing distant metastases and informing the subsequent management in adults with suspected advanced breast cancer. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE ALL<br>• Epistemonikos<br><br>Searches will be limited to exclude:<br>• papers published before 2005<br>• Papers not published in the English language<br>• Animal studies<br>• Conference abstracts and posters<br>• Editorials, letters, news items and commentaries<br>• Theses and dissertations<br>• Clinical trial registry records<br><br>For the economics review the following databases will be searched:<br>• Embase<br>• MEDLINE ALL<br>• INAHTA International HTA Database |

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| | | 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.<br><br>The full search strategies for all databases will be published in the final review. |
| 5. | Condition or domain being studied | Suspected advanced breast cancer<br><br>Advanced is defined as people with a distant metastasis (M1 using the TNM staging system). |
| 6. | Population | Inclusion: Adults (18 and over) with invasive adenocarcinoma of the breast who have suspected distant metastases (M1). |
| 7. | Intervention | • Fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) [FDG PET-CT] followed by management of the metastases based on the results of the test<br><br>Exclusion<br>• PET-CT used for screening<br>• Imaging analysed using artificial intelligence (AI)<br>• Imaging covering less than chest (or neck or thorax), abdomen and pelvis. |
| 8. | Comparator | • Contrast-enhanced Computed Tomography (CECT) scan<br>• Contrast-enhanced Computed Tomography (CECT) scan, with bone scintigraphy<br><br>Both comparators will be followed by management of the metastases based on the results of the test.<br><br>Exclusion<br>• CECT used for screening<br>• Imaging analysed using artificial intelligence (AI)<br>• Imaging covering less than chest (or neck or thorax), abdomen and pelvis. |
| 9. | Types of study to be included | • Test and treat RCTs<br>• Systematic reviews of test and treat RCTs |
| 10. | Other exclusion criteria | • Abstracts, conference presentations, theses and narrative reviews<br>• Non-human studies<br>• Non-English language studies<br>• RCTs that are not Test and Treat studies |
| 11. | 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 FDG PET-CT scans in practice, and stakeholders identified this area for update. |

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| | | 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 (CECT) with or without bone scintigraphy, which is current practice for diagnosing metastatic breast cancer, to determine accuracy. |
| 12. | Primary outcomes (critical outcomes) | Critical outcomes:<br>• Overall survival (time to event data)<br>• Breast cancer-specific survival (time to event data or event data if time to event not available) – breast cancer mortality will be accepted if breast cancer-specific survival is not reported<br><br>Any statistically significant difference will be taken as clinically meaningful for the critical outcomes.<br><br>**Timepoints:**<br>The longest follow-up periods will be prioritised for all outcomes if multiple time points are reported. |
| 13. | Secondary outcomes (important outcomes) | • Quality of life (all validated measures including EQ-5D)<br>• Changes to management or treatment (event data), for example:<br>  ○ People who avoided treatments aimed at non-metastatic disease<br>  ○ People who started treatment for metastatic disease<br><br>**Minimal important differences**<br>• Quality of life MID values from the literature:<br>  ○ FACT-G total: 3-7 points<br>  ○ FACT-B total: 7-8 points<br>  ○ TOI (trial outcome index) of FACT-B: 5-6 points<br>  ○ BCS of FACT-B: 2-3 points<br>  ○ EORTC QLQ-C30: improvement 11 points and deterioration minus 8 points<br>  ○ WHOQOL-100: 1 point<br><br>Any statistically significant difference will be used to assess whether an effect is clinically meaningful for the rest of the important outcomes.<br><br>**Timepoints:**<br>The longest follow-up periods will be prioritised for all outcomes if multiple time points are reported. |
| 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.<br><br>Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. |

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| | | 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.<br><br>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.<br><br>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.<br><br>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:<br>at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) will be screened<br>• 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.<br>• 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. |
| 15. | Risk of bias (quality) assessment | Quality assessment of individual studies will be performed using the following checklists:<br>• ROBIS tool for systematic reviews<br>• Cochrane RoB tool v.2 for RCTs<br>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 hazard ratios or risk 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, $I^2$ values of greater than 40% and 60% will be considered as serious and very serious heterogeneity, respectively. Where $I^2$ >40% in a fixed effects model, a random effects model will be fitted if it reduces the heterogeneity. Where $I^2$ is 80% or above, consideration will be given to whether the data should be pooled. Heterogeneity will be explored as appropriate using 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. |

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| | | 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/<br><br>Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias |
| 17. | Analysis of sub-groups | Evidence will be subgrouped only for critical outcomes by the following:<br>• Location of metastases (bone vs visceral)<br>• Receptor types (HER2-positive, triple negative, ER+/HER2-)<br>• Invasive lobular carcinoma vs all other types.<br>• Inflammatory breast cancer vs all other types<br>• Size of tumour (T1 to T2 vs T3+)<br>• Nodal status (N0 vs N1 to N3)<br><br>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<br>☐ Diagnostic<br>☐ Prognostic<br>☐ Qualitative<br>☐ Epidemiologic<br>☐ Service Delivery<br>☐ Other (please specify) |
| 19. | Language | English |
| 20. | Country | England |
| 21. | Anticipated or actual start date | June 2025 |
| 22. | Anticipated completion date | June 2026 |
| 23 | Stage of review at time of this submission | **Review stage** / **Started** / **Completed**<br>Preliminary searches / ☐ / X<br>Piloting of the study selection process / ☐ / X<br>Formal screening of search results against eligibility criteria / ☐ / X |

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| | | Data extraction | ☐ | X |
| | | Risk of bias (quality) assessment | ☐ | X |
| | | Data analysis | ☐ | X |
| 24. | Named contact | **24a. Named contact**<br>NICE<br><br>**24b. Named contact e-mail**<br>breastcancerupdate@nice.org.uk<br><br>**24c. Organisational affiliation of the review**<br>National Institute for Health and Care Excellence (NICE) | | |
| 25. | Review team members | From the Guideline Development Team<br><br>• Marie Harrisingh, Topic lead<br>• Olivia Crane, Senior technical analyst<br>• Adefisayo Abba-Abba, Technical analyst<br>• Yolanda Martinez, Technical analyst<br>• James Hawkins, Health economist adviser<br>• Tzujung Lai, Health economist analyst<br>• Andrea Heath, Information specialist | | |
| 26. | Funding sources/sponsor | This systematic review is being completed by the Centre for Guidelines which receives funding from 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: Advanced breast cancer: diagnosis and treatment. | | |
| 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:<br>notifying registered stakeholders of publication | | |

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| | | publicising the guideline through NICE's newsletter and alerts<br>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 | Advanced breast cancer, FDG PET-CT, CECT, distant metastasis, Stage 4 breast cancer, diagnosis |
| 33. | Details of existing review of same topic by same authors | Not applicable |
| 34. | Current review status | ☐ Ongoing<br>☐ Completed but not published<br>☐ Completed and published<br>☐ Completed, published and being updated<br>☒ Discontinued |
| 35. | Additional information | None |
| 36. | Details of final publication | www.nice.org.uk |

## Diagnostic test accuracy review protocol (review question 2)

| ID | Field | Content |
|---|---|---|
| 1. | Review title | Diagnostic accuracy and cost effectiveness of PET-CT and contrast-enhanced CT with or without bone scintigraphy for detecting distant metastases in people who have suspected advanced breast cancer. |
| 2. | Review question | In adults with suspected advanced breast cancer, what is the diagnostic accuracy and cost effectiveness of:<br>• FDG PET-CT<br>• contrast-enhanced CT (with or without bone scintigraphy)<br>for detecting distant metastases?<br><br>*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. |
| 3. | Objective | To evaluate and compare the accuracy and cost effectiveness of FDG PET-CT and contrast-enhanced CT with or without bone scintigraphy for diagnosing distant metastases in adults with suspected advanced breast cancer. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE ALL<br>• Epistemonikos |

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| | | Searches will be limited to exclude:<br>• papers published before 2005<br>• Papers not published in the English language<br>• Animal studies<br>• Conference abstracts and posters<br>• Editorials, letters, news items and commentaries<br>• Theses and dissertations<br>• Clinical trial registry records<br><br>For the economics review the following databases will be searched:<br>• Embase<br>• MEDLINE ALL<br>• INAHTA International HTA Database<br><br>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.<br><br>The full search strategies for all databases will be published in the final review. |
| 5. | Condition or domain being studied | Suspected advanced breast cancer<br><br>Advanced is defined as people with a distant metastasis (M1 using the TNM staging system). |
| 6. | Population | Inclusion: Adults (18 and over) with invasive adenocarcinoma of the breast who have suspected distant metastases (M1). |
| 7. | Index Tests | • Fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) [FDG PET-CT]<br>• Contrast-enhanced Computed Tomography (CECT) scan<br>• Contrast-enhanced Computed Tomography (CECT) scan, with bone scintigraphy<br><br>Exclusion<br>• PET-CT used for screening<br>• Imaging analysed using artificial intelligence (AI)<br>• Imaging covering less than chest (or neck or thorax), abdomen and pelvis. |
| 8. | Reference standard | • Histopathology from surgery or biopsy confirming metastasis<br>• Clinical follow-up involving expert decision making with support of imaging (other than the index tests alone) and / or histological data. |
| 9. | Types of study to be included | • Diagnostic accuracy cross-sectional studies and cohort studies.<br>• Systematic reviews of diagnostic accuracy cross-sectional or cohort studies.<br>• Where there are no cross-sectional or cohort studies identified, case-control studies will be included. |

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| 10. | 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<br>• Diagnostic case-control studies that separately recruit diseased and non-diseased groups |
| 11. | 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.<br><br>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. |
| 12. | 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.<br><br>Diagnostic accuracy outcomes:<br>• Sensitivity and specificity<br>• Positive and negative likelihood ratios<br><br>**Thresholds**<br>• Sensitivity<br>  ○ Upper threshold = 90%<br>  ○ Lower threshold = 70%<br>• Specificity<br>  ○ Upper threshold = 80%<br>  ○ Lower threshold = 60% |
| 13. | Data extraction (selection and coding) | All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated.<br><br>Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol.<br><br>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.<br><br>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. |

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| | | 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.<br><br>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:<br>• at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) will be screened<br>• 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.<br>• 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. |
| 14. | Risk of bias (quality) assessment | Quality assessment of individual studies will be performed using the following checklists:<br>• ROBIS tool for systematic reviews<br>• QUADAS-2 for diagnostic accuracy studies<br>The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer. |
| 15. | 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.<br>Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively.<br>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.<br>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).<br>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.<br>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) |

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| | | toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/<br>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).<br><br>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.<br><br>Where data can be disambiguated it will be separated into the subgroups identified in section 16 (below).<br><br>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. |
| 16. | Analysis of sub-groups | Evidence will be subgrouped by the following:<br>• Location of metastases (bone or visceral)<br>• Receptor types (HER2-positive, triple negative, ER+/HER2-)<br>• Invasive lobular carcinoma vs all other types.<br>• Inflammatory breast cancer vs all other types<br>• Size of primary tumour (T1 to T2 vs T3+)<br>• Nodal status (N0 vs N1 to N3)<br><br>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. |
| 17. | Type and method of review | ☐ Intervention<br>☒ Diagnostic<br>☐ Prognostic<br>☐ Qualitative<br>☐ Epidemiologic<br>☐ Service Delivery<br>☐ Other (please specify) |
| 18. | Language | English |
| 19. | Country | England |
| 20. | Anticipated or actual start date | June 2025 |

| | | | | |
|---|---|---|---|---|
| 21. | Anticipated completion date | June 2026 | | |
| 22 | Stage of review at time of this submission | **Review stage** | **Started** | **Completed** |
| | | Preliminary searches | ☐ | ☑ |
| | | Piloting of the study selection process | ☐ | ☑ |
| | | Piloting of the study selection process | ☐ | ☑ |
| | | Piloting of the study selection process | ☐ | ☑ |
| | | Piloting of the study selection process | ☐ | ☑ |
| | | Piloting of the study selection process | ☐ | ☑ |
| 23. | Named contact | **24a. Named contact**<br>NICE<br><br>**24b. Named contact e-mail**<br>breastcancerupdate@nice.org.uk<br><br>**24c. Organisational affiliation of the review**<br>National Institute for Health and Care Excellence (NICE) | | |
| 24. | Review team members | From the Guideline Development Team<br><br>• Marie Harrisingh, Topic lead<br>• Olivia Crane, Senior technical analyst<br>• Adefisayo Abba-Abba, Technical analyst<br>• Yolanda Martinez, Technical analyst<br>• James Hawkins, Health economist adviser<br>• Tzujung Lai, Health economist analyst<br>• Andrea Heath, Information specialist | | |
| 25. | Funding sources/sponsor | This systematic review is being completed by the Centre for Guidelines which receives funding from NICE. | | |
| 26. | 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. | | |
| 27. | 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 | | |

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| | | NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Advanced breast cancer: diagnosis and treatment |
| 28. | Other registration details | None |
| 29. | Reference/URL for published protocol | Not applicable |
| 30. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• 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. |
| 31. | Keywords | Advanced breast cancer, FDG PET-CT, CECT, distant metastasis, Stage 4 breast cancer, diagnosis |
| 32. | Details of existing review of same topic by same authors | Not applicable |
| 33. | Current review status | ☐ Ongoing<br>☐ Completed but not published<br>☒ Completed and published<br>☐ Completed, published and being updated<br>☐ Discontinued |
| 34. | Additional information | none |
| 35. | Details of final publication | www.nice.org.uk |

## B2: Review protocol for FDG PET-CT and contrast-enhanced CT for monitoring response to treatment

| ID | Field | Content |
|---|---|---|
| 1. | Review title | PET-CT scans for monitoring response to treatment in people who have been or are being treated for advanced breast cancer. |
| 2. | Review question | What is the clinical and cost effectiveness of FDG PET-CT compared to contrast-enhanced CT with or without bone scintigraphy for monitoring response to treatment in people who have been or are being treated for advanced breast cancer? |
| 3. | Objective | To evaluate the clinical and cost effectiveness of FDG PET-CT compared to contrast-enhanced CT with or without bone scintigraphy for monitoring response to treatment in people who have been or are being treated for advanced breast cancer. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL) |

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| | | • Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE ALL<br>• Epistemonikos (for systematic reviews only)<br><br>Searches will be limited to exclude:<br>• Papers published before 2005 Papers not published in the English language<br>• Animal studies<br>• Conference abstracts and posters<br>• Editorials, letters, news items and commentaries<br>• Theses and dissertations<br>• Clinical trial registry records<br><br>For the economics review the following databases will be searched:<br>• Embase<br>• MEDLINE ALL<br>• INAHTA International HTA Database<br><br>The following standard NICE filters will be used to limit results by study type: cost effectiveness studies / randomised controlled trials.<br><br>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.<br><br>The full search strategies for all databases will be published in the final review. |
| 5. | Condition or domain being studied | Advanced breast cancer.<br><br>Advanced is defined as with distant metastases (M1 using the TNM staging system). |
| 6. | Population | Inclusion: Adults (18 and over) who are being or have been treated for confirmed invasive adenocarcinoma of the breast with distant metastases (M1).<br><br>Exclusion:<br>• Adults who have not received treatment for invasive adenocarcinoma of the breast with distant metastases (M1)<br>• Adults (18 and over) with metastases to the breast from other primary tumours.<br>• Adults (18 and over) with non-epithelial breast tumours (for example, angiosarcoma, lymphoma). |
| 7. | Intervention | Fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET-CT) for monitoring (i.e. detecting treatment response and progression). |

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| | | Other tracers that may be used with PET-CT will be excluded.<br><br>Imaging analysed using artificial intelligence (AI) will be excluded. |
| 8. | Comparator | Contrast-enhanced CT with or without bone scintigraphy for monitoring (i.e. detecting treatment response and progression).<br><br>Imaging analysed using artificial intelligence (AI) will be excluded.<br><br>Imaging covering less than chest (or neck or thorax), abdomen and pelvis will be excluded. |
| 9. | Types of study to be included | • Systematic reviews of RCTs<br>• RCTs. |
| 10. | Other exclusion criteria | • Abstracts, conference presentations, theses and narrative reviews<br>• Non-human studies<br>• Non-English language studies<br>• Studies where more than 20% of the participants do not have metastatic disease and where subgroup data is not available. |
| 11. | Context | New evidence that could affect recommendations was identified through the NICE surveillance process. As a result of discussions with clinicians during the scoping process, it was proposed that additional areas were going to be included in this update. One of these areas was on the use of PET-CT scans for monitoring response to treatment. |
| 12. | Primary outcomes | • Overall survival (OS) (time to event data)<br>• Cancer-specific survival (time to event data) - equivalent to breast cancer mortality<br>  ○ Some studies may report cancer-specific survival as breast cancer mortality (dichotomous data). This will be extracted as a proxy outcome where cancer-specific survival data is not reported in the study.<br><br>**MIDs:** any statistically significant difference.<br><br>**Timepoints:**<br>• longest reported timepoint from each study will be combined for time to event outcomes.<br>• longest reported timepoint up to and including 5 years, and longest reported timepoint at over 5 years will be reported separately for dichotomous outcomes. |
| 13. | Secondary outcomes | • Change to management or treatment (event data), for example:<br>  ○ People whose treatments were stopped as they were no longer working<br>  ○ People who moved to a further line of treatment.<br>• Quality of life (all validated measures including EQ-5D).<br><br>**MIDs:**<br>• Quality of life MID values from the literature:<br>  ○ FACT-G total: 3-7 points |

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| | | ○ FACT-B total: 7-8 points<br>○ TOI (trial outcome index) of FACT-B: 5-6 points<br>○ BCS of FACT-B: 2-3 points<br>○ WHOQOL-100: 1 point<br><br>Any statistically significant difference will be used for the rest of the important outcomes.<br><br>**Timepoints:**<br>• change to management or treatment: any<br>• Quality of life: longest reported timepoint from each study will be combined |
| 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.<br>Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol.<br>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.<br>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.<br>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. Studies included in an included systematic review will not have a full data extraction form conducted, but study details will be checked and high-level details reported in the review. |
| 15. | Risk of bias (quality) assessment | Quality assessment of individual studies will be performed using the following checklists:<br>• ROBIS tool for systematic reviews.<br>• Cochrane RoB tool v.2 for RCTs.<br><br>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 hazard ratios or risk 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, $I^2$ values of greater than 40% and |

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| | | 60% will be considered as serious and very serious heterogeneity, respectively. Where $I^2$ >40% in a fixed effects model, a random effects model will be fitted if it reduces the heterogeneity. Where $I^2$ is 80% or above, consideration will be given to whether the data should be. Heterogeneity will be explored as appropriate using 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.<br>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/<br>Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias. | | |
| 17. | Analysis of sub-groups | Evidence will be subgrouped only for critical outcomes by the following:<br>• CT with / without bone scintigraphy<br>• Location of metastases (bone vs visceral)<br>• Receptor types (HER2-positive, triple negative, ER+/HER2-)<br>• Invasive lobular carcinoma vs all other types.<br>• Inflammatory breast cancer vs all other types<br><br>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<br>☐ Diagnostic<br>☐ Prognostic<br>☐ Qualitative<br>☐ Epidemiologic<br>☐ Service Delivery<br>☐ Other (please specify) | | |
| 19. | Language | English | | |
| 20. | Country | England | | |
| 21. | Anticipated or actual start date | May 2025 | | |
| 22. | Anticipated completion date | June 2026 | | |
| 23 | Stage of review at time of this submission | **Review stage** | **Started** | **Completed** |
| | | Preliminary searches | ☐ | X |
| | | Piloting of the study selection process | ☐ | X |

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| | | Formal screening of search results against eligibility criteria | ☐ | X |
| | | Data extraction | ☐ | X |
| | | Risk of bias (quality) assessment | ☐ | X |
| | | Data analysis | ☐ | X |
| 24. | Named contact | **5a. Named contact**<br>NICE<br><br>**5b Named contact e-mail**<br>breastcancerupdate@nice.org.uk<br><br>**5e Organisational affiliation of the review**<br>National Institute for Health and Care Excellence (NICE) and National Guideline Alliance | | |
| 25. | Review team members | Marie Harrisingh, Topic Lead<br>Olivia Crane, Senior technical analyst<br>Yolanda Martinez, Technical analyst<br>Adefisayo Abba-Abba, technical analyst<br>James Hawkins, Health economics adviser<br>Tzujung Lai, Health economist<br>Andrea Heath, Information specialist | | |
| 26. | Funding sources/sponsor | This systematic review is being completed by the Centre for Guidelines which receives funding from 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: Advanced breast cancer guideline [NICE guideline webpage]. | | |
| 29. | Other registration details | None | | |
| 30. | Reference/URL for published protocol | Not applicable | | |

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| 31. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>notifying registered stakeholders of publication<br>publicising the guideline through NICE's newsletter and alerts<br>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 | Advanced breast cancer; PET-CT; CECT; bone scintigraphy, monitoring |
| 33. | Details of existing review of same topic by same authors | Not applicable |
| 34. | Current review status | ☐ Ongoing<br>☐ Completed but not published<br>☒ Completed and published<br>☐ Completed, published and being updated<br>☐ Discontinued |
| 35.. | Additional information | None |
| 36. | Details of final publication | www.nice.org.uk |

# Appendix B – Literature search strategies

## B1 Background and development

### Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review.

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

### Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

## B1 Search limits and other restrictions

### Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol 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.

The limit to remove animal studies in the searches has been adapted from:

Dickersin K, Scherer R & Lefebvre C. (1994) Systematic reviews: identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

### Date limits

A date limit of 2005 to present was applied, as stated in the review protocol, because the guideline committee felt that this reflects the dates that the technologies in question have been in use in the NHS.

### B1 Search filters

### Clinical effectiveness searches

Line 39 in the Medline search strategy and lines 39-41 in the Embase search strategy are the "optimised" diagnostic test accuracy filters produced as part of the McMaster Hedges project:

Haynes RB, Wilczynski NL (2004) Optimal search strategies for retrieving scientifically strong studies of diagnosis from MEDLINE: analytical survey. *BMJ,* 328: 1040-2.

Wilczynski NL, Haynes RB et al (2025) EMBASE search strategies for identifying methodologically sound diagnostic studies for use by clinicians and researchers. *BMC Medicine*. 3, 7.

We are aware of the limitations of diagnostic test accuracy filters from the work of Benyon and colleagues (2013) and therefore have supplemented these filters with relevant outcome measure-related terms from the protocol as well as carrying out additional searching without using these filters. See:

Benyon R, Leeflang MMG, McDonald S et al (2013) Search strategies to identify diagnostic accuracy studies in MEDLINE and EMBASE. Cochrane Database of Systematic Reviews. Issue 9, 2013.

### Cost effectiveness searches

Searches for the review of cost effectiveness used various previously reported search filters including:

The sensitive version of the validated NICE cost utility filter was used in the MEDLINE and Embase:

Hubbard W et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

The sensitive version of the MEDLINE filter for health state utility value studies:

Arber et al (2017) Performance of Ovid MEDLINE search filters to identify health state utility studies. *International Journal of Technology Assessment in Health Care*. 33(4), 472-80

… and an adaptation of the terms used in:

Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

## B1 Key decisions

Searches of Epistemonikos were simplified and run as two separate “strands” in order to accommodate the limitations of Epistemonikos platform. Strand 1 corresponds to lines 1-46 in the Medline strategy. Strand 2 corresponds to lines 47-66 in Medline.

Date limits for references from Epistemonikos and the exclusion of records from trials registries were applied in EPPI reviewer rather than in the source database.

## B1 Clinical effectiveness searches

### Database results

| Databases | Date searched | Database platform | Database segment or version | No. of results downloaded |
|---|---|---|---|---|
| Medline ALL | 21st May 2025 | Ovid | 1946 to May 20th 2025 | 3400 |
| Embase | 21st May 2025 | Ovid | 1974 to May 20th 2025 | 4483 |
| Cochrane Database of Systematic Reviews (CDSR) | 21st May 2025 | Wiley | Issue 5 of 12, May 2025 | 1 |
| Cochrane Central Register of Controlled Trials (CENTRAL) | 21st May 2025 | Wiley | Issue 4 of 12, April 2025 | 103 |
| Epistemonikos | 21st May 2025 | - | - | 1935 (strand 1); 731 (strand 2) |

### Search strategy history

### Database name: Medline ALL

| Searches | |
|---|---|
| 1 | exp Breast Neoplasms/ 369540 |
| 2 | exp "Neoplasms, Ductal, Lobular, and Medullary"/ 50242 |
| 3 | Carcinoma, Lobular/ 6273 |
| 4 | Carcinoma, Medullary/ 3450 |
| 5 | Carcinoma, Intraductal, Noninfiltrating/ 11071 |
| 6 | or/1-5 391378 |
| 7 | exp Breast/ 55896 |
| 8 | breast*.ti,ab,kf. 614808 |
| 9 | 7 or 8 624851 |
| 10 | (breast adj milk).ti,ab,kf. 17696 |
| 11 | (breast adj tender*).ti,ab,kf. 613 |
| 12 | 10 or 11 18306 |
| 13 | 9 not 12 606545 |
| 14 | exp Neoplasms/4120612 |
| 15 | 13 and 14 389585 |
| 16 | (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 463885 |

| Searches |
|---|
| 17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 38000 |
| 18 Paget's Disease, Mammary/ 823 |
| 19 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1607 |
| 20 or/15-19 518297 |
| 21 6 or 20 577603 |
| 22 exp Neoplasm Metastasis/ 230891 |
| 23 ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 143164 |
| 24 (breast* or mammar*).ti,ab,kf. 667253 |
| 25 (((stage* or grade* or type*) adj2 ("4" or iv* or "M1" or mBC)) or T4*).ti,ab,kf. 242546 |
| 26 24 and 25 13305 |
| 27 or/22-23,26 358767 |
| 28 21 and 27 171047 |
| 29 exp Positron-Emission Tomography/ 87783 |
| 30 Positron Emission Tomography Computed Tomography/ 23742 |
| 31 Tomography, X-Ray Computed/ 438567 |
| 32 petct.tw. 121 |
| 33 ct.tw. 481196 |
| 34 cect.tw. 3838 |
| 35 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).tw. 1330 |
| 36 tomograph*.tw. 569362 |
| 37 or/29-36 1060602 |
| 38 28 and 37 7297 |
| 39 (sensitiv: or predictive value:).mp. or accurac:.tw. 2882523 |
| 40 specificity.tw. 614622 |
| 41 likelihood ratio*.tw. 21873 |
| 42 (lr or plr or nlr).tw. 47131 |
| 43 "test-and-treat".tw. 1570 |
| 44 diagnos*.ti. 750281 |
| 45 or/39-44 3756813 |
| 46 38 and 45 1983 |
| 47 exp *Breast/ or *"breast disease"/ 40940 |
| 48 (di or dg).fs. 4451431 |
| 49 47 and 48 12175 |
| 50 *Breast Neoplasms/di, dg 49050 |
| 51 exp Neoplasm Metastasis/ 230891 |
| 52 (49 or 50) and 51 4338 |
| 53 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti. 291399 |

| Searches |
|---|
| 54 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti. 16199 |
| 55 (paget* and (breast* or mammary or nipple*)).ti. 787 |
| 56 or/52-55 307935 |
| 57 exp *Positron-Emission Tomography/ 43638 |
| 58 *Positron Emission Tomography Computed Tomography/ 11829 |
| 59 *Tomography, X-Ray Computed/ 131336 |
| 60 petct.ti. 25 |
| 61 ct.ti. 115458 |
| 62 cect.ti. 310 |
| 63 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti. 209 |
| 64 tomograph*.ti. 146136 |
| 65 or/57-64 316585 |
| 66 56 and 65 3141 |
| 67 46 or 66 4307 |
| 68 limit 67 to (english language and yr="2005 -Current") 3578 |
| 69 animals/ 7681269 |
| 70 exp Animals, Laboratory/ 1000502 |
| 71 exp Animal Experimentation/ 10718 |
| 72 exp Models, Animal/ 684479 |
| 73 exp Rodentia/ 3720179 |
| 74 (rat or rats or mouse or mice or rodent*).ti. 1530952 |
| 75 or/69-74 7813487 |
| 76 75 not humans/ 5436987 |
| 77 68 not 76 3513 |
| 78 limit 77 to (clinical conference or comment or congress or editorial or letter or news or overall) 113 |
| 79 77 not 78 3400 |

## Database name: Embase

| Searches |
|---|
| 1 exp breast cancer/ 649177 |
| 2 exp breast carcinoma/ 117209 |
| 3 exp medullary carcinoma/ 13971 |
| 4 ductal breast carcinoma in situ/ 23027 |
| 5 exp breast tumor/ 737862 |
| 6 exp lobular carcinoma/ 6889 |
| 7 or/1-6 750090 |
| 8 exp breast/ 131711 |
| 9 breast*.ti,ab,kf. 854621 |
| 10 8 or 9 888280 |
| 11 (breast adj milk).ti,ab,kf. 23045 |

| Searches | |
|---|---|
| 12 | (breast adj tender*).ti,ab,kf. 819 |
| 13 | 11 or 12 23858 |
| 14 | 10 not 13 864422 |
| 15 | exp neoplasm/ 6326656 |
| 16 | 14 and 15 672460 |
| 17 | (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 667274 |
| 18 | (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 45362 |
| 19 | exp Paget nipple disease/ 8069 |
| 20 | (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1995 |
| 21 | or/16-20 744143 |
| 22 | 7 or 21 879022 |
| 23 | metastatic breast cancer/ 33115 |
| 24 | ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 210912 |
| 25 | (breast* or mammar*).ti,ab,kf. 911754 |
| 26 | (((stage* or grade* or type*) adj2 ("4" or iv* or "M1" or mBC)) or T4*).ti,ab,kf. 412602 |
| 27 | 25 and 26 25937 |
| 28 | or/23-24,27 232127 |
| 29 | 22 and 28 228196 |
| 30 | exp positron emission tomography/ 271684 |
| 31 | exp computer assisted tomography/ or exp x-ray tomography/ 1605477 |
| 32 | petct.tw. 1284 |
| 33 | ct.tw. 833617 |
| 34 | cect.tw. 6891 |
| 35 | (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).tw. 2051 |
| 36 | tomograph*.tw. 727236 |
| 37 | or/30-36 2044588 |
| 38 | 29 and 37 17431 |
| 39 | sensitiv*.tw. 2300504 |
| 40 | diagnostic accuracy.sh. 343089 |
| 41 | diagnostic.tw. 1402469 |
| 42 | specificity.tw. 803069 |
| 43 | likelihood ratio*.tw. 29691 |
| 44 | (lr or plr or nlr).tw. 70336 |
| 45 | "test-and-treat".tw. 2331 |
| 46 | diagnos*.ti. 896062 |
| 47 | or/39-46 4383270 |
| 48 | 38 and 47 4162 |
| 49 | exp *breast/ or *"breast disease"/ 38835 |
| 50 | di.fs. 3834220 |

| Searches |
|---|
| 51 49 and 50 4728 |
| 52 exp *breast cancer/di 55943 |
| 53 exp *breast carcinoma/di 12111 |
| 54 exp *medullary carcinoma/di 1830 |
| 55 *ductal breast carcinoma in situ/di 2009 |
| 56 exp *breast tumor/di 68069 |
| 57 exp *lobular carcinoma/di 429 |
| 58 exp metastasis/ 902432 |
| 59 (51 or 52 or 53 or 54 or 55 or 56 or 57) and 58 14463 |
| 60 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti. 406279 |
| 61 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti. 17179 |
| 62 (paget* and (breast* or mammary or nipple*)).ti. 813 |
| 63 or/59-62 425619 |
| 64 exp *positron emission tomography/ 84778 |
| 65 exp *computer assisted tomography/ or exp *x-ray tomography/ 342343 |
| 66 petct.ti. 211 |
| 67 ct.ti. 176587 |
| 68 cect.ti. 458 |
| 69 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti. 256 |
| 70 tomograph*.ti. 173852 |
| 71 or/64-70 459061 |
| 72 63 and 71 5671 |
| 73 48 or 72 8693 |
| 74 limit 73 to (english language and yr="2005 -Current") 7635 |
| 75 animal/ 1703637 |
| 76 nonhuman/ 8145866 |
| 77 exp Animal Experiment/ 3358476 |
| 78 exp Experimental Animal/ 893770 |
| 79 animal model/ 1916835 |
| 80 exp Rodent/ 4311562 |
| 81 (rat or rats or mouse or mice or rodent*).ti. 1715655 |
| 82 or/75-81 10730312 |
| 83 82 not human/ 7601048 |
| 84 74 not 83 7349 |
| 85 limit 84 to (editorial or letter) 135 |
| 86 84 not 85 7214 |
| 87 conference*.db,pt,su. 6266709 |
| 88 86 not 87 4623 |
| 89 limit 88 to "remove clinical trial (clinicaltrials.gov) records" 4483 |

**Database name: Cochrane Database of Systematic Reviews and CENTRAL**

| **Searches** | | |
|---|---|---|
| ID | Search | Hits |
| #1 | (breast* NEAR/5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw | 49644 |
| #2 | (mammar* NEAR/5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw | 322 |
| #3 | (paget* and (breast* or mammary or nipple*)):ti,ab,kw | 99 |
| #4 | {or #1-#3} | 49748 |
| #5 | ((breast* or mammar* or TNBC or (triple NEAR/3 negativ*) or (triple-negativ*) or BRCA*) NEAR/3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)):ti,ab,kw | 18599 |
| #6 | (breast* or mammar*):ti,ab,kw | 69342 |
| #7 | (((stage* or grade* or type*) NEAR/2 ("4" or iv* or "M1" or mBC)) or T4*):ti,ab,kw | 41438 |
| #8 | #6 AND #7 | 2903 |
| #9 | #5 OR #8 | 20016 |
| #10 | #4 AND #9 | 19153 |
| #11 | petct:ti,ab | 2550 |
| #12 | ct:ti,ab | 43458 |
| #13 | cect:ti,ab | 285 |
| #14 | (CAT NEXT ((electron-beam*) or (electron beam*) or examination* or imag* or scan* or (x ray*) or (x-ray*))):ti,ab | 36 |
| #15 | tomograph*:ti,ab | 25958 |
| #16 | {or #11-#15} | 61529 |
| #17 | #10 and #16 | 1128 |
| #18 | (sensitiv* or "predictive value" or "predictive values") | 117937 |
| #19 | accurac*:ti,ab | 26050 |
| #20 | specificity:ti,ab | 14543 |
| #21 | ("likelihood ratio" OR "likelihood ratios"):ti,ab | 974 |
| #22 | (lr or plr or nlr):ti,ab | 3036 |
| #23 | ("test-and-treat" OR "test and treat"):ti,ab | 237 |
| #24 | diagnos*:ti | 20947 |
| #25 | {or #18-#24} | 157552 |
| #26 | #17 AND #25 | 162 |
| #27 | (breast* NEAR/5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti | 34827 |
| #28 | (mammar* NEAR/5 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti | 111 |
| #29 | (paget* and (breast* or mammary or nipple*)):ti | 1 |
| #30 | {or #27-#29} | 34923 |
| #31 | petct:ti | 770 |
| #32 | ct:ti | 6768 |

| Searches |
| --- |
| #33 cect:ti 39 |
| #34 (CAT NEXT ((electron-beam*) or (electron beam*) or examination* or imag* or scan* or (x ray*) or (x-ray*))):ti 1 |
| #35 tomograph*:ti 4993 |
| #36 {or #31-#35} 11620 |
| #37 #30 AND #36 300 |
| #38 #26 OR #37 427 |
| #39 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an570462 |
| #40 "conference":pt 258258 |
| #41 #38 NOT (#39 OR #40) 195 |
| #42 #41 with Publication Year from 2005 to 2025, in Trials 103 |
| #43 #41 with Cochrane Library publication date Between Jan 2005 and Dec 2025, in Cochrane Reviews 1 |

## Database name: Epistemonikos

| Searches |
| --- |
| ***Strand 1*** |
| (title:(((breast* OR mammar* OR tnbc OR (triple AND negativ*) OR (triple-negativ*) OR brca*) AND (metasta* OR advanc* OR second* OR recur* OR disseminat* OR incur* OR malign* OR carcino* OR invasive OR oligometasta*)) OR ((breast* OR mammar*) AND (((stage* OR grade* OR type*) AND ("4" OR iv* OR "m1" OR mbc)) OR t4*))) OR abstract:(((breast* OR mammar* OR tnbc OR (triple AND negativ*) OR (triple-negativ*) OR brca*) AND (metasta* OR advanc* OR second* OR recur* OR disseminat* OR incur* OR malign* OR carcino* OR invasive OR oligometasta*)) OR ((breast* OR mammar*) AND (((stage* OR grade* OR type*) AND ("4" OR iv* OR "m1" OR mbc)) OR t4*)))) AND (title:(petct OR ct OR cect OR (cat AND ((electron-beam*) OR (electron beam*) OR examination* OR imag* OR scan* OR (x ray*) OR (x-ray*))) OR tomograph*) OR abstract:(petct OR ct OR cect OR (cat AND ((electron-beam*) OR (electron beam*) OR examination* OR imag* OR scan* OR (x ray*) OR (x-ray*))) OR tomograph*)) AND (title:(sensitiv* OR "predictive value" OR "predictive values" OR accurac* OR specificity OR "likelihood ratio" OR "likelihood ratios" OR lr OR plr OR nlr OR "test-and-treat" OR "test AND treat" OR diagnos*) OR abstract:(sensitiv* OR "predictive value" OR "predictive values" OR accurac* OR specificity OR "likelihood ratio" OR "likelihood ratios" OR lr OR plr OR nlr OR "test-and-treat" OR "test AND treat" OR diagnos*)) |
| ***Strand 2*** |
| title:((breast* AND (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (paget* AND (breast* OR mammary OR nipple*))) |

| Searches |
| --- |
| AND title:(petct OR ct OR cect OR (cat AND ((electron-beam*) OR (electron beam*) OR examination* OR imag* OR scan* OR (x ray*) OR (x-ray*))) OR tomograph*) |

## B1 Cost-effectiveness searches

## Database results

| Databases | Date searched | Database platform | Database segment or version | No. of results downloaded |
|---|---|---|---|---|
| Medline ALL | 22nd May 2025 | Ovid | 1946 to 21st May 2025 | 138 |
| Embase | 22nd May 2025 | Ovid | 1974 to 21st May 2025 | 222 |
| INAHTA International HTA Database | 28th May 2025 | - | - | 63 |

## Search strategy history

## Database name: Medline ALL

| Searches | | |
|---|---|---|
| 1 | exp Breast Neoplasms/ | 368522 |
| 2 | exp "Neoplasms, Ductal, Lobular, and Medullary"/ | 50141 |
| 3 | Carcinoma, Lobular/ | 6270 |
| 4 | Carcinoma, Medullary/ | 3447 |
| 5 | Carcinoma, Intraductal, Noninfiltrating/ | 11058 |
| 6 | or/1-5 | 390287 |
| 7 | exp Breast/ | 55835 |
| 8 | breast*.ti,ab,kf. | 613373 |
| 9 | 7 or 8 | 623414 |
| 10 | (breast adj milk).ti,ab,kf. | 17652 |
| 11 | (breast adj tender*).ti,ab,kf. | 612 |
| 12 | 10 or 11 | 18261 |
| 13 | 9 not 12 | 605153 |
| 14 | exp Neoplasms/ | 4111269 |
| 15 | 13 and 14 | 388403 |
| 16 | (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. | 462761 |
| 17 | (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. | 37961 |
| 18 | Paget's Disease, Mammary/ | 823 |
| 19 | (paget* and (breast* or mammary or nipple*)).ti,ab,kf. | 1606 |
| 20 | or/15-19 | 517108 |
| 21 | 6 or 20 | 576325 |
| 22 | exp Neoplasm Metastasis/ | 230442 |

| Searches |
|---|
| 23 ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 142935 |
| 24 (breast* or mammar*).ti,ab,kf. 665775 |
| 25 (((stage* or grade* or type*) adj2 ("4" or iv* or "M1" or mBC)) or T4*).ti,ab,kf. 241969 |
| 26 24 and 25 13277 |
| 27 or/22-23,26 358126 |
| 28 21 and 27 170774 |
| 29 exp Positron-Emission Tomography/ 87477 |
| 30 Positron Emission Tomography Computed Tomography/ 23599 |
| 31 Tomography, X-Ray Computed/ 437771 |
| 32 petct.tw. 121 |
| 33 ct.tw. 479915 |
| 34 cect.tw. 3828 |
| 35 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).tw. 1329 |
| 36 tomograph*.tw. 568077 |
| 37 or/29-36 1058363 |
| 38 28 and 37 7277 |
| 39 (sensitiv: or predictive value:).mp. or accurac:.tw. 2873766 |
| 40 specificity.tw. 612842 |
| 41 likelihood ratio*.tw. 21811 |
| 42 (lr or plr or nlr).tw. 46849 |
| 43 "test-and-treat".tw. 1562 |
| 44 diagnos*.ti. 748911 |
| 45 or/39-44 3746554 |
| 46 38 and 45 1974 |
| 47 exp *Breast/ or *"breast disease"/ 40916 |
| 48 (di or dg).fs. 4441248 |
| 49 47 and 48 12166 |
| 50 *Breast Neoplasms/di, dg 48871 |
| 51 exp Neoplasm Metastasis/ 230442 |
| 52 (49 or 50) and 51 4322 |
| 53 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti. 290661 |
| 54 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti. 16189 |
| 55 (paget* and (breast* or mammary or nipple*)).ti. 787 |
| 56 or/52-55 307185 |
| 57 exp *Positron-Emission Tomography/ 43429 |
| 58 *Positron Emission Tomography Computed Tomography/ 11735 |
| 59 *Tomography, X-Ray Computed/ 130976 |
| 60 petct.ti. 25 |
| 61 ct.ti. 115172 |

| Searches |
|---|
| 62 cect.ti. 311 |
| 63 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti. 209 |
| 64 tomograph*.ti. 145916 |
| 65 or/57-64 315844 |
| 66 56 and 65 3127 |
| 67 46 or 66 4291 |
| 68 limit 67 to (english language and yr="2005 -Current") 3562 |
| 69 animals/ 7665219 |
| 70 exp Animals, Laboratory/ 997968 |
| 71 exp Animal Experimentation/ 10709 |
| 72 exp Models, Animal/ 682287 |
| 73 exp Rodentia/ 3713295 |
| 74 (rat or rats or mouse or mice or rodent*).ti. 1529238 |
| 75 or/69-74 7797504 |
| 76 75 not humans/ 5428563 |
| 77 68 not 76 3497 |
| 78 limit 77 to (clinical conference or comment or congress or editorial or letter or news or overall) 113 |
| 79 77 not 78 3384 |
| 80 Cost-Benefit Analysis/ 97786 |
| 81 Quality-Adjusted Life Years/ 17821 |
| 82 Markov Chains/ 17074 |
| 83 exp Models, Economic/ 16828 |
| 84 cost*.ti. 157550 |
| 85 (cost* adj2 utilit*).tw. 8712 |
| 86 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. 319807 |
| 87 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 54041 |
| 88 (qualit* adj2 adjust* adj2 life*).tw. 20272 |
| 89 QALY*.tw. 16488 |
| 90 (incremental* adj2 cost*).tw. 19740 |
| 91 ICER.tw. 7209 |
| 92 utilities.tw. 10472 |
| 93 markov*.tw. 35561 |
| 94 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. 59334 |
| 95 ((utility or effective*) adj2 analys*).tw. 28592 |
| 96 (willing* adj2 pay*).tw. 11606 |
| 97 (EQ5D* or EQ-5D*).tw. 16089 |
| 98 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 4781 |
| 99 (european* adj2 quality adj3 ("5" or five)).tw. 865 |
| 100 or/80-99 565481 |
| 101 Quality-Adjusted Life Years/ 17821 |

| Searches |
|---|
| 102 (quality adjusted or adjusted life year$).ti,ab,kf. 28632 |
| 103 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. 16944 |
| 104 (illness state$1 or health state$1).ti,ab,kf. 9407 |
| 105 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2222 |
| 106 (multiattribute$ or multi attribute$).ti,ab,kf. 1588 |
| 107 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. 23388 |
| 108 utilities.ti,ab,kf. 10598 |
| 109 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or euroqol or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. 21009 |
| 110 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. 7144 |
| 111 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. 29247 |
| 112 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. 2700 |
| 113 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. 17819 |
| 114 quality of life/ and ec.fs. 11386 |
| 115 quality of life/ and (health adj3 status).ti,ab,kf. 13146 |
| 116 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ 18901 |
| 117 ((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. 64171 |
| 118 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf. 6049 |
| 119 *quality of life/ and (quality of life or qol).ti. 70729 |
| 120 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf. 48687 |
| 121 quality of life/ and health-related quality of life.ti,ab,kf. 51187 |
| 122 models, economic/ 11591 |
| 123 or/101-122 255277 |
| 124 Economics/ 27544 |
| 125 Value of life/ 5837 |
| 126 exp "Costs and Cost Analysis"/ 278874 |
| 127 exp Economics, Hospital/ 26198 |
| 128 exp Economics, Medical/ 14461 |
| 129 Economics, Nursing/ 4013 |
| 130 Economics, Pharmaceutical/ 3163 |
| 131 exp "Fees and Charges"/ 31683 |
| 132 exp Budgets/ 14346 |
| 133 budget*.ti,ab. 39658 |
| 134 cost*.ti,ab. 896113 |
| 135 (economic* or pharmaco?economic*).ti. 67676 |
| 136 (price* or pricing*).ti,ab. 60154 |
| 137 (cua or cea or cca or cba or cma).ti,ab. 60733 |

| Searches | | |
|---|---|---|
| 138 | (financ* or fee or fees).ti,ab. | 184878 |
| 139 | (value adj2 (money or monetary)).ti,ab. | 3413 |
| 140 | or/124-139 | 1340362 |
| 141 | 100 or 123 or 140 | 1599794 |
| 142 | 79 and 141 | 138 |

## Database name: Embase

| Searches | | |
|---|---|---|
| 1 | exp breast cancer/ | 649293 |
| 2 | exp breast carcinoma/ | 117214 |
| 3 | exp medullary carcinoma/ | 13972 |
| 4 | ductal breast carcinoma in situ/ | 23028 |
| 5 | exp breast tumor/ | 737979 |
| 6 | exp lobular carcinoma/ | 6890 |
| 7 | or/1-6 | 750208 |
| 8 | exp breast/ | 131714 |
| 9 | breast*.ti,ab,kf. | 854783 |
| 10 | 8 or 9 | 888445 |
| 11 | (breast adj milk).ti,ab,kf. | 23048 |
| 12 | (breast adj tender*).ti,ab,kf. | 820 |
| 13 | 11 or 12 | 23862 |
| 14 | 10 not 13 | 864583 |
| 15 | exp neoplasm/ | 6327825 |
| 16 | 14 and 15 | 672590 |
| 17 | (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. | 667404 |
| 18 | (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. | 45363 |
| 19 | exp Paget nipple disease/ | 8069 |
| 20 | (paget* and (breast* or mammary or nipple*)).ti,ab,kf. | 1995 |
| 21 | or/16-20 | 744277 |
| 22 | 7 or 21 | 879158 |
| 23 | metastatic breast cancer/ | 33122 |
| 24 | ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. | 210940 |
| 25 | (breast* or mammar*).ti,ab,kf. | 911917 |
| 26 | (((stage* or grade* or type*) adj2 ("4" or iv* or "M1" or mBC)) or T4*).ti,ab,kf. | 412703 |
| 27 | 25 and 26 | 25941 |
| 28 | or/23-24,27 | 232157 |
| 29 | 22 and 28 | 228226 |

| Searches | |
|---|---|
| 30 | exp positron emission tomography/ 271713 |
| 31 | exp computer assisted tomography/ or exp x-ray tomography/ 1605682 |
| 32 | petct.tw. 1284 |
| 33 | ct.tw. 833775 |
| 34 | cect.tw. 6892 |
| 35 | (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).tw. 2051 |
| 36 | tomograph*.tw. 727407 |
| 37 | or/30-36 2044880 |
| 38 | 29 and 37 17431 |
| 39 | sensitiv*.tw. 2300958 |
| 40 | diagnostic accuracy.sh. 343138 |
| 41 | diagnostic.tw. 1402866 |
| 42 | specificity.tw. 803244 |
| 43 | likelihood ratio*.tw. 29693 |
| 44 | (lr or plr or nlr).tw. 70358 |
| 45 | "test-and-treat".tw. 2332 |
| 46 | diagnos*.ti. 896235 |
| 47 | or/39-46 4384151 |
| 48 | 38 and 47 4162 |
| 49 | exp *breast/ or *"breast disease"/ 38836 |
| 50 | di.fs. 3834220 |
| 51 | 49 and 50 4728 |
| 52 | exp *breast cancer/di 55943 |
| 53 | exp *breast carcinoma/di 12111 |
| 54 | exp *medullary carcinoma/di 1830 |
| 55 | *ductal breast carcinoma in situ/di 2009 |
| 56 | exp *breast tumor/di 68069 |
| 57 | exp *lobular carcinoma/di 429 |
| 58 | exp metastasis/ 902729 |
| 59 | (51 or 52 or 53 or 54 or 55 or 56 or 57) and 58 14463 |
| 60 | (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti. 406366 |
| 61 | (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti. 17179 |
| 62 | (paget* and (breast* or mammary or nipple*)).ti. 813 |
| 63 | or/59-62 425706 |
| 64 | exp *positron emission tomography/ 84798 |
| 65 | exp *computer assisted tomography/ or exp *x-ray tomography/ 342416 |
| 66 | petct.ti. 211 |
| 67 | ct.ti. 176622 |
| 68 | cect.ti. 458 |
| 69 | (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti. 256 |
| 70 | tomograph*.ti. 173878 |

| Searches |
|---|
| 71 or/64-70 459146 |
| 72 63 and 71 5672 |
| 73 48 or 72 8694 |
| 74 limit 73 to (english language and yr="2005 -Current") 7636 |
| 75 animal/ 1703680 |
| 76 nonhuman/ 8147200 |
| 77 exp Animal Experiment/ 3358972 |
| 78 exp Experimental Animal/ 893926 |
| 79 animal model/ 1917202 |
| 80 exp Rodent/ 4312028 |
| 81 (rat or rats or mouse or mice or rodent*).ti. 1715776 |
| 82 or/75-81 10731739 |
| 83 82 not human/ 7601835 |
| 84 74 not 83 7350 |
| 85 limit 84 to (editorial or letter) 135 |
| 86 84 not 85 7215 |
| 87 conference*.db,pt,su. 6267799 |
| 88 86 not 87 4624 |
| 89 limit 88 to "remove clinical trial (clinicaltrials.gov) records" 4484 |
| 90 cost utility analysis/ 13892 |
| 91 quality adjusted life year/ 40388 |
| 92 cost*.ti. 210951 |
| 93 (cost* adj2 utilit*).tw. 14297 |
| 94 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. 438856 |
| 95 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 75445 |
| 96 (qualit* adj2 adjust* adj2 life*).tw. 30736 |
| 97 QALY*.tw. 30156 |
| 98 (incremental* adj2 cost*).tw. 32123 |
| 99 ICER.tw. 14970 |
| 100 utilities.tw. 16657 |
| 101 markov*.tw. 44546 |
| 102 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. 80453 |
| 103 ((utility or effective*) adj2 analys*).tw. 42861 |
| 104 (willing* adj2 pay*).tw. 17007 |
| 105 (EQ5D* or EQ-5D*).tw. 30799 |
| 106 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 6341 |
| 107 (european* adj2 quality adj3 ("5" or five)).tw. 1186 |
| 108 or/90-107 714592 |
| 109 quality-adjusted life year/ 40388 |
| 110 (quality adjusted or adjusted life year$).ti,ab,kf. 41111 |
| 111 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. 30883 |

| Searches |
|---|
| 112 (illness state$1 or health state$1).ti,ab,kf. 16401 |
| 113 (hui or hui1 or hui2 or hui3).ti,ab,kf. 3626 |
| 114 (multiattribute$ or multi attribute$).ti,ab,kf. 1783 |
| 115 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. 36752 |
| 116 utilities.ti,ab,kf. 16898 |
| 117 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or euroqol or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. 37268 |
| 118 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. 10599 |
| 119 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. 50402 |
| 120 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. 3970 |
| 121 "quality of life"/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. 38251 |
| 122 "quality of life"/ and (pe or de).fs. 10948 |
| 123 "quality of life"/ and (health adj3 status).ti,ab,kf. 24246 |
| 124 (quality of life or qol).ti,ab,kf. and "cost benefit analysis"/ 7467 |
| 125 ((qol or hrqol or quality of life).ti,kf. or *"quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. 89618 |
| 126 "cost benefit analysis"/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf. 1387 |
| 127 *"quality of life"/ and (quality of life or qol).ti. 127429 |
| 128 "quality of life"/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf. 122458 |
| 129 "quality of life"/ and health-related quality of life.ti,ab,kf. 91065 |
| 130 exp economic model/ 4911 |
| 131 or/109-130 437823 |
| 132 Health economics/ 37268 |
| 133 exp health care cost/ 369440 |
| 134 exp Fee/ 46579 |
| 135 exp Budget/ 36324 |
| 136 Funding/ 82784 |
| 137 budget*.ti,ab. 52336 |
| 138 cost*.ti,ab. 1190995 |
| 139 (economic* or pharmaco?economic*).ti. 84066 |
| 140 (price* or pricing*).ti,ab. 81627 |
| 141 (cua or cea or cca or cba or cma).ti,ab. 88630 |
| 142 (financ* or fee or fees).ti,ab. 267755 |
| 143 (value adj2 (money or monetary)).ti,ab. 4536 |
| 144 or/132-143 1842324 |
| 145 108 or 131 or 144 2267384 |
| 146 89 and 145 222 |

**Database name: INAHTA International HTA Database**

Note that the total number of results from this database was reduced to 63 when on-screen limits for English language publications and publications from 2005 onwards were applied.

| Line | Query | Hits |
|---|---|---|
| 24 | #23 AND #22 | 108 |
| 23 | #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 | 1271 |
| 22 | #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 | 1070 |
| 21 | tomograph* | 475 |
| 20 | CAT AND (electron* OR examination* OR imag* OR scan* OR ray* OR xray* OR x-ray*) | 6 |
| 19 | cect | 0 |
| 18 | ((electron* OR imag* OR scan* OR ray* OR xray* OR x-ray*))[title] | 778 |
| 17 | FDG* | 70 |
| 16 | 18F* | 19 |
| 15 | pet/ct | 228 |
| 14 | pet–ct | 228 |
| 13 | pet-ct | 71 |
| 12 | petct | 1 |
| 11 | "Tomography, X-Ray Computed"[mh] | 183 |
| 10 | "Positron Emission Tomography Computed Tomography"[mh] | 31 |
| 9 | "Positron-Emission Tomography"[mhe] | 147 |
| 8 | TNBC OR (triple AND negativ*) OR BRCA* | 76 |
| 7 | breast* OR mammar* OR paget* | 1013 |
| 6 | "Paget's Disease, Mammary"[mh] | 0 |
| 5 | "Carcinoma, Intraductal, Noninfiltrating"[mh] | 4 |
| 4 | "Carcinoma, Medullary"[mh] | 4 |
| 3 | "Carcinoma, Lobular"[mh] | 0 |
| 2 | "Neoplasms, Ductal, Lobular, and Medullary"[mhe] | 18 |
| 1 | "Breast Neoplasms"[mhe] | 717 |

## B2 Background and development

### Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review.

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

### Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

### Prior work

The search strategy was adapted from the original CG81 search but changed structurally due to changes to the review question.

## B2 Search limits and other restrictions

### Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol 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.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic reviews: identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

### Date limits

A date limit of 20 years was applied in adherence to the review protocol for the effectiveness search. A default 15 year date limit was applied for the cost-effectiveness search.

### B2 Search filters and classifiers

### Effectiveness searches

RCT filters:

- McMaster Therapy – Medline – "best balance of sensitivity and specificity" version
    - Haynes RB e al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ, 330, 1179-1183.
- McMaster Therapy – Embase "best balance of sensitivity and specificity" version.
    - Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

### Cost effectiveness searches

In line with the review protocol, the sensitive version of the validated NICE cost utility filter was used in the MEDLINE and Embase strategies without amendment.

> Hubbard W et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

### B2 Key decisions

Translations of the databases for the effectiveness and cost-effectiveness searches were done as appropriate to the size and interface of the individual databases.

### B2 Clinical effectiveness searches

### Database results

| Databases | Date searched | Database platform | Database segment or version | No. of results downloaded |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Cochrane Central Register of Controlled Trials (CENTRAL) | 09/07/2025 | Wiley | Cochrane Central Register of Controlled Trials Issue 6 of 12, June 202 | 456 |
| Cochrane Database of Systematic Reviews (CDSR) | 09/07/2025 | Wiley | Cochrane Database of Systematic Reviews Issue 7 of 12, July 2025 | 0 |
| Embase | 09/07/2025 | Ovid | Embase <1974 to 2025 July 08> | 186 |
| Epistemonikos | 09/07/2025 | https://www.epistemonikos.org/ | | 219 |
| MEDLINE ALL | 09/07/2025 | Ovid | Ovid MEDLINE(R) ALL <1946 to July 08, 2025> | 85 |

**Search strategy history**

**Database name: Cochrane Central Register of Controlled Trials (CENTRAL)**

| **Searches** | | |
|---|---|---|
| #1 | [mh “Breast Neoplasms”] | 20894 |
| #2 | [mh “Neoplasms, Ductal, Lobular, and Medullary”] | 1036 |
| #3 | [mh ^“Carcinoma, Lobular”] | 219 |
| #4 | [mh ^“Carcinoma, Medullary”] | 21 |
| #5 | [mh ^“Carcinoma, Intraductal, Noninfiltrating”] | 312 |
| #6 | {OR #1-#5} | 21222 |
| #7 | [mh Breast] | 1156 |
| #8 | breast*:ti,ab,kw | 69224 |
| #9 | #7 or #8 | 69246 |
| #10 | (breast NEXT milk):ti,ab,kw | 3464 |
| #11 | (breast NEXT tender*):ti,ab,kw | 425 |
| #12 | #10 or #11 | 3887 |
| #13 | #9 not #12 | 65359 |

| Searches |
|---|
| #14 [mh Neoplasms] 128505 |
| #15 #13 and #14 22802 |
| #16 (breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw 50155 |
| #17 (mammar* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw 317 |
| #18 [mh ^“Paget’s Disease, Mammary”] 3 |
| #19 (paget* and (breast* or mammary or nipple*)):ti,ab,kw 99 |
| #20 {OR #15-#19} 50535 |
| #21 #6 or #20 50839 |
| #22 [mh “Neoplasm Metastasis”] 7711 |
| #23 ((breast* or mammar* or TNBC or (triple NEAR/3 negativ*) or BRCA*) NEAR/3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)):ti,ab,kw 18749 |
| #24 (breast* or mammar*):ti,ab,kw 70038 |
| #25 (((stage* or grade* or type*) NEAR/2 ("4" or iv* or "M1" or mBC)) or T4*):ti,ab,kw 41887 |
| #26 #24 and #25 2924 |
| #27 #22 or #23 or #26 26386 |
| #28 #21 and #27 20259 |
| #29 [mh “Positron-Emission Tomography”] 1910 |
| #30 [mh “Tomography, X-Ray Computed”] 8895 |
| #31 [mh ^“Tomography, Emission-Computed”] 675 |
| #32 [mh ^“Fluorodeoxyglucose F18”] 944 |
| #33 petct:ti,ab,kw 2615 |
| #34 ct:ti,ab,kw 81851 |
| #35 cect:ti,ab,kw 287 |
| #36 (CAT NEXT ((electron-beam*) or (electron beam*) or examination* or imag* or scan* or (x ray*) or (x-ray*))):ti,ab,kw 36 |
| #37 tomogra*:ti,ab,kw 40376 |
| #38 (fluorodeoxyglucose* or 18F* or (FDG PET*) or (FDG-PET*)):ti,ab,kw 4175 |
| #39 {OR #29-#38} 107848 |
| #40 #28 and #39 1813 |
| #41 [mh “Treatment Outcome”] 204461 |
| #42 [mh ^“Monitoring, Physiologic”] 2782 |
| #43 (monitor* NEAR/2 (treatment* or therap* or disease*)):ti,ab,kw 6080 |
| #44 (response* NEAR/3 (monitor* or evaluat* or assess* or treat* or therap* or categori* or progress* or regress* or disease*)):ti,ab,kw 82386 |
| #45 PERCIST:ti,ab,kw 48 |
| #46 {OR #41-#45} 278732 |

| Searches |
|---|
| #47 #40 and #46 with Cochrane Library publication date Between Jan 2005 and Jul 2025, in Cochrane Reviews, Cochrane Protocols 0 |
| #48 #40 and #46 with Publication Year from 2005 to 2025, in Trials 729 |
| #49 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 578519 |
| #50 "conference":pt 261367 |
| #51 #49 or #50 839886 |
| #52 #48 not #51 456 |

**Database name: Cochrane Database of Systematic Reviews (CDSR)**

| Searches |
|---|
| #1 [mh “Breast Neoplasms”] 20894 |
| #2 [mh “Neoplasms, Ductal, Lobular, and Medullary”] 1036 |
| #3 [mh ^“Carcinoma, Lobular”] 219 |
| #4 [mh ^“Carcinoma, Medullary”] 21 |
| #5 [mh ^“Carcinoma, Intraductal, Noninfiltrating”] 312 |
| #6 {OR #1-#5} 21222 |
| #7 [mh Breast] 1156 |
| #8 breast*:ti,ab,kw 69224 |
| #9 #7 or #8 69246 |
| #10 (breast NEXT milk):ti,ab,kw 3464 |
| #11 (breast NEXT tender*):ti,ab,kw 425 |
| #12 #10 or #11 3887 |
| #13 #9 not #12 65359 |
| #14 [mh Neoplasms] 128505 |
| #15 #13 and #14 22802 |
| #16 (breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw 50155 |
| #17 (mammar* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw 317 |
| #18 [mh ^“Paget’s Disease, Mammary”] 3 |
| #19 (paget* and (breast* or mammary or nipple*)):ti,ab,kw 99 |
| #20 {OR #15-#19} 50535 |
| #21 #6 or #20 50839 |
| #22 [mh “Neoplasm Metastasis”] 7711 |

| Searches |
|---|
| #23 ((breast* or mammar* or TNBC or (triple NEAR/3 negativ*) or BRCA*) NEAR/3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)):ti,ab,kw 18749 |
| #24 (breast* or mammar*):ti,ab,kw 70038 |
| #25 (((stage* or grade* or type*) NEAR/2 ("4" or iv* or "M1" or mBC)) or T4*):ti,ab,kw 41887 |
| #26 #24 and #25 2924 |
| #27 #22 or #23 or #26 26386 |
| #28 #21 and #27 20259 |
| #29 [mh “Positron-Emission Tomography”] 1910 |
| #30 [mh “Tomography, X-Ray Computed”] 8895 |
| #31 [mh ^“Tomography, Emission-Computed”] 675 |
| #32 [mh ^“Fluorodeoxyglucose F18”] 944 |
| #33 petct:ti,ab,kw 2615 |
| #34 ct:ti,ab,kw 81851 |
| #35 cect:ti,ab,kw 287 |
| #36 (CAT NEXT ((electron-beam*) or (electron beam*) or examination* or imag* or scan* or (x ray*) or (x-ray*))):ti,ab,kw 36 |
| #37 tomogra*:ti,ab,kw 40376 |
| #38 (fluorodeoxyglucose* or 18F* or (FDG PET*) or (FDG-PET*)):ti,ab,kw 4175 |
| #39 {OR #29-#38} 107848 |
| #40 #28 and #39 1813 |
| #41 [mh “Treatment Outcome”] 204461 |
| #42 [mh ^“Monitoring, Physiologic”] 2782 |
| #43 (monitor* NEAR/2 (treatment* or therap* or disease*)):ti,ab,kw 6080 |
| #44 (response* NEAR/3 (monitor* or evaluat* or assess* or treat* or therap* or categori* or progress* or regress* or disease*)):ti,ab,kw 82386 |
| #45 PERCIST:ti,ab,kw 48 |
| #46 {OR #41-#45} 278732 |
| #47 #40 and #46 with Cochrane Library publication date Between Jan 2005 and Jul 2025, in Cochrane Reviews, Cochrane Protocols 0 |

**Database name: Embase**

| Searches |
|---|
| 1 exp breast cancer/ 665293 |
| 2 exp breast carcinoma/ 118573 |
| 3 exp medullary carcinoma/ 14188 |
| 4 ductal breast carcinoma in situ/ 23394 |
| 5 exp breast tumor/ 754445 |
| 6 exp lobular carcinoma/ 7114 |

| Searches |
|---|
| 7 or/1-6 766870 |
| 8 exp breast/ 132609 |
| 9 breast*.ti,ab,kf. 876300 |
| 10 8 or 9 910145 |
| 11 (breast adj milk).ti,ab,kf. 23915 |
| 12 (breast adj tender*).ti,ab,kf. 853 |
| 13 11 or 12 24761 |
| 14 10 not 13 885384 |
| 15 exp neoplasm/ 6452532 |
| 16 14 and 15 689580 |
| 17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 683952 |
| 18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 45610 |
| 19 exp Paget nipple disease/ 8074 |
| 20 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 2010 |
| 21 or/16-20 761845 |
| 22 7 or 21 897638 |
| 23 metastatic breast cancer/ 35704 |
| 24 ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 216980 |
| 25 (breast* or mammar*).ti,ab,kf. 933839 |
| 26 (((stage* or grade* or type*) adj2 ("4" or iv* or "M1" or mBC)) or T4*).ti,ab,kf. 424609 |
| 27 25 and 26 27081 |
| 28 or/23-24,27 238701 |
| 29 22 and 28 234603 |
| 30 exp positron emission tomography/ 279687 |
| 31 exp computer assisted tomography/ 1632791 |
| 32 fluorodeoxyglucose f 18/ 88521 |
| 33 petct.ti,ab,kf. 1345 |
| 34 ct.ti,ab,kf. 868572 |
| 35 cect.ti,ab,kf. 7108 |
| 36 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti,ab,kf. 2154 |
| 37 tomogra*.ti,ab,kf. 789959 |
| 38 (fluorodeoxyglucose* or FDG PET* or 18F* or 2 fluoro*).ti,ab,kf. 121510 |
| 39 or/30-38 2114459 |
| 40 29 and 39 18345 |

| Searches |
|---|
| 41 exp treatment outcome/ 3065710 |
| 42 exp patient monitoring/ 315081 |
| 43 physiologic monitoring/ 8060 |
| 44 (monitor* adj2 (treatment* or therap* or disease*)).ti,ab,kf. 105658 |
| 45 (response* adj3 (monitor* or evaluat* or assess* or treat* or therap* or categori* or progress* or regress* or disease*)).ti,ab,kf. 589787 |
| 46 PERCIST.ti,ab,kf. 1116 |
| 47 or/41-46 3766700 |
| 48 40 and 47 4525 |
| 49 random:.tw. 2456486 |
| 50 placebo:.mp. 634862 |
| 51 double-blind:.tw. 323078 |
| 52 or/49-51 2762397 |
| 53 48 and 52 499 |
| 54 limit 53 to english language 496 |
| 55 limit 54 to yr="2005 -Current" 483 |
| 56 animal/ 1717744 |
| 57 nonhuman/ 8212500 |
| 58 exp Animal Experiment/ 3385548 |
| 59 exp Experimental Animal/ 900619 |
| 60 animal model/ 1938583 |
| 61 exp Rodent/ 4345874 |
| 62 (rat or rats or mouse or mice or rodent*).ti. 1725007 |
| 63 or/56-62 10821367 |
| 64 63 not human/ 7648072 |
| 65 55 not 64 477 |
| 66 limit 65 to (editorial or letter) 0 |
| 67 65 not 66 477 |
| 68 conference*.db,pt,su. 6323907 |
| 69 67 not 68 263 |
| 70 limit 69 to "remove clinical trial (clinicaltrials.gov) records" 186 |

**Database name: Epistimonikos**

| Searches |
|---|
| **Search 1** |
| (title:((breast* OR mammar* OR tnbc OR (triple AND negativ*) OR brca*)) OR abstract:((breast* OR mammar* OR tnbc OR (triple AND negativ*) OR brca*))) AND (title:((metasta* OR advanc* OR second* OR recur* OR disseminat* OR incur* OR malign* OR carcino* OR invasive OR oligometasta*)) OR abstract:((metasta* OR advanc* OR second* OR recur* OR disseminat* OR incur* OR malign* OR carcino* |

| Searches |
| --- |
| OR invasive OR oligometasta*))) OR (title:((breast* OR mammar*) OR ((stage* OR grade* OR type*) AND ("4" OR "t4" OR iv* OR "m1" OR mbc))) OR abstract:((breast* OR mammar*) OR ((stage* OR grade* OR type*) AND ("4" OR "t4" OR iv* OR "m1" OR mbc)))) |
| **AND** (title:((petct OR ct OR cect OR tomogra* OR fluorodeoxyglucose* OR 18f* OR "fdg pet" OR "fdg-pet")) OR abstract:((petct OR ct OR cect OR tomogra* OR fluorodeoxyglucose* OR 18f* OR "fdg pet" OR "fdg-pet"))) |
| **AND** (title:((monitor* AND (treatment* OR therap* OR disease*))) OR abstract:((monitor* AND (treatment* OR therap* OR disease*) |
| 40 (after date and SR limits) |
| **Search 2** |
| (title:((breast* OR mammar* OR tnbc OR (triple AND negativ*) OR brca*)) OR abstract:((breast* OR mammar* OR tnbc OR (triple AND negativ*) OR brca*))) AND (title:((metasta* OR advanc* OR second* OR recur* OR disseminat* OR incur* OR malign* OR carcino* OR invasive OR oligometasta*)) OR abstract:((metasta* OR advanc* OR second* OR recur* OR disseminat* OR incur* OR malign* OR carcino* OR invasive OR oligometasta*))) OR (title:((breast* OR mammar*) OR ((stage* OR grade* OR type*) AND ("4" OR "t4" OR iv* OR "m1" OR mbc))) OR abstract:((breast* OR mammar*) OR ((stage* OR grade* OR type*) AND ("4" OR "t4" OR iv* OR "m1" OR mbc)))) |
| **AND** (title:((petct OR ct OR cect OR tomogra* OR fluorodeoxyglucose* OR 18f* OR "fdg pet" OR "fdg-pet")) OR abstract:((petct OR ct OR cect OR tomogra* OR fluorodeoxyglucose* OR 18f* OR "fdg pet" OR "fdg-pet"))) |
| **AND** (title:((response* AND (monitor* OR evaluat* OR assess* OR treat* OR therap* OR categori* OR progress* OR regress* OR disease*))) OR abstract:((response* AND (monitor* OR evaluat* OR assess* OR treat* OR therap* OR categori* OR progress* OR regress* OR disease*) |
| 195 (after date and SR limits) |

**Database name: MEDLINE ALL**

| Searches | | |
| --- | --- | --- |
| 1 | exp Breast Neoplasms/ | 370666 |
| 2 | exp "Neoplasms, Ductal, Lobular, and Medullary"/ | 50437 |
| 3 | Carcinoma, Lobular/ | 6298 |
| 4 | Carcinoma, Medullary/ | 3453 |

| Searches |
|---|
| 5 Carcinoma, Intraductal, Noninfiltrating/ 11084 |
| 6 or/1-5 392659 |
| 7 exp Breast/ 55996 |
| 8 breast*.ti,ab,kf. 618531 |
| 9 7 or 8 628575 |
| 10 (breast adj milk).ti,ab,kf. 17787 |
| 11 (breast adj tender*).ti,ab,kf. 613 |
| 12 10 or 11 18397 |
| 13 9 not 12 610178 |
| 14 exp Neoplasms/ 4131296 |
| 15 13 and 14 390925 |
| 16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 466604 |
| 17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 38026 |
| 18 Paget's Disease, Mammary/ 824 |
| 19 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1610 |
| 20 or/15-19 521271 |
| 21 6 or 20 580722 |
| 22 exp Neoplasm Metastasis/ 231372 |
| 23 ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 143863 |
| 24 (breast* or mammar*).ti,ab,kf. 671073 |
| 25 (((stage* or grade* or type*) adj2 ("4" or iv* or "M1" or mBC)) or T4*).ti,ab,kf. 243951 |
| 26 24 and 25 13388 |
| 27 or/22-23,26 359944 |
| 28 21 and 27 171845 |
| 29 exp Positron-Emission Tomography/ 88280 |
| 30 exp Tomography, X-Ray Computed/ 525935 |
| 31 Tomography, Emission-Computed/ 24617 |
| 32 Fluorodeoxyglucose F18/ 39739 |
| 33 petct.ti,ab,kf. 138 |
| 34 ct.ti,ab,kf. 495767 |
| 35 cect.ti,ab,kf. 3972 |
| 36 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti,ab,kf. 1358 |
| 37 tomogra*.ti,ab,kf. 601475 |
| 38 (fluorodeoxyglucose* or FDG PET* or 18F* or 2 fluoro*).ti,ab,kf. 72754 |

| Searches |
|---|
| 39 or/29-38 1117806 |
| 40 28 and 39 7713 |
| 41 exp Treatment Outcome/ 1356012 |
| 42 Monitoring, Physiologic/ 60639 |
| 43 (monitor* adj2 (treatment* or therap* or disease*)).ti,ab,kf. 66922 |
| 44 (response* adj3 (monitor* or evaluat* or assess* or treat* or therap* or categori* or progress* or regress* or disease*)).ti,ab,kf. 350176 |
| 45 PERCIST.ti,ab,kf. 365 |
| 46 or/41-45 1754255 |
| 47 40 and 46 1391 |
| 48 exp Randomized Controlled Trial/ 644552 |
| 49 randomi?ed.mp. 1197553 |
| 50 placebo.mp. 268904 |
| 51 or/48-50 1267578 |
| 52 47 and 51 102 |
| 53 limit 52 to english language 101 |
| 54 limit 53 to yr="2005 -Current" 85 |
| 55 animals/ 7697807 |
| 56 exp Animals, Laboratory/ 1003303 |
| 57 exp Animal Experimentation/ 10721 |
| 58 exp Models, Animal/ 686761 |
| 59 exp Rodentia/ 3728007 |
| 60 (rat or rats or mouse or mice or rodent*).ti. 1534211 |
| 61 or/55-60 7831384 |
| 62 61 not humans/ 5446029 |
| 63 54 not 62 85 |
| 64 limit 63 to (clinical conference or comment or congress or editorial or letter or news or overall) 0 |
| 65 63 not 64 85 |

## B2 Cost-effectiveness searches

### Database results

| Databases | Date searched | Database platform | Database segment or version | No. of results downloaded |
|---|---|---|---|---|
| Embase | 09/07/2025 | Ovid | Embase <1974 to 2025 July 08> | 30 |

| Databases | Date searched | Database platform | Database segment or version | No. of results downloaded |
|---|---|---|---|---|
| International HTA Database | 09/07/2025 | https://database.inahta.org/ | | 15 |
| MEDLINE ALL | 09/07/2025 | Ovid | Ovid MEDLINE(R) ALL <1946 to July 08, 2025> | 10 |

**Database name: Embase**

| Searches |
|---|
| 1 exp breast cancer/ 665293 |
| 2 exp breast carcinoma/ 118573 |
| 3 exp medullary carcinoma/ 14188 |
| 4 ductal breast carcinoma in situ/ 23394 |
| 5 exp breast tumor/ 754445 |
| 6 exp lobular carcinoma/ 7114 |
| 7 or/1-6 766870 |
| 8 exp breast/ 132609 |
| 9 breast*.ti,ab,kf. 876300 |
| 10 8 or 9 910145 |
| 11 (breast adj milk).ti,ab,kf. 23915 |
| 12 (breast adj tender*).ti,ab,kf. 853 |
| 13 11 or 12 24761 |
| 14 10 not 13 885384 |
| 15 exp neoplasm/ 6452532 |
| 16 14 and 15 689580 |
| 17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 683952 |
| 18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 45610 |
| 19 exp Paget nipple disease/ 8074 |
| 20 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 2010 |
| 21 or/16-20 761845 |
| 22 7 or 21 897638 |
| 23 metastatic breast cancer/ 35704 |

| Searches |
|---|
| 24 ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 216980 |
| 25 (breast* or mammar*).ti,ab,kf. 933839 |
| 26 (((stage* or grade* or type*) adj2 ("4" or iv* or "M1" or mBC)) or T4*).ti,ab,kf. 424609 |
| 27 25 and 26 27081 |
| 28 or/23-24,27 238701 |
| 29 22 and 28 234603 |
| 30 exp positron emission tomography/ 279687 |
| 31 exp computer assisted tomography/ 1632791 |
| 32 fluorodeoxyglucose f 18/ 88521 |
| 33 petct.ti,ab,kf. 1345 |
| 34 ct.ti,ab,kf. 868572 |
| 35 cect.ti,ab,kf. 7108 |
| 36 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti,ab,kf. 2154 |
| 37 tomogra*.ti,ab,kf. 789959 |
| 38 (fluorodeoxyglucose* or FDG PET* or 18F* or 2 fluoro*).ti,ab,kf. 121510 |
| 39 or/30-38 2114459 |
| 40 29 and 39 18345 |
| 41 exp treatment outcome/ 3065710 |
| 42 exp patient monitoring/ 315081 |
| 43 physiologic monitoring/ 8060 |
| 44 (monitor* adj2 (treatment* or therap* or disease*)).ti,ab,kf. 105658 |
| 45 (response* adj3 (monitor* or evaluat* or assess* or treat* or therap* or categori* or progress* or regress* or disease*)).ti,ab,kf. 589787 |
| 46 PERCIST.ti,ab,kf. 1116 |
| 47 or/41-46 3766700 |
| 48 40 and 47 4525 |
| 49 cost utility analysis/ 14267 |
| 50 quality adjusted life year/ 41099 |
| 51 cost*.ti. 213496 |
| 52 (cost* adj2 utilit*).tw. 14711 |
| 53 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. 452952 |
| 54 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 77681 |
| 55 (qualit* adj2 adjust* adj2 life*).tw. 31307 |
| 56 QALY*.tw. 30660 |
| 57 (incremental* adj2 cost*).tw. 32727 |
| 58 ICER.tw. 15219 |

| Searches |
|---|
| 59 utilities.tw. 16872 |
| 60 markov*.tw. 45007 |
| 61 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. 82271 |
| 62 ((utility or effective*) adj2 analys*).tw. 44095 |
| 63 (willing* adj2 pay*).tw. 17256 |
| 64 (EQ5D* or EQ-5D*).tw. 32544 |
| 65 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 6648 |
| 66 (european* adj2 quality adj3 ("5" or five)).tw. 1270 |
| 67 or/49-66 734441 |
| 68 48 and 67 85 |
| 69 limit 68 to english language 85 |
| 70 limit 69 to yr="2010 -Current" 75 |
| 71 animal/ 1717744 |
| 72 nonhuman/ 8212500 |
| 73 exp Animal Experiment/ 3385548 |
| 74 exp Experimental Animal/ 900619 |
| 75 animal model/ 1938583 |
| 76 exp Rodent/ 4345874 |
| 77 (rat or rats or mouse or mice or rodent*).ti. 1725007 |
| 78 or/71-77 10821367 |
| 79 78 not human/ 7648072 |
| 80 70 not 79 75 |
| 81 limit 80 to (editorial or letter) 0 |
| 82 80 not 81 75 |
| 83 conference*.db,pt,su. 6323907 |
| 84 82 not 83 37 |
| 85 limit 84 to "remove clinical trial (clinicaltrials.gov) records" 30 |

**Database name: International HTA Database**

| Searches |
|---|
| (((monitor* or evaluate or evaluati* or assess* or treat* or therapy or therapeutic or progress* or regress* or disease* or PERCIST)) OR (("Monitoring, Physiologic"[mh])) OR (("Treatment Outcome"[mhe]))) AND (((petct or ct or cect or tomography or fluorodeoxyglucose* or fdg pet or fdg-pet)) OR (("Fluorodeoxyglucose F18"[mh])) OR (("Tomography, Emission-Computed"[mh])) OR (("Tomography, X-Ray Computed"[mhe]) ) OR ( ("Positron Emission Tomography Computed Tomography"[mhe]))) AND (((breast* or mammar* or tnbc or brca*)) OR ((triple AND negativ*) AND (metasta* or advanc* or second* or recur* |

| Searches |
| --- |
| or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)) OR (("Neoplasm Metastasis"[mhe]))) |
| **After date and language limits - 15 results** |

**Database name: MEDLINE ALL**

| Searches |
| --- |
| 1 exp Breast Neoplasms/ 370666 |
| 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ 50437 |
| 3 Carcinoma, Lobular/ 6298 |
| 4 Carcinoma, Medullary/ 3453 |
| 5 Carcinoma, Intraductal, Noninfiltrating/ 11084 |
| 6 or/1-5 392659 |
| 7 exp Breast/ 55996 |
| 8 breast*.ti,ab,kf. 618531 |
| 9 7 or 8 628575 |
| 10 (breast adj milk).ti,ab,kf. 17787 |
| 11 (breast adj tender*).ti,ab,kf. 613 |
| 12 10 or 11 18397 |
| 13 9 not 12 610178 |
| 14 exp Neoplasms/ 4131296 |
| 15 13 and 14 390925 |
| 16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 466604 |
| 17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 38026 |
| 18 Paget's Disease, Mammary/ 824 |
| 19 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1610 |
| 20 or/15-19 521271 |
| 21 6 or 20 580722 |
| 22 exp Neoplasm Metastasis/ 231372 |
| 23 ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 143863 |
| 24 (breast* or mammar*).ti,ab,kf. 671073 |
| 25 (((stage* or grade* or type*) adj2 ("4" or iv* or "M1" or mBC)) or T4*).ti,ab,kf. 243951 |
| 26 24 and 25 13388 |
| 27 or/22-23,26 359944 |

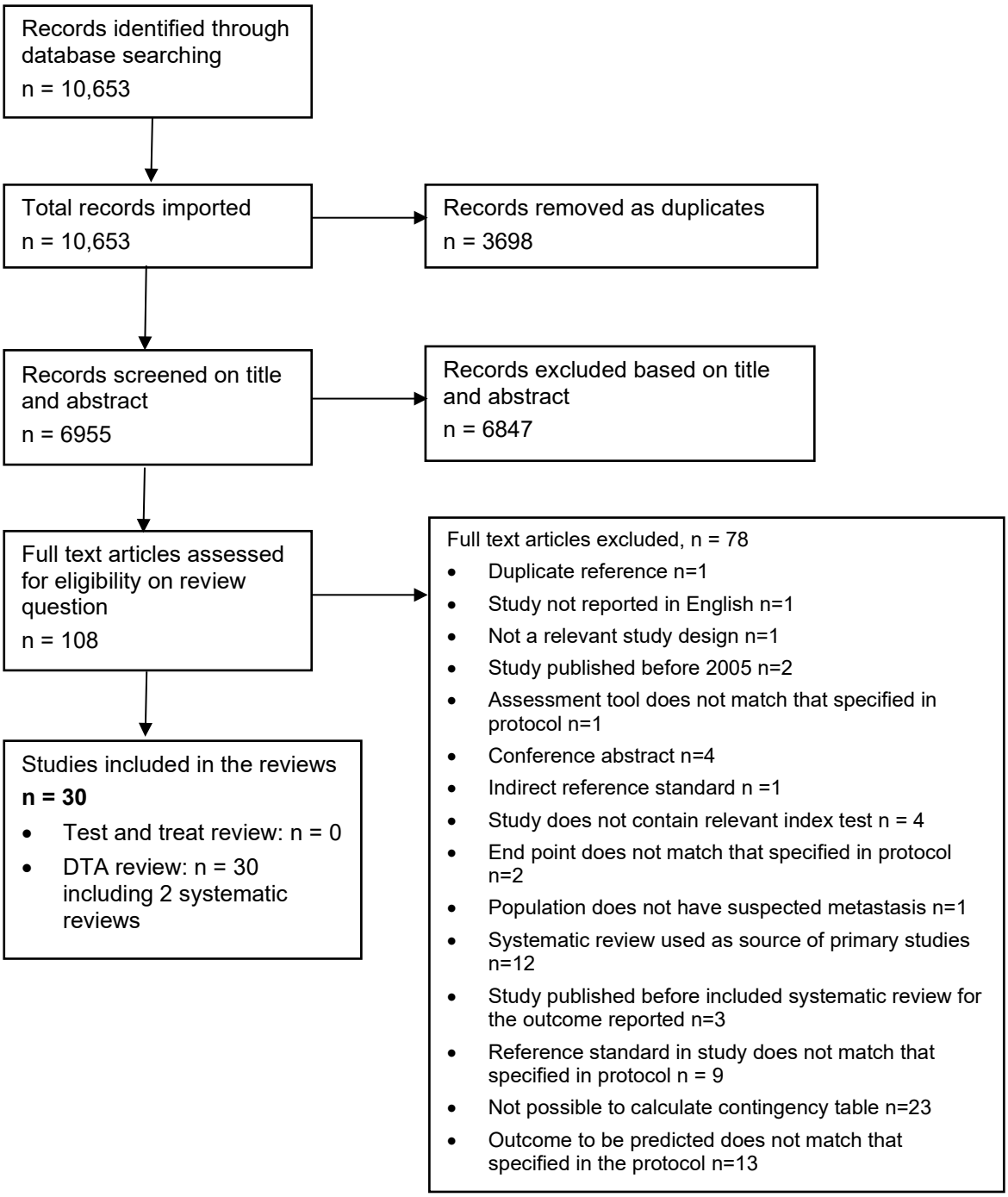
| Searches |
|---|
| 28 21 and 27 171845 |
| 29 exp Positron-Emission Tomography/ 88280 |
| 30 exp Tomography, X-Ray Computed/ 525935 |
| 31 Tomography, Emission-Computed/ 24617 |
| 32 Fluorodeoxyglucose F18/ 39739 |
| 33 petct.ti,ab,kf. 138 |
| 34 ct.ti,ab,kf. 495767 |
| 35 cect.ti,ab,kf. 3972 |
| 36 (CAT adj (electron-beam* or examination* or imag* or scan* or x ray*)).ti,ab,kf. 1358 |
| 37 tomogra*.ti,ab,kf. 601475 |
| 38 (fluorodeoxyglucose* or FDG PET* or 18F* or 2 fluoro*).ti,ab,kf. 72754 |
| 39 or/29-38 1117806 |
| 40 28 and 39 7713 |
| 41 exp Treatment Outcome/ 1356012 |
| 42 Monitoring, Physiologic/ 60639 |
| 43 (monitor* adj2 (treatment* or therap* or disease*)).ti,ab,kf. 66922 |
| 44 (response* adj3 (monitor* or evaluat* or assess* or treat* or therap* or categori* or progress* or regress* or disease*)).ti,ab,kf. 350176 |
| 45 PERCIST.ti,ab,kf. 365 |
| 46 or/41-45 1754255 |
| 47 40 and 46 1391 |
| 48 Cost-Benefit Analysis/ 98298 |
| 49 Quality-Adjusted Life Years/ 18085 |
| 50 Markov Chains/ 17227 |
| 51 exp Models, Economic/ 16899 |
| 52 cost*.ti. 158678 |
| 53 (cost* adj2 utilit*).tw. 8813 |
| 54 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. 324663 |
| 55 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 54751 |
| 56 (qualit* adj2 adjust* adj2 life*).tw. 20512 |
| 57 QALY*.tw. 16703 |
| 58 (incremental* adj2 cost*).tw. 19972 |
| 59 ICER.tw. 7329 |
| 60 utilities.tw. 10569 |
| 61 markov*.tw. 35961 |
| 62 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. 59827 |
| 63 ((utility or effective*) adj2 analys*).tw. 28977 |
| 64 (willing* adj2 pay*).tw. 11776 |

| Searches |
| --- |
| 65 (EQ5D* or EQ-5D*).tw. 16401 |
| 66 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 4898 |
| 67 (european* adj2 quality adj3 ("5" or five)).tw. 885 |
| 68 or/48-67 572372 |
| 69 47 and 68 18 |
| 70 limit 69 to english language 18 |
| 71 limit 70 to yr="2010 -Current" 10 |
| 72 animals/ 7697807 |
| 73 exp Animals, Laboratory/ 1003303 |
| 74 exp Animal Experimentation/ 10721 |
| 75 exp Models, Animal/ 686761 |
| 76 exp Rodentia/ 3728007 |
| 77 (rat or rats or mouse or mice or rodent*).ti. 1534211 |
| 78 or/72-77 7831384 |
| 79 78 not humans/ 5446029 |
| 80 71 not 79 10 |
| 81 limit 80 to (clinical conference or comment or congress or editorial or letter or news or overall) 0 |
| 82 80 not 81 10 |

# Appendix C – Effectiveness and diagnostic evidence study selection

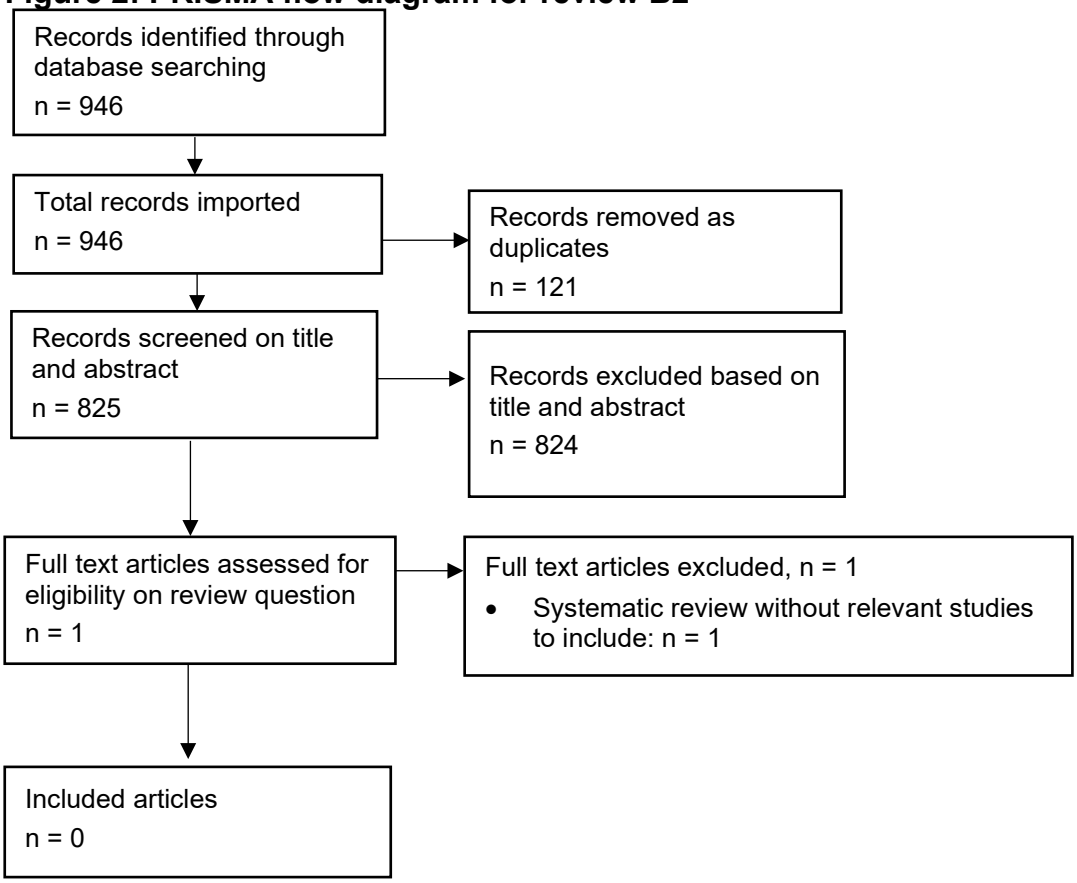
## Review B1

### Figure 1: PRISMA flow diagram for review B1



**Review B2**

**Figure 2: PRISMA flow diagram for review B2**



# Appendix D – Effectiveness and diagnostic evidence

## Review B1

Full data extractions are reported for the 8 studies not included in either of the included systematic reviews. Risk of bias summary is reported for all 29 included studies.

## Systematic reviews

### Shen et al., 2025

| | |
|---|---|
| **Bibliographic Reference** | Shen, Fangqian; Liu, Qi; Wang, Yishuang; Chen, Can; Ma, Hu; Comparison of [18F] FDG PET/CT and [18F]FDG PET/MRI in the Detection of Distant Metastases in Breast Cancer: A Meta-Analysis.; Clinical breast cancer; 2025; vol. 25 (no. 2); e113-e123e4 |

### Study Characteristics

| | |
|---|---|
| **Study design** | Systematic review |
| **Study details** | Dates searched<br><br>until 22nd September 2023<br><br>Databases searched<br><br>PubMed and Embase<br><br>Sources of funding<br><br>Not reported |
| **Inclusion criteria** | Studies assessing the diagnostic efficacy of [ 18F] FDG PET-CT and/or [ 18F] FDG PET-MRI in detecting distant metastases in breast cancer patients<br><br>Studies including over 10 participants |
| **Exclusion criteria** | Abstracts without full texts<br><br>Irrelevant titles and abstracts<br><br>Duplicated articles<br><br>Case reports<br><br>Letters<br><br>Reviews |

| | |
|---|---|
| | Meta-analysis<br><br>Non-English full-text articles<br><br>Editorial comments<br><br>Studies lacking necessary data, which was unclear or incomplete, for calculating specificity and sensitivity of the studied imaging modality<br><br>Studies using other different radiotracers, or PET without CT or MRI |
| **Index test** | [18F] FDG PET-CT |
| **Reference standard** | Pathology<br><br>Imaging follow-up |
| **Outcome(s)** | Any metastasis<br><br>- Any distant metastases of breast cancer |
| **Number of studies included in the systematic review** | 29 |
| **Studies from the systematic review that are relevant for use in the current review** | Abo-Sheisha et al., 2014<br><br>Aukema et al., 2010<br><br>Carkaci et al., 2009<br><br>Choi et al., 2012<br><br>Gajjala et al., 2018<br><br>Garg et al., 2016<br><br>Goktas et al., 2018<br><br>Ko et al., 2020<br><br>Koolen et al., 2012<br><br>Krammer et al., 2015<br><br>Manohar et al., 2013<br><br>Melsaether et al., 2016 |

| | |
|---|---|
| | Niikura et al., 2011<br><br>Reigger et al., 2012<br><br>Vogsen et al., 2021b |
| **Studies from the systematic review that are not relevant for use in the current review** | Reason for not being relevant to use in the current review in brackets:<br><br>Bhoriwal et al., 2021 (results include axillary metastasis)<br><br>Botsikas et al., 2018 (FDG PET-CT of upper abdomen and thorax only)<br><br>Bruckmann et al., 2021 (index test was PET/MRI)<br><br>Chandra et al., 2019 (preoperative population without suspected metastasis)<br><br>Fuster et al., 2008 (preoperative population without suspected metastasis)<br><br>Grueneisen et al., 2017 (index test was PET/MRI)<br><br>Jung et al., 2014 (data reported as lesion-based without reporting patient-based data)<br><br>Kirchner et al., 2020 (index test was PET/MRI)<br><br>Morawitz et al., 2023 (index test was PET/MRI)<br><br>Sawicki et al., 2016 (data reported as lesion-based without reporting patient-based data)<br><br>Schmidt et al., 2007 (data reported as lesion-based without reporting patient-based data)<br><br>Umutlu et al., 2021 (index test was PET/MRI)<br><br>Yang et al., 2008 (distant metastases reported in combination with axillary node and supraclavicular node metastases)<br><br>Yilmaz et al., 2019 (parameters used for assessing diagnostic accuracy were unclear and do not reflect clinical practice) |
| **Additional comments** | QUADAS-2 assessment was as an overall summary of all included studies without reporting individual assessment for each study. |

### Critical appraisal - Critical Appraisal - ROBIS systematic review checklist

| Section | Question | Answer |
|---|---|---|
| Overall study ratings | Overall risk of bias | High<br>*(No information about the screening process and whether this was done independently by 2 reviewers. Bivariate meta-analysis was not used. Risk of bias assessment was reported as a summary of all included studies without reporting the assessment for each study.)* |
| Overall study ratings | Applicability as a source of data | Fully applicable |

### Xia et al., 2023

| | |
|---|---|
| **Bibliographic Reference** | Xia, Longjie; Lai, Jianqin; Huang, Di; Qiu, Shenghui; Hu, Huiqiong; Luo, Yunxiang; Cao, Jie; Comparing the diagnostic efficacy of [18F]FDG PET/CT and [18F]FDG PET/MRI for detecting bone metastases in breast cancer: a meta-analysis.; Radiology and oncology; 2023; vol. 57 (no. 3); 299-309 |

### Study Characteristics

| | |
|---|---|
| **Study design** | Systematic review |
| **Study details** | Dates searched<br><br>- From inception to February 2023<br><br>Databases searched<br><br>- PubMed<br><br>- Embase<br><br>- Web of Science<br><br>- Cochrane Library<br><br>Sources of funding<br><br>- National Natural Science Foundation of China [81871943 to JC]<br><br>- Guangdong Provincial Clinical Research Centre for Digestive Diseases [2020B1111170004] |

| | |
|---|---|
| | - Guangzhou High-level Key Clinical Specialty Construction Project [No.9]<br><br>- The Project of Key Medical Discipline in Guangzhou [2021-2023] |
| **Inclusion criteria** | Studies including over 10 participants<br><br>Studies evaluating the diagnostic performance of [18F] FDG PET-CT and/or [18F] FDG PET-MRI in detecting bone metastases in breast cancer patients |
| **Exclusion criteria** | Abstracts without full texts<br><br>Irrelevant titles and abstracts<br><br>Duplicated articles<br><br>Case reports<br><br>Letters<br><br>Reviews<br><br>Meta-analysis<br><br>Non-English full-text articles<br><br>Editorial comments<br><br>Studies lacking necessary data, which was unclear or incomplete, for calculating specificity and sensitivity of the studied imaging modality<br><br>Studies using other different radiotracers, or PET without CT or MRI<br><br>Additional studies reporting the same data, where the latest of the studies has been included |
| **Index test** | FDG PET-CT |
| **Reference standard** | Pathology<br><br>Imaging follow-up |
| **Outcome(s)** | Bone metastasis |
| **Number of studies included in the systematic review** | 16 studies included (15 reporting on FDG PET-CT) |
| **Studies from the systematic review that** | Melsaether et al., 2016<br><br>Niikura et al., 2011 |

| | |
|---|---|
| **are relevant for use in the current review** | Catalano et al., 2015<br><br>Balci et al., 2012<br><br>Manohar et al., 2012<br><br>Rager et al., 2018<br><br>Shawky et al., 2020 |
| **Studies from the systematic review that are not relevant for use in the current review** | Reason for not being relevant to use in the current review in brackets:<br><br>Botsikas et al., 2018 (PET-CT only covered thorax and upper abdomen)<br><br>Bruckmann et al., 2021 (Only assessed accuracy of PET-MRI)<br><br>Sawicki et al., 2016 (Insufficient information to calculate 2x2 data)<br><br>Hahn et al., 2011 (Bone scan was used as reference standard)<br><br>Riegger et al., 2012 (Outcome of interest presented as lesion-based analysis)<br><br>Demir et al., 2017 (Outcome of interest presented as lesion-based analysis)<br><br>Hansen et al., 2021 (Outcome of interest presented as lesion-based analysis)<br><br>Niikura et al., 2016 (Insufficient information to calculate 2x2 data)<br><br>Teke et al., 2015 (Outcome of interest presented as lesion-based analysis) |
| **Additional comments** | QUADAS-2 assessment was presented as an overall summary of all included studies without reporting individual assessment for each study. |

### Critical appraisal - Critical Appraisal - ROBIS systematic review checklist

| Section | Question | Answer |
|---|---|---|
| Overall study ratings | Overall risk of bias | High<br>*(Concerns around the eligibility criteria for including studies in the review (insufficient information provided to judge whether appropriate studies were included) and not addressing the quality of individual studies in the synthesis were identified.)* |
| Overall study ratings | Applicability as a source of data | Partially applicable<br>*(Study focused on a single metastatic site and it is unclear whether the population included in the review were all suspected with metastasis)* |

## Primary diagnostic test accuracy studies

### Abd-Elkader et al., 2020

| | |
|---|---|
| **Bibliographic Reference** | Abd-Elkader, M.A.M.; Hassan, A.A.E.-K.; Omar, N.N.M.; Sherif, M.F.H.; Abdel-Tawab, M.; The added value of hybrid 18F-FDG PET/CT over CT in the detection of breast cancer metastatic deposits; Egyptian Journal of Radiology and Nuclear Medicine; 2020; vol. 51 (no. 1); 115 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Retrospective cohort study |
| **Study details** | Study location<br><br>- Egypt<br><br>Setting<br><br>- Not recorded<br><br>Study dates<br><br>- April 2015 and March 2019<br><br>Sources of funding<br><br>- Not financially supported by any institute |
| **Inclusion criteria** | Women with pathologically proven breast cancer referred for PET-CT examination |
| **Exclusion criteria** | Co-existence of another malignancy, recent biopsy or surgery, or local radiotherapy within 1 month before PET-CT scan |
| **Number of participants** | N = 77 |
| **Length of follow-up** | Not recorded |
| **Loss to follow-up** | 6 |
| **Index test(s)** | FDG PET-CT<br><br>- Brain to mid-thigh<br><br>Contrast-enhanced CT<br><br>- Brain to mid-thigh |

| | |
|---|---|
| **Reference standard (s)** | Combination of...<br><br>clinical and radiological follow-up<br><br>Imaging modalities used for follow-up included bone scintigraphy (9 patients), whole spine MRI (2 patients) and abdominal ultrasound (3 patients). No additional information provided. |
| **Additional comments** | None |
| **Target condition** | - Bone metastasis<br><br>- Lymph node metastasis (data not relevant for this review because it is unclear whether axillary lymph nodes were included in the lymph node metastasis referred to)<br><br>- Hepatic metastasis |

### Population characteristics

### Study-level characteristics

| Characteristic | Study (N = 71) |
|---|---|
| **% Female**<br><br>Sample size | n = 71 ; % = 100 |
| **Age** (years)<br><br>Mean (range) | 54.7 (30 to 79) |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | High<br>*(Insufficient information provided on the selection of participants and reference standard domains, and flow and timing domain is at high risk of bias because study did not provide reasons for loss to follow-up and provided insufficient information on reference standard.)* |
| Overall risk of bias and directness | Directness | Partially applicable<br>*(Unclear whether the patients included in the study were suspected of metastasis before undergoing PET-CT)* |

### Abo-Sheisha et al., 2014

| | |
|---|---|
| **Bibliographic Reference** | Abo-Sheisha, D.M.; Badawy, M.E.; The diagnostic value of PET/CT in recurrence and distant metastasis in breast cancer patients and impact on disease free survival; Egyptian Journal of Radiology and Nuclear Medicine; 2014; vol. 45 (no. 4); 1317 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Concern as to whether reference standard results were impacted by whether the index test results were known)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Aukema et al., 2010

| | |
|---|---|
| **Bibliographic Reference** | Aukema, T S; Rutgers, E J Th; Vogel, W V; Teertstra, H J; Oldenburg, H S; Vrancken Peeters, M T F D; Wesseling, J; Russell, N S; Valdes Olmos, R A; The role of FDG PET/CT in patients with locoregional breast cancer recurrence: a comparison to conventional imaging techniques.; European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology; 2010; vol. 36 (no. 4); 387-92 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(No detail on recruitment and exclusion criteria; no information on whether interpretation of reference standard was done with or without knowledge of index test results)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Balci et al., 2012

| | |
|---|---|
| **Bibliographic Reference** | Balci, Tansel A; Koc, Zehra P; Komek, Halil; Bone scan or (18)f-fluorodeoxyglucose positron emission tomography/computed tomography; which modality better shows bone metastases of breast cancer?.; Breast care (Basel, Switzerland); 2012; vol. 7 (no. 5); 389-93 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Unclear whether participants were enrolled consecutively or randomly and whether inappropriate exclusions were avoided; unclear whether interpreters of the reference standard had knowledge of the index test results)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Bruckmann et al., 2021

| | |
|---|---|
| **Bibliographic Reference** | Bruckmann, Nils Martin; Kirchner, Julian; Umutlu, Lale; Fendler, Wolfgang Peter; Seifert, Robert; Herrmann, Ken; Bittner, Ann-Kathrin; Hoffmann, Oliver; Mohrmann, Svjetlana; Antke, Christina; Schimmoller, Lars; Ingenwerth, Marc; Breuckmann, Katharina; Stang, Andreas; Buchbender, Christian; Antoch, Gerald; Sawicki, Lino M; Prospective comparison of the diagnostic accuracy of 18F-FDG PET/MRI, MRI, CT, and bone scintigraphy for the detection of bone metastases in the initial staging of primary breast cancer patients.; European radiology; 2021; vol. 31 (no. 11); 8714-8724 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Prospective cohort study |
| **Study details** | Study location<br><br>- Germany<br><br>Setting<br><br>- University hospitals<br><br>Study dates<br><br>- March 2018 and March 2020<br><br>Sources of funding<br><br>- The study was funded by Deutsche Forschungsgemeinschaft, the German Research Foundation (BU3075/2-1) |

| | |
|---|---|
| **Inclusion criteria** | Newly diagnosed, treatment-naïve T2 tumour or higher T-stage<br><br>Newly diagnosed, treatment naïve triple-negative tumour of every size<br><br>Newly diagnosed, treatment-naïve tumour with molecular high risk (T1c, Ki67>14%, HER2-new over-expression, G3) |
| **Exclusion criteria** | Contraindications to MRI or MRI contrast agents<br><br>Missing imaging of a modality<br><br>Pregnancy or breast-feeding<br><br>Former malignancies in the last 5 years |
| **Number of participants** | N = 154 |
| **Length of follow-up** | - In patients with suspected metastasis, mean delay for follow-up examination = 3.8±1.3 months.<br><br>- For all women who underwent follow-up, mean delay was 7.4 ± 5.1 months |
| **Loss to follow-up** | 0 |
| **Index test(s)** | Contrast-enhanced CT<br><br>Thoraco-abdominal multi-slice contrast-enhanced CT (pelvic bones metastasis also reported). Only parts of the limbs that were pictured in the field of view of all modalities were included in the evaluation |
| **Reference standard (s)** | Histopathology or imaging follow-up<br><br>In all patients with suspected osseous metastasis in any of the imaging modalities at least one osseous lesion was histologically sampled. Due to clinical and ethical standards, a histological confirmation of some malignant lesions was not available, and a surrogate reference standard was applied taking into account all follow-up imaging. In all patients with suspected metastases, CT or MRI was performed as follow-up examination (mean delay 3.8 ± 1.3 month). In total, follow-up examinations were performed in 60 women, comprising 33 thoraco-abdominal CT, 22 whole-body MRI, and 5 patients receiving both examinations (mean delay 7.4 ± 5.1 month).<br><br>The remaining patients, who did not undergo follow-up imaging, have been showing no clinical signs of bone metastases.<br><br>Any increase of size or a decrease of size of suspicious lesions after therapy or newly occurred cortical destruction were regarded as signs of malignancy. |
| **Additional comments** | • Pelvic bones metastasis were also reported for CECT (even though it was described as being thoraco-abdominal).<br>• Inclusion criteria were chosen according to clinical ESMO guidelines to set elevated pre-test probability for distant metastases. |

| | |
|---|---|
| | • Bone scintigraphy was done and reported separately from CECT |
| **Target condition** | - Bone metastases |

### Population characteristics

### Study-level characteristics

| Characteristic | Study (N = 154) |
|---|---|
| **% Female**<br><br>No of events | n = 154 ; % = 100 |
| **Age**<br><br>Mean (SD) | 53.8 (11.9) |
| **Histological tumour types - Ductal invasive/NST**<br><br>No of events | n = 136 ; % = 88 |
| **Histological tumour types - Lobular invasive**<br><br>No of events | n = 13 ; % = 8 |
| **Histological tumour types - Mucinous invasive**<br><br>No of events | n = 1 ; % = 1 |
| **Histological tumour types - Mixed type**<br><br>No of events | n = 1 ; % = 1 |
| **Receptor subtype - Progesterone receptor positive**<br><br>No of events | n = 107 ; % = 69 |
| **Receptor subtype - Progesterone receptor negative**<br><br>No of events | n = 47 ; % = 31 |
| **Receptor subtype - Oestrogen receptor positive**<br><br>No of events | n = 115 ; % = 75 |
| **Receptor subtype - Oestrogen receptor negative**<br><br>No of events | n = 39 ; % = 25 |
| **Receptor subtype - HER2 expression = 0**<br><br>No of events | n = 55 ; % = 36 |

| Characteristic | Study (N = 154) |
|---|---|
| **Receptor subtype - HER2 expression = 1+**<br><br>No of events | n = 50 ; % = 32 |
| **Receptor subtype - HER2 expression = 2+**<br><br>No of events | n = 23 ; % = 15 |
| **Receptor subtype - HER2 expression = 3+**<br><br>No of events | n = 26 ; % = 17 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | High<br>*(Unclear if index test and reference standard results were blindly interpreted. People with suspected bone metastasis had histological confirmation or imaging follow-up. People with no clinical signs of bone metastasis did not undergo follow-up imaging and length of follow-up in these people was not reported.)* |
| Overall risk of bias and directness | Directness | Partially applicable<br>*(Unclear whether patients included were suspected of metastasis and unclear whether index test (CECT) included the pelvis in the scan or if the pelvic region was evaluated coincidentally)* |

### Carkaci et al., 2009

| | |
|---|---|
| **Bibliographic Reference** | Carkaci, Selin; Macapinlac, Homer A; Cristofanilli, Massimo; Mawlawi, Osama; Rohren, Eric; Gonzalez Angulo, Ana M; Dawood, Shaheenah; Resetkova, Erika; Le-Petross, Huong T; Yang, Wei-Tse; Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data.; Journal of nuclear medicine : official publication, Society of Nuclear Medicine; 2009; vol. 50 (no. 2); 231-8 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | High<br>*(Concerns around the reference standard being the same imaging as the index text for at least 8 participants)* |

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Directness | Directly applicable |

### Catalano et al., 2015

| | |
|---|---|
| **Bibliographic Reference** | Catalano, O A; Nicolai, E; Rosen, B R; Luongo, A; Catalano, M; Iannace, C; Guimaraes, A; Vangel, M G; Mahmood, U; Soricelli, A; Salvatore, M; Comparison of CE-FDG-PET/CT with CE-FDG-PET/MR in the evaluation of osseous metastases in breast cancer patients.; British journal of cancer; 2015; vol. 112 (no. 9); 1452-60 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Some concerns with the selection of patients and the reference standard interpretation)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Choi et al., 2012

| | |
|---|---|
| **Bibliographic Reference** | Choi, Young Jin; Shin, Young Duck; Kang, Yoon Hee; Lee, Moon Soo; Lee, Min Koo; Cho, Byung Sun; Kang, Yoon Jung; Park, Ju Seung; The Effects of Preoperative (18)F-FDG PET/CT in Breast Cancer Patients in Comparison to the Conventional Imaging Study.; Journal of breast cancer; 2012; vol. 15 (no. 4); 441-8 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Unclear if reference standard was conducted blind.)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Dirisamer et al., 2010

| | |
|---|---|
| **Bibliographic Reference** | Dirisamer, Albert; Halpern, Benjamin S; Flory, Daniel; Wolf, Florian; Beheshti, Mohsen; Mayerhoefer, Marius E; Langsteger, Werner; Integrated contrast-enhanced diagnostic whole-body PET/CT as a first-line restaging modality in patients with suspected metastatic recurrence of breast cancer.; European journal of radiology; 2010; vol. 73 (no. 2); 294-9 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Retrospective cohort study |
| **Study details** | Study location<br><br>- Vienna, Austria<br><br>Setting<br><br>- Not recorded<br><br>Study dates<br><br>- 2004 to 2007<br><br>Sources of funding<br><br>- Not recorded |
| **Inclusion criteria** | Patients with suspected breast cancer recurrence free of metastases after first line of treatment |
| **Exclusion criteria** | Insufficient follow-up information, local recurrence and/or already known metastases |
| **Number of participants** | N=52 |
| **Length of follow-up** | Not recorded |
| **Loss to follow-up** | None |
| **Index test(s)** | FDG PET-CT<br><br>Contrast-enhanced CT |
| **Reference standard (s)** | Combination of...<br><br>Histological verification from biopsy and follow-up examinations<br><br>- Chest wall recurrence was proven by histology |

| | |
|---|---|
| | - Pulmonary and abdominal metastases were proven by CT/MRI follow-up studies and/or histology<br><br>- Bone metastasis were proven by follow-up examinations using scintigraphy and/or CT/MRI.<br><br>- Lymph nodes metastasis was confirmed by histology and/or follow-up with PET and CT.<br><br>Lesions proved by follow-up were classified malign if a growth could be found within 6 months<br><br>Absence of disease was established by clinical and imaging follow-up in 10 patients |
| **Additional comments** | None |
| **Target condition** | Distant metastases |

### Population characteristics

### Study-level characteristics

| Characteristic | Study (N = 52) |
|---|---|
| **% Female**<br><br>Sample size | n = NR ; % = NR |
| **Histological tumour types - Ductal**<br><br>Sample size | n = 27 ; % = 51.9 |
| **Histological tumour types - Lobular**<br><br>Sample size | n = 25 ; % = 48.1 |
| **Time interval of recurrence** (years)<br>Time period between last therapy and FDG-PET-CT<br><br>Mean (range) | 5.9 (1 to 19) |
| **Time interval of recurrence - For ductal carcinoma group**<br><br>Mean (range) | 5.2 (NR) |
| **Time interval of recurrence - For lobular carcinoma group**<br><br>Mean (range) | 5.8 (NR) |
| **Indication for PET-CT imaging - Tumour marker elevation** | n = 32 |

| Characteristic | Study (N = 52) |
|---|---|
| Sample size | |
| **Indication for PET-CT imaging - Clinical deterioration**<br><br>Sample size | n = 16 |
| **Indication for PET-CT imaging - Suspicious findings on other imaging studies**<br><br>Sample size | n = 48 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | High<br>*(Insufficient information provided on participant selection, inappropriate exclusions may have been made. Unclear whether reference standard was interpreted without knowledge of index test results.)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Evangelista et al., 2012

| | |
|---|---|
| **Bibliographic Reference** | Evangelista, Laura; Panunzio, Annalori; Cervino, Anna Rita; Vinante, Lorenzo; Al-Nahhas, Adil; Rubello, Domenico; Muzzio, Pier Carlo; Polverosi, Roberta; Indeterminate pulmonary nodules on CT images in breast cancer patient: the additional value of 18F-FDG PET/CT.; Journal of medical imaging and radiation oncology; 2012; vol. 56 (no. 4); 417-24 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Retrospective cohort study |
| **Study details** | Study location<br><br>- Italy<br><br>Setting<br><br>- Hospital<br><br>Study dates |

| | |
|---|---|
| | - March 2007 to May 2011<br><br>Sources of funding<br><br>- Not reported |
| **Inclusion criteria** | Consecutive breast cancer patients referred to perform FDG PET-CT for the evaluation of indeterminate solid lung nodules detected on previous CECT scans |
| **Exclusion criteria** | None reported |
| **Number of participants** | N = 29 |
| **Length of follow-up** | Only reported for people who could not have biopsy and were followed by imaging (at least 24 months) |
| **Loss to follow-up** | 0 |
| **Index test(s)** | Whole body 18F-FDG PET-CT.<br><br>All patients were advised to fast for at least 6 h before the integrated PET-CT examination. Images from the proximal femur to the base of the skull were acquired for 3 min per bed position. Processed images were displayed in coronal, transverse and sagittal planes. |
| **Reference standard (s)** | Histopathology or imaging follow-up<br><br>To evaluate the disease relapse and the nature of lung nodules, all patients underwent CT-guided biopsy (for ethical and multidisciplinary reasons only few lesions for each patient were biopsied) or were followed by imaging for at least 24 months from the PET-CT examination. The characterisation of lung nodules was verified by histology specimens in 9 patients and imaging studies in the remaining population. |
| **Additional comments** | Only subgroup data (invasive ductal breast cancer) was sufficiently reported to calculate diagnostic test accuracy |
| **Target condition** | Lung metastasis |

### Population characteristics

### Study-level characteristics

| Characteristic | Study (N = 29) |
|---|---|
| **Age**<br><br>Mean (SD) | 65 (12) |
| **Histological tumour types - Ductal carcinoma in situ** | n = 2 ; % = 7 |

| Characteristic | Study (N = 29) |
|---|---|
| No of events | |
| **Histological tumour types - Invasive ductal carcinoma**<br><br>No of events | n = 21 ; % = 72 |
| **Histological tumour types - Invasive lobular carcinoma**<br><br>No of events | n = 4 ; % = 14 |
| **Histological tumour types - Others (not specified)**<br><br>No of events | n = 2 ; % = 7 |
| **Receptor subtype - Oestrogen receptor negative**<br><br>No of events | n = 3 ; % = 10 |
| **Receptor subtype - Oestrogen receptor positive**<br><br>No of events | n = 22 ; % = 76 |
| **Receptor subtype - Oestrogen receptor status unknown**<br><br>No of events | n = 4 ; % = 14 |
| **Receptor subtype - Progesterone receptor negative**<br><br>No of events | n = 5 ; % = 17 |
| **Receptor subtype - Progesterone receptor positive**<br><br>No of events | n = 20 ; % = 69 |
| **Receptor subtype - Progesterone receptor status unknown**<br><br>No of events | n = 4 ; % = 14 |
| **Receptor subtype - HER2 negative**<br><br>No of events | n = 17 ; % = 57 |
| **Receptor subtype - HER2 positive**<br><br>No of events | n = 5 ; % = 15 |
| **Receptor subtype - HER2 status unknown**<br><br>No of events | n = 8 ; % = 28 |
| **Nodal status of primary tumour - Lymph node involvement - Yes**<br><br>Sample size | n = 5 ; % = 17 |
| **Nodal status of primary tumour - Lymph node involvement - No**<br><br>Sample size | n = 24 ; % = 83 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Exclusion criteria were not reported. Study did not report whether index test and reference standard results and were blindly interpreted.)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Gajjala et al., 2018

| | |
|---|---|
| **Bibliographic Reference** | Gajjala, Sivanath Reddy; Hulikal, Narendra; Kadiyala, Silpa; Kottu, Radhika; Kalawat, Tekchand; Whole-body 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) for staging locally advanced breast cancer: A prospective study from a tertiary cancer centre in south India.; The Indian journal of medical research; 2018; vol. 147 (no. 3); 256-262 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Prospective cohort study |
| **Study details** | Study location<br><br>Tirupati, India<br><br>Setting<br><br>Medical Science Institute<br><br>Study dates<br><br>April 2013 to December 2014<br><br>Sources of funding<br><br>No funding received |
| **Inclusion criteria** | Biopsy-proven, unilateral, newly diagnosed locally advances breast cancer |
| **Exclusion criteria** | Early breast cancer, already received treatment elsewhere, male patients with breast cancer, and patients who did not give consent to participate in the study |

| | |
|---|---|
| **Number of participants** | N=61 |
| **Length of follow-up** | Not reported |
| **Loss to follow-up** | None |
| **Index test(s)** | FDG PET-CT |
| **Reference standard (s)** | Pathological confirmation from biopsy |
| **Target condition** | Distant metastases |

### Population characteristics

### Study-level characteristics

| Characteristic | Study (N = 61) |
|---|---|
| **% Female**<br><br>Sample size | n = 61 ; % = 100 |
| **Age**<br><br>Mean (SD) | 51.27 (10.57) |
| **Histological tumour types**<br><br>Nominal | 61 |
| **Histological tumour types - Invasive duct cell carcinoma**<br><br>Nominal | 60 |
| **Histological tumour types - Metaplastic carcinoma**<br><br>Nominal | 1 |
| **Receptor subtype**<br><br>Sample size | n = 61 ; % = 100 |
| **Receptor subtype - Luminal-A**<br><br>Sample size | n = 8 ; % = 13 |
| **Receptor subtype - Luminal-B**<br><br>Sample size | n = 30 ; % = 49 |

| Characteristic | Study (N = 61) |
|---|---|
| **Receptor subtype - HER2**<br><br>Sample size | n = 7 ; % = 11.5 |
| **Receptor subtype - TNBC**<br><br>Sample size | n = 16 ; % = 26.5 |
| **Nodal status of primary tumour - Lymph node involvement - Yes**<br><br>Sample size | n = 60 ; % = 98 |
| **Nodal status of primary tumour - Lymph node involvement - No**<br><br>Sample size | n = 1 ; % = 2 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Unclear on timing of reference standard being conducted in relation to index test and also prior knowledge of index test before interpreting reference standard and voce versa)* |
| Overall risk of bias and directness | Directness | Partially applicable<br>*(Unclear if patients were suspected of metastasis as an indication for PET-CT)* |

### Garg et al., 2016

| | |
|---|---|
| **Bibliographic Reference** | Garg, Pankaj Kumar; Deo, Suryanarayana V S; Kumar, Rakesh; Shukla, Nootan Kumar; Thulkar, Sanjay; Gogia, Ajay; Sharma, Daya Nand; Mathur, Sandeep R; Staging PET-CT Scanning Provides Superior Detection of Lymph Nodes and Distant Metastases than Traditional Imaging in Locally Advanced Breast Cancer.; World journal of surgery; 2016; vol. 40 (no. 8); 2036-42 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Not reported if patient selection was random or consecutive)* |

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Directness | Partially applicable<br>*(Unclear if patients were suspected of metastasis at enrolment)* |

### Goktas et al., 2018

| | |
|---|---|
| **Bibliographic Reference** | Goktas, Inan; Cayvarli, Hakan; The Role of 18F-FDG PET/CT in Evaluating Elevated Levels of Tumor Markers in Breast Cancer.; Molecular imaging and radionuclide therapy; 2018; vol. 27 (no. 1); 3-9 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Unclear if reference standard was interpreted without knowledge of index test)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Groheux et al., 2014

| | |
|---|---|
| **Bibliographic Reference** | Groheux, David; Hindie, Elif; Marty, Michel; Espie, Marc; Rubello, Domenico; Vercellino, Laetitia; Bousquet, Guilhem; Ohnona, Jessica; Toubert, Marie-Elisabeth; Merlet, Pascal; Misset, Jean-Louis; 18F-FDG-PET/CT in staging, restaging, and treatment response assessment of male breast cancer.; European journal of radiology; 2014; vol. 83 (no. 10); 1925-33 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Retrospective cohort study |
| **Study details** | Study location<br><br>- France<br><br>Setting<br><br>- Hospital<br><br>Study dates |

| | |
|---|---|
| | - October 2006 to October 2012<br><br>Sources of funding<br><br>- None |
| **Inclusion criteria** | Male patients with breast cancer referred for 18F-FDG PET-CT imaging |
| **Exclusion criteria** | None reported |
| **Number of participants** | N = 15 |
| **Length of follow-up** | - At least 6 months |
| **Loss to follow-up** | 1 |
| **Index test(s)** | FDG PET-CT<br><br>Performed from mid-thigh level to the base of the skull, with the arms raised, using a Gemini XL instrument. CT data was acquired without contrast-enhancement using the following parameters: 120 kV; 100 mAs; pitch 0.94; slice thickness 2.5 mm. PET data was collected in a 3-dimensional mode, with 2 min per-table-position, and reconstructed.<br><br>FDG PET-CT images were interpreted by 2 board-certified nuclear medicine physicians and differences resolved by consensus with the help of a third reader. |
| **Reference standard (s)** | Combination of...<br><br>Histopathology, further work-up and/or patient follow-up<br><br>18F-FDG-PET-CT findings (regional lymph nodes and distant metastases) considered suspicious for malignancy were compared to biopsy results, further work-up and/or patient follow-up.<br><br>A negative procedure was classified as TN only if no metastases occurred during a follow-up of at least 6 months. |
| **Additional comments** | • Each PET-CT examination was classified in one of the followed indication: baseline staging, restaging and treatment response assessment. Restaging was defined as the search for recurrence because of the elevated tumour marker level, suspicious symptoms, and/or abnormalities encountered on conventional imaging studies during follow-up.<br>• If restaging PET-CT imaging confirmed the presence of recurrence, findings at PET-CT were used to adapt treatment. Response assessment was defined as evaluation of response to chemotherapy in the neoadjuvant setting or in the metastatic setting. True positive |

| | |
|---|---|
| | cases were taken as such if metastasis was confirmed at any stage (baseline staging, restaging and treatment response assessment).<br>• 1 participant was classified as 'not determinable' because follow-up was less than 6 months, this participant was excluded from the analysis. |
| **Target condition** | Distant metastases<br><br>Bone metastasis<br><br>Visceral metastasis |

### Population characteristics

### Study-level characteristics

| Characteristic | Study (N = 15) |
|---|---|
| **% Female**<br><br>Sample size | n = 0 ; % = 0 |
| **Histological tumour types - Invasive ductal carcinoma**<br><br>No of events | n = 13 ; % = 86 |
| **Histological tumour types - Invasive cribriform carcinoma**<br><br>No of events | n = 1 ; % = 7 |
| **Histological tumour types - Unknown**<br><br>No of events | n = 1 ; % = 7 |
| **Receptor subtype - Oestrogen receptor positive**<br><br>No of events | n = 13 ; % = 87 |
| **Receptor subtype - Oestrogen receptor negative**<br><br>No of events | n = 0 ; % = 0 |
| **Receptor subtype - Oestrogen receptor unknown**<br><br>No of events | n = 2 ; % = 13 |
| **Receptor subtype - Progesterone receptor positive**<br><br>No of events | n = 11 ; % = 74 |
| **Receptor subtype - Progesterone receptor negative**<br><br>No of events | n = 2 ; % = 13 |

| Characteristic | Study (N = 15) |
|---|---|
| **Receptor subtype - Progesterone receptor unknown**<br><br>No of events | n = 2 ; % = 13 |
| **Receptor subtype - HER2 status - Positive**<br><br>No of events | n = 1 ; % = 7 |
| **Receptor subtype - HER2 status - Negative**<br><br>No of events | n = 12 ; % = 80 |
| **Receptor subtype - HER2 status - unknown**<br><br>No of events | n = 2 ; % = 13 |
| **Receptor subtype - Triple negative breast cancer**<br><br>No of events | n = 0 ; % = 0 |
| **Size of tumour - Grade 1**<br><br>Sample size | n = 1 ; % = 7 |
| **Size of tumour - Grade 2**<br><br>Sample size | n = 10 ; % = 66 |
| **Size of tumour - Grade 3**<br><br>Sample size | n = 3 ; % = 20 |
| **Size of tumour - Unknown**<br><br>Sample size | n = 1 ; % = 7 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Unclear if index test and reference standard results were blindly interpreted.)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Ko et al., 2020

| | |
|---|---|
| **Bibliographic Reference** | Ko, Heidi; Baghdadi, Yaser; Love, Charito; Sparano, Joseph A; Clinical Utility of 18F-FDG PET/CT in Staging Localized Breast Cancer Before |

Initiating Preoperative Systemic Therapy.; Journal of the National Comprehensive Cancer Network : JNCCN; 2020; vol. 18 (no. 9); 1240-1246

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Not clear if the reference standard was interpreted without knowledge of the results of the index test)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Koolen et al., 2012

| | |
|---|---|
| **Bibliographic Reference** | Koolen, Bas B; Vrancken Peeters, Marie-Jeanne T F D; Aukema, Tjeerd S; Vogel, Wouter V; Oldenburg, Hester S A; van der Hage, Jos A; Hoefnagel, Cornelis A; Stokkel, Marcel P M; Loo, Claudette E; Rodenhuis, Sjoerd; Rutgers, Emiel J Th; Valdes Olmos, Renato A; 18F-FDG PET/CT as a staging procedure in primary stage II and III breast cancer: comparison with conventional imaging techniques.; Breast cancer research and treatment; 2012; vol. 131 (no. 1); 117-26 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | High<br>*(The investigators knew the results of other diagnostic procedures and it is not clear what impact the non-blinding would have had on the interpretation of the scan results)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Krammer et al., 2015

| | |
|---|---|
| **Bibliographic Reference** | Krammer, J; Schnitzer, A; Kaiser, C G; Buesing, K A; Sperk, E; Brade, J; Wasgindt, S; Suetterlin, M; Schoenberg, S O; Sutton, E J; Wasser, K; (18) F-FDG PET/CT for initial staging in breast cancer patients - Is there a relevant impact on treatment planning compared to conventional staging modalities?.; European radiology; 2015; vol. 25 (no. 8); 2460-9 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Insufficient information on participant selection and whether index test and reference standards were interpreted blindly)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Lee et al., 2021

| | |
|---|---|
| **Bibliographic Reference** | Lee, Jeeyeon; Park, Ho Yong; Kim, Wan Wook; Park, Chan Sub; Lee, Ryu Kyung; Kim, Hye Jung; Kim, Won Hwa; Lee, Sang Woo; Jeong, Shin Young; Chae, Yee Soo; Lee, Soo Jung; Park, Ji Young; Park, Jee-Young; Jung, Jin Hyang; Value of accurate diagnosis for metastatic supraclavicular lymph nodes in breast cancer: assessment with neck US, CT, and 18F-FDG PET/CT.; Diagnostic and interventional radiology (Ankara, Turkey); 2021; vol. 27 (no. 3); 323-328 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Retrospective cohort study |
| **Study details** | Study location<br><br>- Korea<br><br>Setting<br><br>- Not reported<br><br>Study dates<br><br>- 2008 to 2013<br><br>Sources of funding<br><br>- Not reported |
| **Inclusion criteria** | Patients with breast cancer who had undergone surgery |
| **Exclusion criteria** | None reported |
| **Number of participants** | N = 1148 |

| | |
|---|---|
| | (N = 64 included in this review, which were patients with locoregional recurrence only. This subpopulation was selected because it was the closest match to the inclusion criteria for this review) |
| **Length of follow-up** | 6 months to 1 year |
| **Loss to follow-up** | None |
| **Index test(s)** | FDG PET-CT<br><br>Scan was conducted from the skull vertex to the knee level. PET-CT scan was conducted using a 16-slice or 64-slice CT Discovery PET-CT 600 (maximum spatial resolutions of 5.1mm) or CT Discovery PET-CT 690 apparatus (maximum spatial resolutions of 4.9mm) at 1.5minutes per bed position. Images obtained from the Discovery PET-CT scanners were reconstructed with a 192x192 matrix, an ordered subset expectation maximum iterative reconstruction algorithm (4 iterations, 16 subsets), a Gaussian filter of 6.4 mm, and a slice thickness of 3.27 mm (Discovery PET-CT 600 or 690). |
| **Reference standard (s)** | Pathological confirmation from biopsy<br><br>Fine needle aspiration (FNAC) was performed under ultrasound with each lesion aspirated with a 21-guage needle using the to-and-fro technique. FNAC slides were prepared for Papanicolaou staining based on the standard method and assessed for diagnostic accuracy, confirmed by and experienced cytopathologist. |
| **Additional comments** | Among the 1148 patients enrolled, only those with suspicious SCNs in the Neck US, chest CT or PET-CT underwent fine-needle aspiration cytology (FNAC) to confirm true metastasis. |
| **Target condition** | Supraclavicular lymph node metastasis |

### Population characteristics

### Study-level characteristics

| **Characteristic** | **Study (N = 1148)** |
|---|---|
| **Age** (years)<br><br>Mean (SD) | 50.1 (10.4) |
| **Histological tumour types - Invasive ductal carcinoma**<br><br>Sample size | n = 1053 ; % = 91.7 |
| **Histological tumour types - Invasive lobular carcinoma**<br><br>Sample size | n = 38 ; % = 3.3 |

| Characteristic | Study (N = 1148) |
|---|---|
| **Histological tumour types - Mucinous carcinoma**<br><br>Sample size | n = 27 ; % = 2.4 |
| **Histological tumour types - Others**<br><br>Sample size | n = 30 ; % = 2.6 |
| **Receptor subtype - Oestrogen receptor (ER) positive**<br><br>Sample size | n = 798 ; % = 69.5 |
| **Receptor subtype - Progesterone receptor (PR) positive**<br><br>Sample size | n = 690 ; % = 60.1 |
| **Receptor subtype - c-erbB2 gene positive**<br><br>Sample size | n = 221 ; % = 19.3 |
| **Receptor subtype - Triple-negative breast cancer**<br><br>Sample size | n = 86 ; % = 7.5 |
| **Size of tumour - Clinical tumour sizes**<br><br>Mean (SD) | 2.3 (1.5) |
| **Size of tumour - Pathological tumour sizes**<br><br>Mean (SD) | 1.8 (1.1) |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | High<br>*(Serious concerns regarding the selection of patients into the study and the index test, unclear risk of bias in reference standard and flow and timing domains.)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Manohar et al., 2013

| | |
|---|---|
| **Bibliographic Reference** | Manohar, Kuruva; Mittal, Bhagwant R; Bhoil, Amit; Bhattacharya, Anish; Singh, Gurpreet; Role of 18F-FDG PET/CT in identifying distant metastatic disease missed by conventional imaging in patients with locally advanced |

breast cancer.; Nuclear medicine communications; 2013; vol. 34 (no. 6); 557-61

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(No information on participant enrolment and blinding to index test or reference standard provided)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Manohar et al., 2012

| | |
|---|---|
| **Bibliographic Reference** | Manohar, Kuruva; Mittal, Bhagwant Rai; Senthil, Raja; Kashyap, Raghava; Bhattacharya, Anish; Singh, Gurpreet; Clinical utility of F-18 FDG PET/CT in recurrent breast carcinoma.; Nuclear medicine communications; 2012; vol. 33 (no. 6); 591-6 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Unclear if interpreters of the reference standard had knowledge of the index test results.)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Melsaether et al., 2016

| | |
|---|---|
| **Bibliographic Reference** | Melsaether, Amy N; Raad, Roy A; Pujara, Akshat C; Ponzo, Fabio D; Pysarenko, Kristine M; Jhaveri, Komal; Babb, James S; Sigmund, Eric E; Kim, Sungheon G; Moy, Linda A; Comparison of Whole-Body (18)F FDG PET/MR Imaging and Whole-Body (18)F FDG PET/CT in Terms of Lesion Detection and Radiation Dose in Patients with Breast Cancer.; Radiology; 2016; vol. 281 (no. 1); 193-202 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Unclear if reference standard interpreters were blinded to index test)* |
| Overall risk of bias and directness | Directness | Partially applicable<br>*(Not all patients included were suspected of metastasis prior to PET-CT)* |

### Niikura et al., 2011

| | |
|---|---|
| **Bibliographic Reference** | Niikura, Naoki; Costelloe, Colleen M; Madewell, John E; Hayashi, Naoki; Yu, Tse-Kuan; Liu, Jun; Palla, Shana L; Tokuda, Yutaka; Theriault, Richard L; Hortobagyi, Gabriel N; Ueno, Naoto T; FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer.; The oncologist; 2011; vol. 16 (no. 8); 1111-9 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Low |
| Overall risk of bias and directness | Directness | Directly applicable |

### Rager et al., 2018

| | |
|---|---|
| **Bibliographic Reference** | Rager, Olivier; Lee-Felker, Stephanie A; Tabouret-Viaud, Claire; Felker, Ely R; Poncet, Antoine; Amzalag, Gael; Garibotto, Valentina; Zaidi, Habib; Walter, Martin A; Accuracy of whole-body HDP SPECT/CT, FDG PET/CT, and their combination for detecting bone metastases in breast cancer: an intra-personal comparison.; American journal of nuclear medicine and molecular imaging; 2018; vol. 8 (no. 3); 159-168 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Some concerns regarding blinding when interpreting the results of the reference standard and some concerns on the applicability of the reference standard.)* |

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Directness | Partially applicable<br>*(Some concerns with the applicability of the reference standard)* |

### Riegger et al., 2012

| | |
|---|---|
| **Bibliographic Reference** | Riegger, C; Herrmann, J; Nagarajah, J; Hecktor, J; Kuemmel, S; Otterbach, F; Hahn, S; Bockisch, A; Lauenstein, T; Antoch, G; Heusner, T A; Whole-body FDG PET/CT is more accurate than conventional imaging for staging primary breast cancer patients.; European journal of nuclear medicine and molecular imaging; 2012; vol. 39 (no. 5); 852-63 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Low |
| Overall risk of bias and directness | Directness | Directly applicable |

### Shawky et al., 2020

| | |
|---|---|
| **Bibliographic Reference** | Shawky, M.; Ali, Z.A.E.; Hashem, D.H.; Houseni, M.; Role of positron-emission tomography/computed tomography (PET/CT) in breast cancer; Egyptian Journal of Radiology and Nuclear Medicine; 2020; vol. 51 (no. 1); 125 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Prospective cohort study |
| **Study details** | Study location<br><br>- Egypt<br><br>Setting<br><br>- Not reported<br><br>Study dates<br><br>- From January 2016 to December 2017<br><br>Sources of funding |

| | |
|---|---|
| | - No funding received |
| **Inclusion criteria** | Breast cancer, started treatment and referred for whole body PET-CT and CECT<br><br>Histologically proven breast cancer. Some participants had positive operative history (modified radical mastectomy, simple mastectomy, and lumpectomy). Participants who received chemotherapy with last cycle for more than 3 weeks and radiotherapy with last session for more than 2 months were also included. |
| **Exclusion criteria** | Early post-operative cases, uncontrolled diabetes mellitus and impaired renal function |
| **Number of participants** | N=30 |
| **Length of follow-up** | 6 to 12 months |
| **Loss to follow-up** | None |
| **Index test(s)** | FDG PET-CT<br><br>Contrast-enhanced CT |
| **Reference standard (s)** | Combination of...<br><br>Histopathological analysis, clinical and imaging follow-up,<br><br>- No additional information provided |
| **Additional comments** | None |
| **Target condition** | Distant metastases |

### Population characteristics

### Study-level characteristics

| Characteristic | Study (N = 30) |
|---|---|
| **% Female**<br><br>Sample size | n = 30 ; % = 100 |
| **Age**<br><br>Mean (SD) | 53.56 (10.64) |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Insufficient information on the selection of participants and not clear if the index test results were interpreted without knowledge of the results of the reference standard and vice versa)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Usmani et al., 2024

| | |
|---|---|
| **Bibliographic Reference** | Usmani, Sharjeel; Al Riyami, Khulood; Jain, Anjali; Alajmi, Adil Aljarrah; AlBaimani, Khalid; Dumasig, Paul; Al Busaidi, Asiya; Al Sukati, Rashid; Enhancing precision in bone metastasis diagnosis for lobular breast cancer: reassessing the role of 18 F-FDG PET/CT.; Nuclear medicine communications; 2024; vol. 45 (no. 10); 858-864 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Retrospective cohort study |
| **Study details** | Study location<br><br>- Oman<br><br>Setting<br><br>- Cancer Care and Research Centre<br><br>Study dates<br><br>- August 2021 and December 2023<br><br>Sources of funding<br><br>- Not reported |
| **Inclusion criteria** | All patients with histopathological diagnosis of invasive lobular carcinoma which underwent 18F-FDG PET-CT imaging |
| **Exclusion criteria** | Cases with missing demographics and scan specific data<br><br>18F-FDG PET-CT scan done in restaging setting for patients who received prior therapy including chemotherapy or hormonal therapy<br><br>Unavailability of follow-up imaging |

| | |
|---|---|
| **Number of participants** | N = 21 |
| **Length of follow-up** | At least 6 months |
| **Loss to follow-up** | None |
| **Index test(s)** | FDG PET-CT<br><br>Whole body, low dose, nonbreath hold CT. Intravenous contrast agent not given and water was used as negative oral contrast. |
| **Reference standard (s)** | Combination of...<br><br>Radiological imaging and clinical follow-up of at least 6 months.<br><br>Follow-up information included physical examination, laboratory tests, tumour markers, and other independent imaging studies (CT, MRI, and bone scan). For CT, the M.D. Anderson criteria were used for follow-up: an increase in the number of lesions and changes in CT characteristics [e.g. a lytic lesion changing to a blastic/sclerotic lesion or an increase in Hounsfield unit of the sclerotic lesion] were considered strong evidence of bone metastases. The frequency of follow-up assessments done according to institutional guideline. The final determinations rely on clinician/multidisciplinary team notes based on clinical examination, laboratory, and imaging findings. |
| **Target condition** | Bone metastasis |

### Population characteristics

### Study-level characteristics

| **Characteristic** | **Study (N = 21)** |
|---|---|
| **Age**<br><br>Mean (SD) | 53.85 (10.6) |
| **Receptor subtype - Oestrogen receptor positive**<br><br>No of events | n = 17 ; % = 81 |
| **Receptor subtype - Progesterone receptor positive**<br><br>No of events | n = 15 ; % = 71 |
| **Receptor subtype - HER2 status - Positive**<br><br>No of events | n = 1 ; % = 5 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Unclear if reference standard results were blindly interpreted.)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Vogsen et al., 2021b

| | |
|---|---|
| **Bibliographic Reference** | Vogsen, Marianne; Jensen, Jeanette Dupont; Christensen, Ivar Yannick; Gerke, Oke; Jylling, Anne Marie Bak; Larsen, Lisbet Bronsro; Braad, Poul-Erik; Soe, Katrine Lydolph; Bille, Camilla; Ewertz, Marianne; Hildebrandt, Malene Grubbe; FDG-PET/CT in high-risk primary breast cancer-a prospective study of stage migration and clinical impact.; Breast cancer research and treatment; 2021; vol. 185 (no. 1); 145-153 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(It was unclear if study authors had results from both index test and reference standard before interpreting them)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Vogsen et al., 2021a

| | |
|---|---|
| **Bibliographic Reference** | Vogsen, Marianne; Jensen, Jeanette Dupont; Gerke, Oke; Jylling, Anne Marie Bak; Asmussen, Jon Thor; Christensen, Ivar Yannick; Braad, Poul-Erik; Thye-Ronn, Peter; Soe, Katrine Lydolph; Ewertz, Marianne; Hildebrandt, Malene Grubbe; Benefits and harms of implementing [18F]FDG-PET/CT for diagnosing recurrent breast cancer: a prospective clinical study.; EJNMMI research; 2021; vol. 11 (no. 1); 93 |

### Study Characteristics

| | |
|---|---|
| **Study type** | Prospective cohort study |
| **Study details** | Study location |

| | |
|---|---|
| | - Denmark<br><br>Setting<br><br>- University hospital<br><br>Study dates<br><br>- September 1, 2017 to August 31, 2019<br><br>Sources of funding<br><br>- Qvesehls Grant<br><br>- Mrs. Astrid Thaysens Grant<br><br>- The Independent Research Fund Denmark (DFF—7016-00359)<br><br>- University of Southern Denmark (Ph.D. Grant)<br><br>- Odense University Hospital (Ph.D. Grant)<br><br>- Center for Personalised Response Monitoring in Oncology (PREMIO), Odense University Hospital, Odense, Denmark. |
| **Inclusion criteria** | Women 18 years or older, signed a consent statement, and had a prior diagnosis of early-stage breast cancer |
| **Exclusion criteria** | Pregnant<br><br>Treated for other invasive cancers at the time of inclusion<br><br>Suffered from other conditions that interfered with the patients' understanding of the study |
| **Number of participants** | N = 225 |
| **Length of follow-up** | 6 months |
| **Loss to follow-up** | 0 |
| **Index test(s)** | FDG PET-CT<br><br>From top skull to mid-thigh was performed 60±5 min p.i. with intravenous injection of 4 MBq [ 18F]FDG per kg bodyweight. PET scans were performed using a standard whole-body acquisition protocol with slice overlaps of 40% (DMI) and 25% (D710) and acquisition times of 1½ min (DMI) and 2½ min (D710) per bed position, respectively. The scan field of view was 70 cm. |

| | |
|---|---|
| | Contrast-enhanced CT<br><br>Scan was done with in vivo contrast (ultravist 370 I/ml) using a CT protocol with a scan field-of-view (FOV) of 70 cm, 120kVp, pitch=0.984, and GE automatic exposure control. |
| **Reference standard (s)** | Pathological confirmation from biopsy<br><br>Biopsies from suitable metastatic lesions served as references. In a few cases with strong clinical confidence in distant metastases, only the biopsy from local recurrences was obtained.<br><br>Clinical follow-up<br><br>If metastatic lesions were detected on [18F]FDG-PET-CT but could not be verified by biopsy, patients were followed by imaging according to the location of the lesion. No patients were diagnosed without biopsy verification. Patients with no signs of metastatic breast cancer on [18F]FDG-PET-CT were followed for six months by medical records to detect false negatives. False-negative was defined if distant recurrence was revealed within six months from the [18F]FDG-PET-CT scan. A patient could have more than one [18F]FDG-PET-CT scan during the study period due to a new referral or uncertainty after the initial scan. However, only the first scan was used for accuracy assessment and the remaining for follow-up. In some cases, MRI was used in addition to biopsy as a follow-up to confirm the absence of metastases, typically in patients with suspected bone metastases. No patients were diagnosed with metastatic breast cancer by MRI alone. |
| **Additional comments** | The assessment of CECT scans was considered a limitation by study authors due to the availability of clinically used bookmarks and knowledge of coming scans, all of which were accessible by the radiologist. This provided the radiologist with information on metastatic lesions, and the accuracy of CECT might therefore be overestimated in this study. |
| **Target condition** | Distant metastases |

### Population characteristics

### Study-level characteristics

| Characteristic | Study (N = 225) |
|---|---|
| **% Female**<br><br>Sample size | n = 225 ; % = 100 |
| **Age**<br>Median (range)<br><br>Custom value | 68.0 (33.3 to 91.2) |

| Characteristic | Study (N = 225) |
|---|---|
| **Histological tumour types - Ductal carcinoma**<br><br>No of events | n = 171 ; % = 76 |
| **Histological tumour types - Lobular carcinoma**<br><br>No of events | n = 18 ; % = 8 |
| **Histological tumour types - Carcinoma NOS**<br><br>No of events | n = 5 ; % = 2.22 |
| **Histological tumour types - Other**<br><br>No of events | n = 28 ; % = 12.4 |
| **Histological tumour types - Unknown**<br><br>No of events | n = 1 ; % = 1.33 |
| **Receptor subtype - Oestrogen receptor negative**<br><br>No of events | n = 45 ; % = 20 |
| **Receptor subtype - Oestrogen receptor positive**<br><br>No of events | n = 172 ; % = 76.44 |
| **Receptor subtype - Oestrogen receptor unknown**<br><br>No of events | n = 8 ; % = 3.56 |
| **Receptor subtype - HER2 status - Normal**<br><br>No of events | n = 164 ; % = 72.9 |
| **Receptor subtype - HER2 status - Positive**<br><br>No of events | n = 23 ; % = 10.2 |
| **Receptor subtype - HER2 status - unknown**<br><br>No of events | n = 38 ; % = 16.9 |
| **Size of tumour - ≤10 mm**<br><br>No of events | n = 43 ; % = 19.1 |
| **Size of tumour - 11 to 20 mm**<br><br>No of events | n = 107 ; % = 47.6 |
| **Size of tumour - 21 to 50 mm**<br><br>No of events | n = 59 ; % = 26.2 |

| Characteristic | Study (N = 225) |
|---|---|
| **Size of tumour - ≥50 mm**<br><br>No of events | n = 7 ; % = 3.11 |
| **Size of tumour - Unknown**<br><br>No of events | n = 9 ; % = 4 |
| **Nodal status of primary tumour - Involvement of lymph node only**<br><br>Sample size | n = 2 ; % = 3.85 |
| **Nodal status of primary tumour - Involvement of mixed organs**<br><br>Sample size | n = 19 ; % = 36.5 |

### Critical appraisal - Critical Appraisal - QUADAS-2

| Section | Question | Answer |
|---|---|---|
| Overall risk of bias and directness | Risk of Bias | High<br>*(CECT: High risk - CECT scans were interpreted with knowledge of reference standard. Unclear if patients were selected consecutively or randomly and if reference standard results were interpreted without knowledge of CECT. PET-CT: Moderate risk - unclear if PET-CT scans were interpreted with knowledge of reference standard. Unclear if patients were selected consecutively or randomly and if reference standard results were interpreted without knowledge of CECT.)* |
| Overall risk of bias and directness | Directness | Directly applicable |

### Review B2

No studies were included in this review.

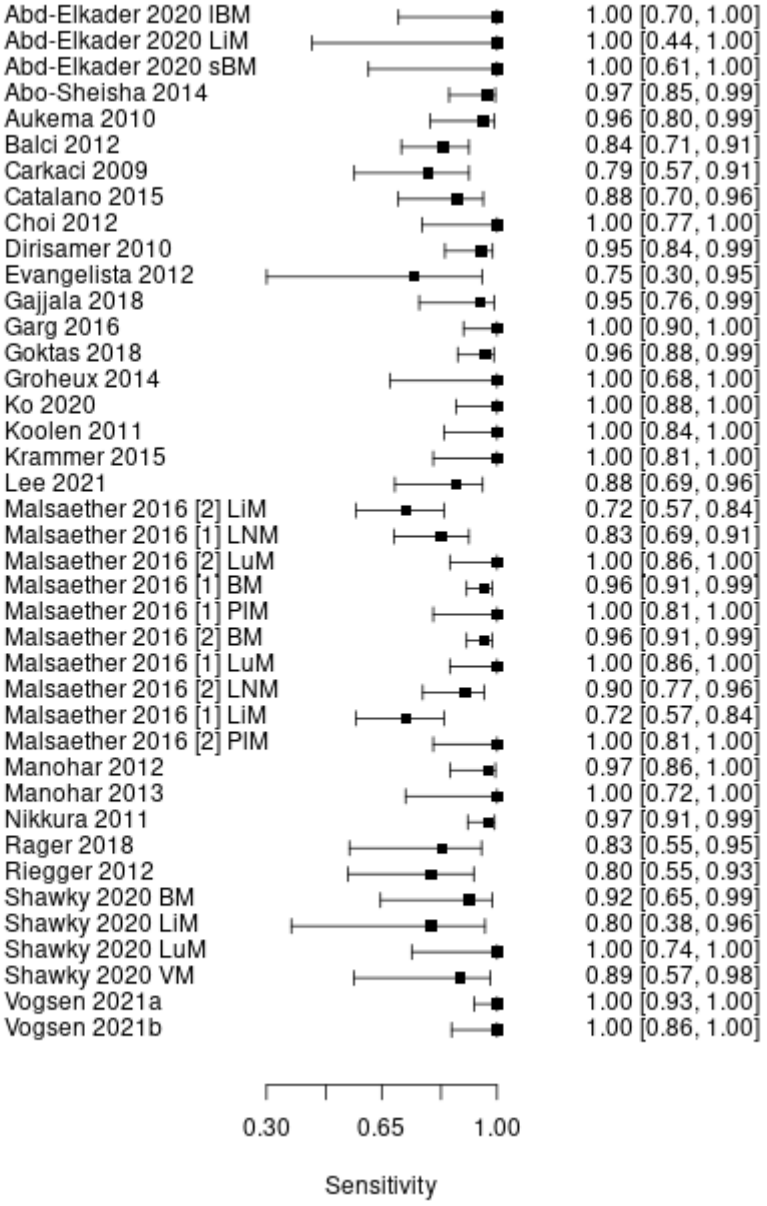
# Appendix E – Forest plots

## Review B1

### Forest plots for FDG PET-CT (mixed population)

Mixed population analyses include all studies other than those which include only participants with lobular breast cancer.

**Figure 3: Forest plot for sensitivity of FDG PET-CT for detecting any distant metastases (mixed population)**




**Meta-analysed sensitivity (95% CI): 0.95 (0.93, 0.97)**

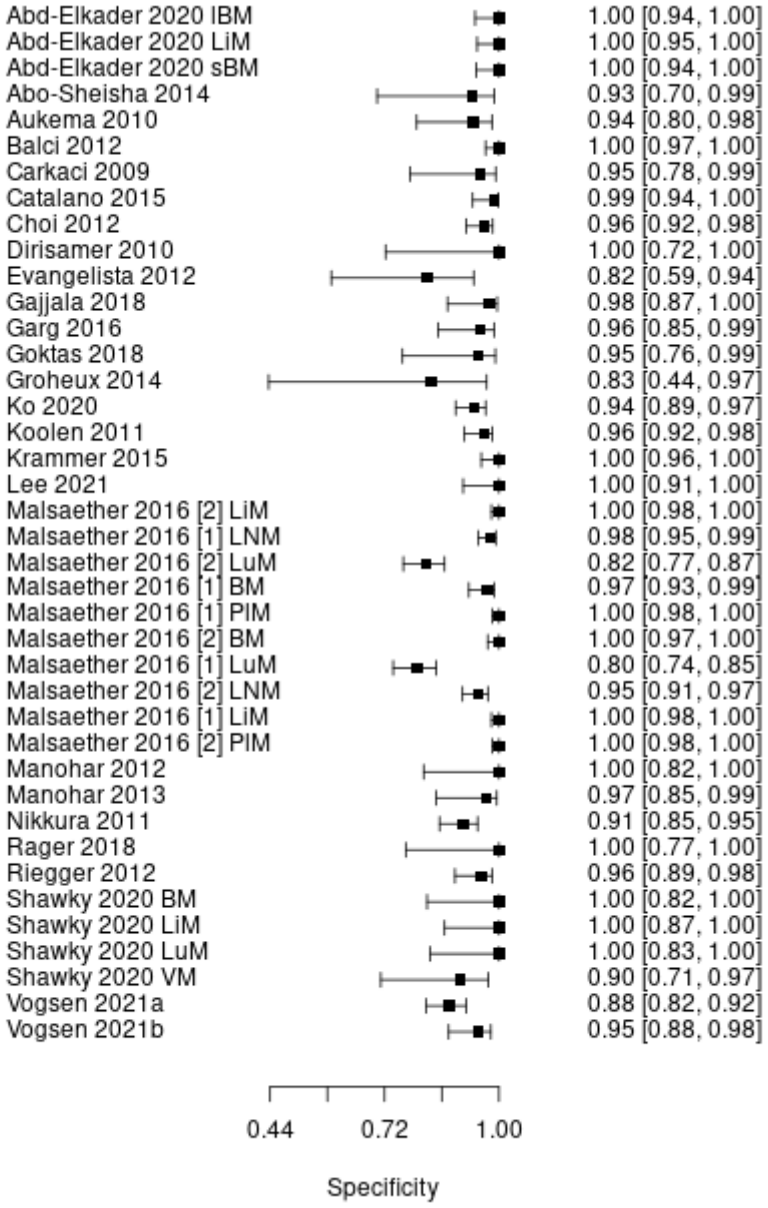
BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; LiM: liver metastasis; LNM: lymph node metastasis; LuM: lung metastasis; FDG PET-CT: fluorodeoxyglucose positron emission

tomography computed tomography; PIM: Pleura metastasis; sBM: sclerotic bone metastasis; VM: visceral metastasis

Note: Number in square bracket indicates interpreter number (some studies included multiple interpretations of the same scans, all of which are included).

Carkaci 2009 included only participants with inflammatory breast cancer

**Figure 4: Forest plot for specificity of FDG PET-CT for detecting any distant metastases (mixed population)**



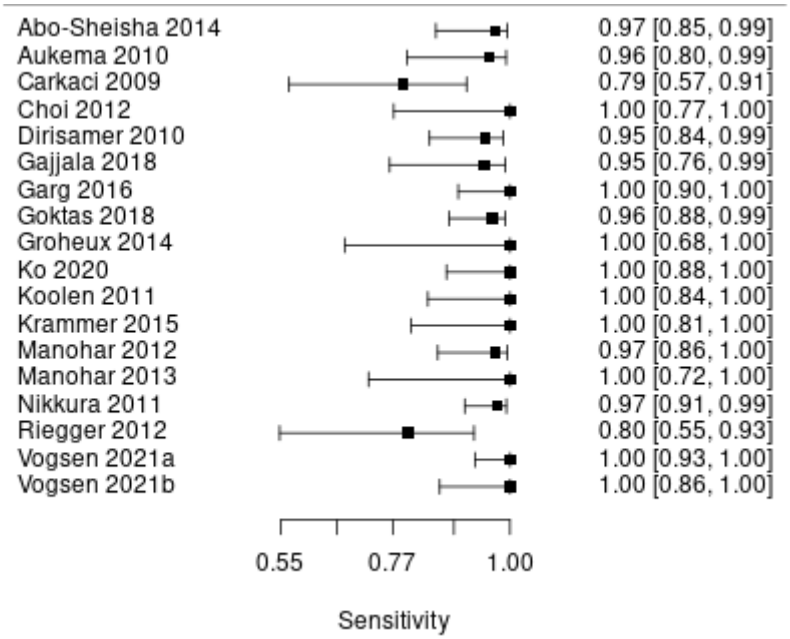

**Meta-analysed specificity (95% CI): 0.98 (0.97, 0.99)**

BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; LiM: liver metastasis; LNM: lymph node metastasis; LuM: lung metastasis; FDG PET-CT: fluorodeoxyglucose positron emission tomography computed tomography; PIM: Pleura metastasis; sBM: sclerotic bone metastasis; VM: visceral metastasis

Note: Number in square bracket indicates interpreter number (some studies included multiple interpretations of the same scans, all of which are included).

Carkaci 2009 included only participants with inflammatory breast cancer

**Figure 5: Forest plot for sensitivity of FDG PET-CT for detecting whole-body distant metastases only (mixed population) (sensitivity analysis)**

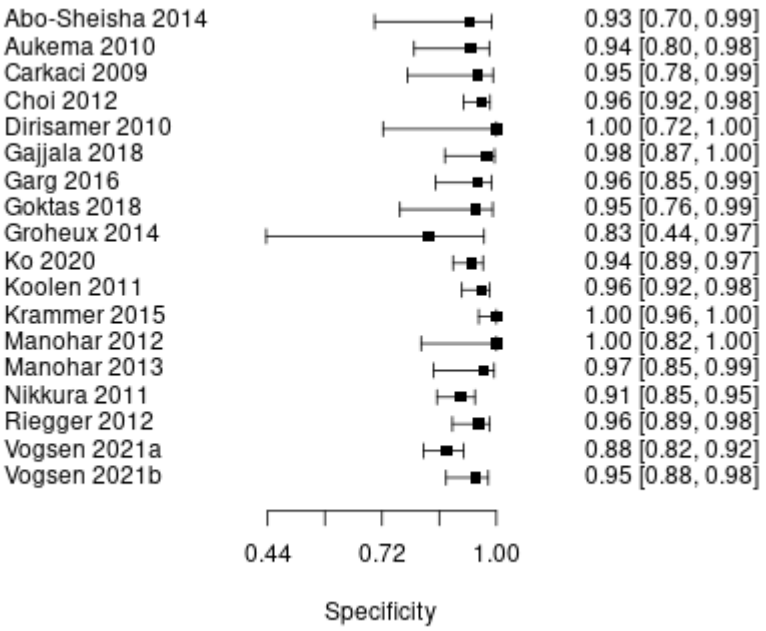



**Meta-analysed sensitivity (95% CI): 0.97 (0.94, 0.99)**

CI: confidence interval; FDG PET-CT: fluorodeoxyglucose positron emission tomography computed tomography

Carkaci 2009 included only participants with inflammatory breast cancer

**Figure 6: Forest plot for specificity of FDG PET-CT for detecting whole-body distant metastases only (mixed population) (sensitivity analysis)**

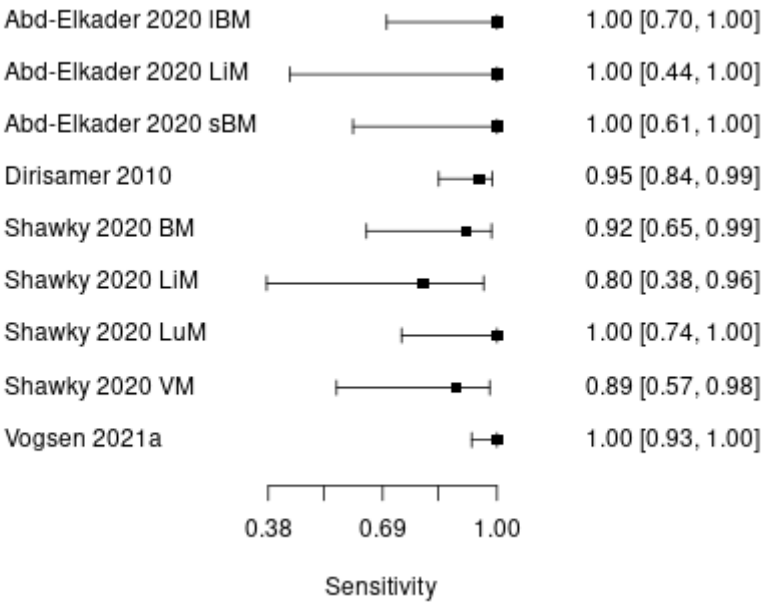



**Meta-analysed specificity (95% CI): 0.95 (0.93, 0.97)**

CI: confidence interval; FDG PET-CT: fluorodeoxyglucose positron emission tomography computed tomography

Carkaci 2009 included only participants with inflammatory breast cancer

**Figure 7: Forest plot for sensitivity of FDG PET-CT for detecting any distant metastases in studies assessing both FDG PET-CT and CECT (mixed population) (sensitivity analysis)**

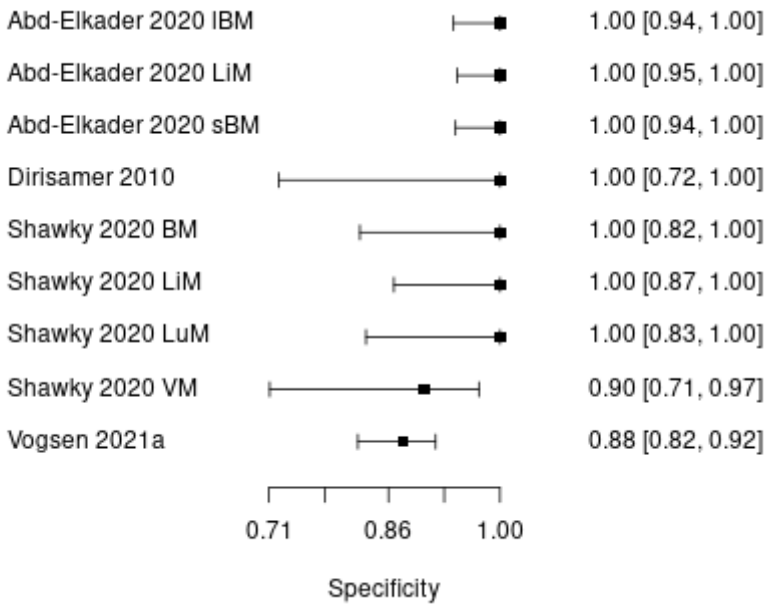


**Meta-analysed sensitivity (95% CI): 0.96 (0.91, 0.99)**

This plot includes only the 4 studies which presented results for both FDG PET-CT and CECT. The same people had both tests in all 4 studies.

BM: bone metastasis; CECT: contrast enhanced computed tomography; CI: confidence interval; lBM: lytic bone metastasis; LiM: liver metastasis; LuM: lung metastasis; FDG PET-CT: fluorodeoxyglucose positron emission tomography computed tomography; sBM: sclerotic bone metastasis; VM: visceral metastasis

## Figure 8: Forest plot for specificity of FDG PET-CT for detecting any distant metastases in studies assessing both FDG PET-CT and CECT (mixed population) (sensitivity analysis)

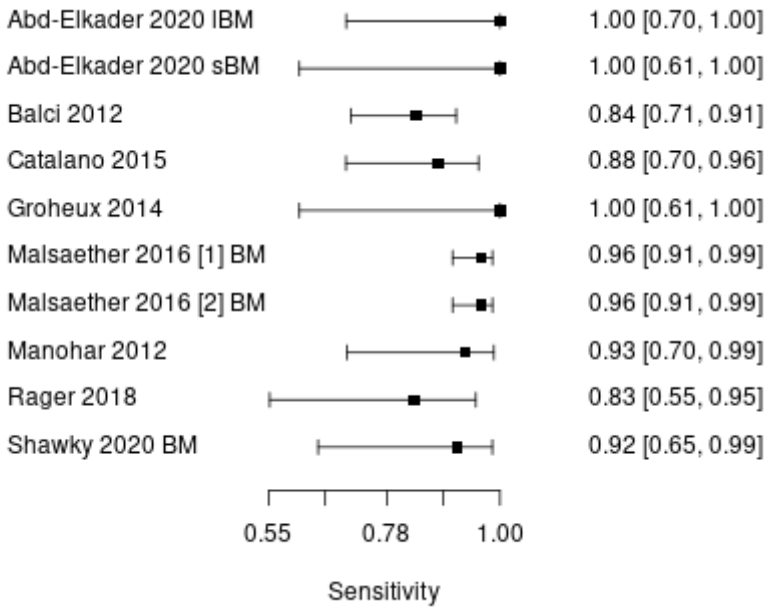



**Meta-analysed sensitivity (95% CI): 1.00 (0.24, 1.00)**

This plot includes only the 4 studies which presented results for both FDG PET-CT and CECT. The same people had both tests in all 4 studies.

BM: bone metastasis; CECT: contrast enhanced computed tomography; CI: confidence interval; lBM: lytic bone metastasis; LiM: liver metastasis; LuM: lung metastasis; FDG PET-CT: fluorodeoxyglucose positron emission tomography computed tomography; sBM: sclerotic bone metastasis; VM: visceral metastasis

**Figure 9: Forest plot for sensitivity of FDG PET-CT for detecting bone metastasis (mixed population)**

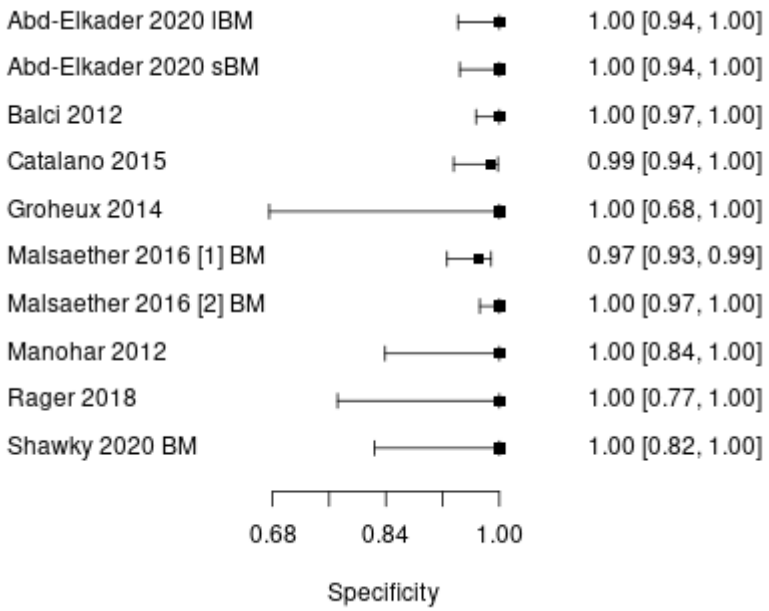



**Meta-analysed sensitivity (95% CI): 0.93 (0.88, 0.96)**

BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; FDG PET-CT: fluorodeoxyglucose positron emission tomography computed tomography; sBM: sclerotic bone metastasis

Note: Number in square bracket indicates interpreter number (some studies included multiple interpretations of the same scans, all of which are included).

**Figure 10: Forest plot for specificity of FDG PET-CT for detecting bone metastasis (mixed population)**

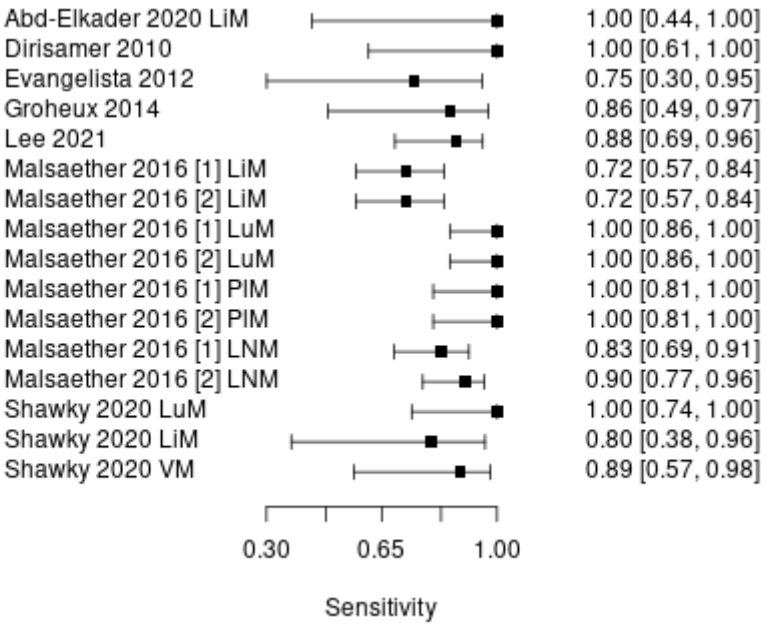



**Meta-analysed specificity (95% CI): 1.00 (0.97, 1.00)**

BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; FDG PET-CT: fluorodeoxyglucose positron emission tomography computed tomography; sBM: sclerotic bone metastasis

Note: Number in square bracket indicates interpreter number (some studies included multiple interpretations of the same scans, all of which are included).

**Figure 11: Forest plot for sensitivity of FDG PET-CT for detecting visceral metastasis (mixed population)**

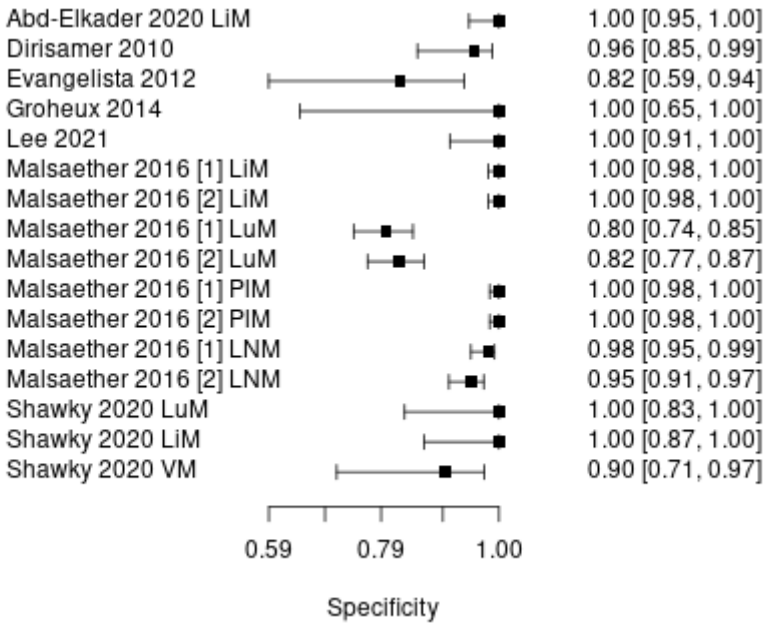



**Meta-analysed sensitivity (95% CI): 0.91 (0.83, 0.96)**

CI: confidence interval; LiM: liver metastasis; LNM: lymph node metastasis; LuM: lung metastasis; FDG PET-CT: fluorodeoxyglucose positron emission tomography computed tomography; PlM: Pleura metastasis; VM: visceral metastasis

Note: Number in square bracket indicates interpreter number (some studies included multiple interpretations of the same scans, all of which are included).

**Figure 12: Forest plot for specificity of FDG PET-CT for detecting visceral metastasis (mixed population)**




**Meta-analysed specificity (95% CI): 1.00 (0.95, 1.00)**

CI: confidence interval; LiM: liver metastasis; LNM: lymph node metastasis; LuM: lung metastasis; FDG PET-CT: fluorodeoxyglucose positron emission tomography computed tomography; PlM: Pleura metastasis; VM: visceral metastasis

Note: Number in square bracket indicates interpreter number (some studies included multiple interpretations of the same scans, all of which are included).

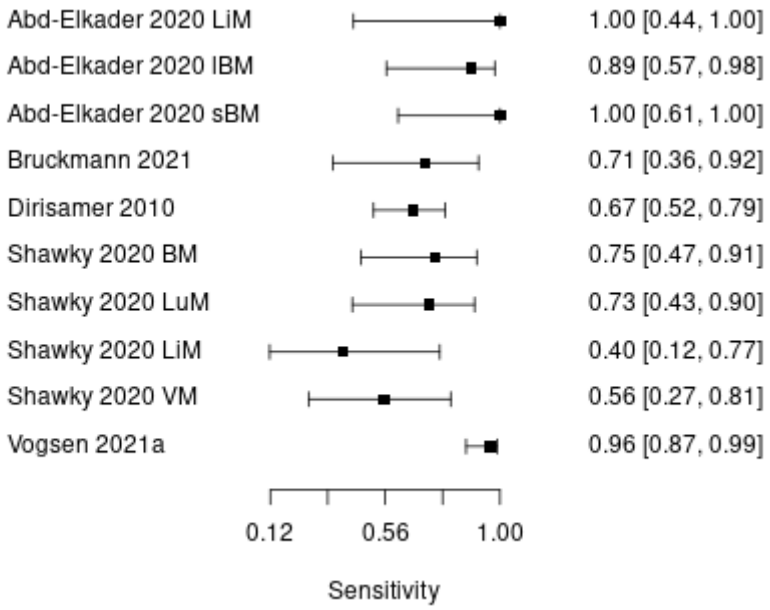
## Forest plots for FDG PET-CT (lobular breast cancer only)

No meta-analysis conducted as only one study identified. Forest plots for single studies are not presented.

## Forest plots for CECT

All studies and analyses for CECT are mixed population. Mixed population analyses include all studies other than those which include only participants with lobular breast cancer.

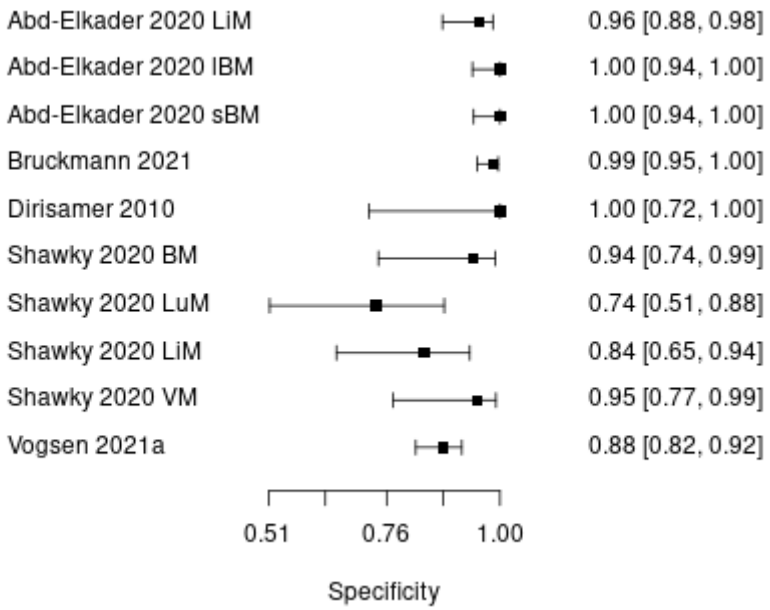
**Figure 13: Forest plot for sensitivity of CECT for detecting any distant metastases**




**Meta-analysed sensitivity (95% CI): 0.80 (0.65, 0.89)**

BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; LiM: liver metastasis; LuM: lung metastasis; CECT: contrast enhanced computed tomography; sBM: sclerotic bone metastasis; VM: visceral metastasis

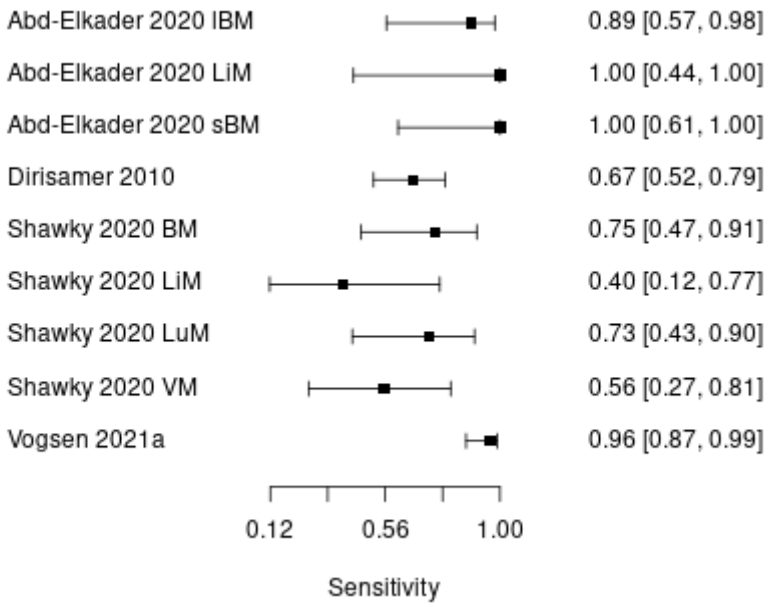
**Figure 14: Forest plot for specificity of CECT for detecting any distant metastases**




**Meta-analysed specificity (95% CI): 0.96 (0.89, 0.98)**

BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; LiM: liver metastasis; LuM: lung metastasis; CECT: contrast enhanced computed tomography; sBM: sclerotic bone metastasis; VM: visceral metastasis

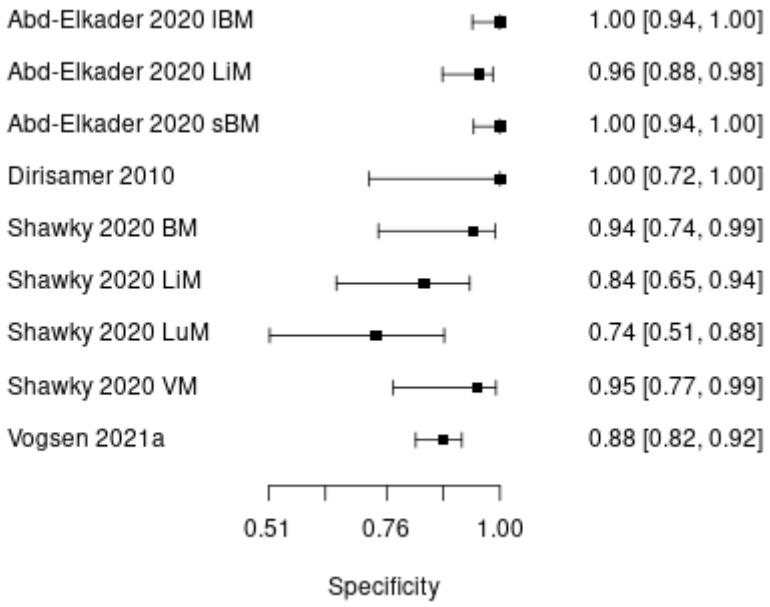
**Figure 15: Forest plot for sensitivity of CECT for detecting any distant metastases in studies assessing both FDG PET-CT and CECT**




**Meta-analysed sensitivity (95% CI): 0.81 (0.64, 0.91)**

BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; LiM: liver metastasis; LuM: lung metastasis; CECT: contrast enhanced computed tomography; sBM: sclerotic bone metastasis; VM: visceral metastasis

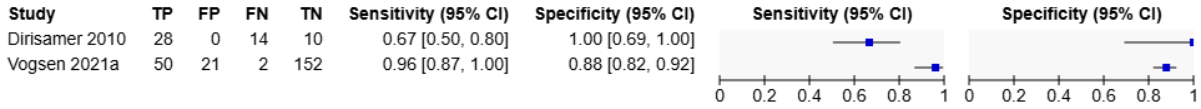
## Figure 16: Forest plot for sensitivity of CECT for detecting any distant metastases in studies assessing both FDG PET-CT and CECT




**Meta-analysed sensitivity (95% CI): 0.95 (0.87, 0.99)**

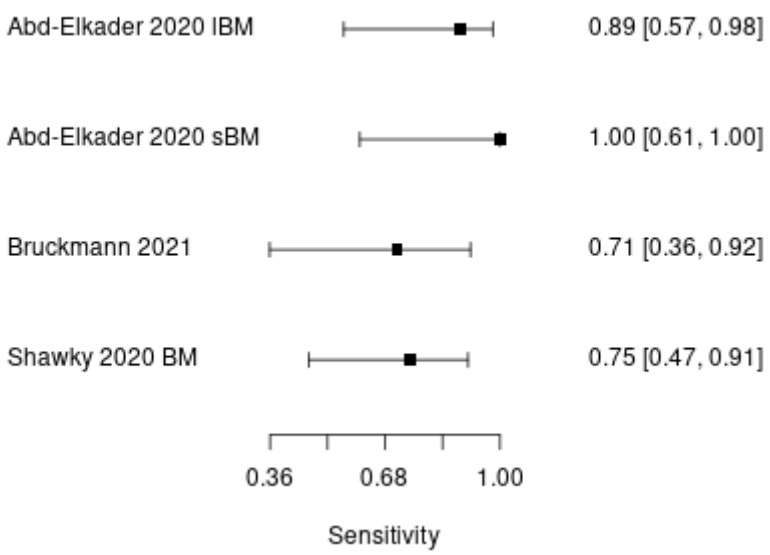
BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; LiM: liver metastasis; LuM: lung metastasis; CECT: contrast enhanced computed tomography; sBM: sclerotic bone metastasis; VM: visceral metastasis

## Figure 17: Forest plot for sensitivity and specificity of CECT for detecting whole-body distant metastases only (sensitivity analysis)




CECT: contrast enhanced computed tomography

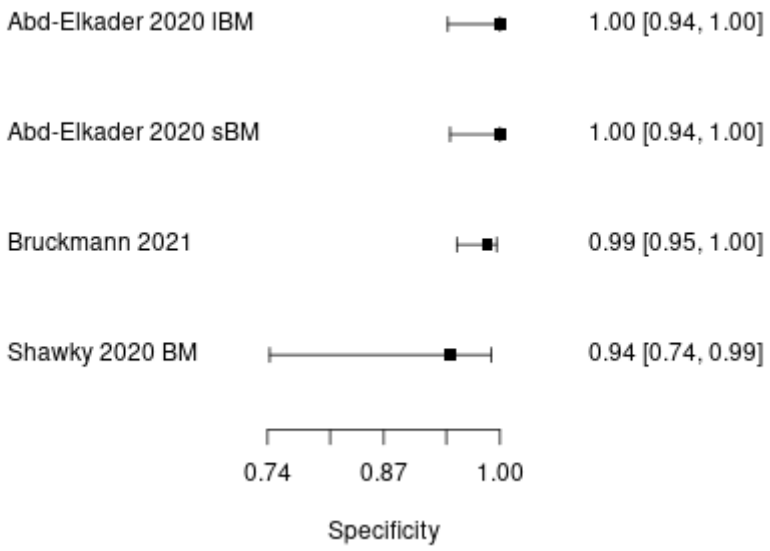
**Figure 18: Forest plot for sensitivity of CECT for detecting bone metastasis**




**Meta-analysed sensitivity (95% CI): 0.83 (0.63, 0.93)**

BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; CECT: contrast enhanced computed tomography; sBM: sclerotic bone metastasis

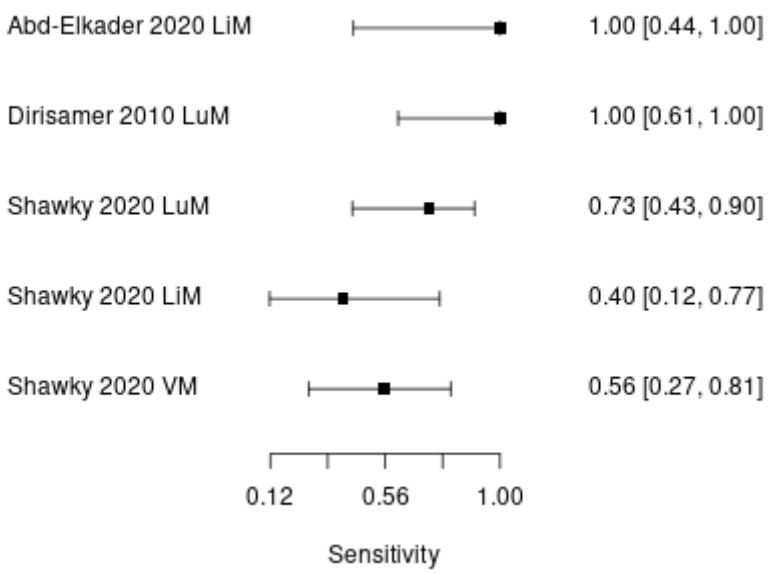
**Figure 19: Forest plot for specificity of CECT for detecting bone metastasis**




**Meta-analysed specificity (95% CI): 0.99 (0.95, 0.99)**

BM: bone metastasis; CI: confidence interval; lBM: lytic bone metastasis; CECT: contrast enhanced computed tomography; sBM: sclerotic bone metastasis

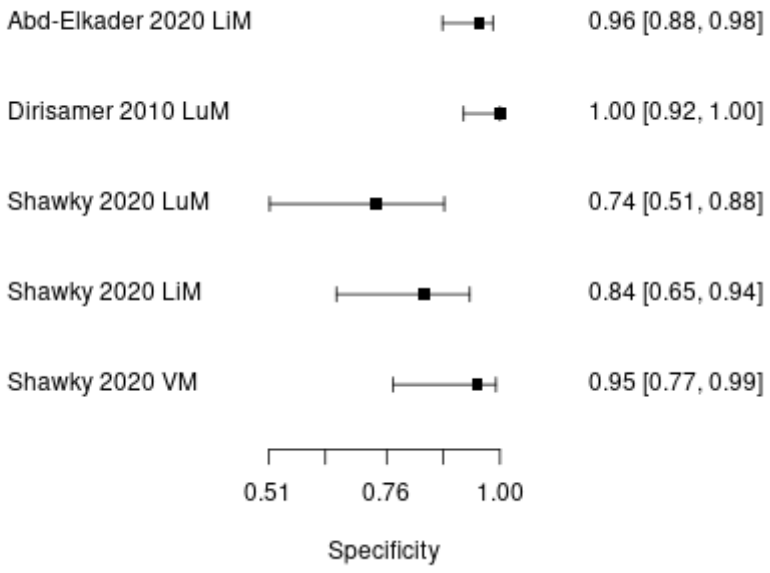
**Figure 20: Forest plot for sensitivity of CECT for detecting visceral metastasis**




**Meta-analysed sensitivity (95% CI): 0.76 (0.44, 0.92)**

CI: confidence interval; LiM: liver metastasis; LuM: lung metastasis; CECT: contrast enhanced computed tomography; VM: visceral metastasis

**Figure 21: Forest plot for specificity of CECT for detecting visceral metastasis**




**Meta-analysed specificity (95% CI): 0.93 (0.80, 0.98)**

CI: confidence interval; LiM: liver metastasis; LuM: lung metastasis; CECT: contrast enhanced computed tomography; VM: visceral metastasis

### Review B2

No studies were included in this review.

# Appendix F – GRADE tables

## Review B1

### GRADE tables for FDG PET-CT (mixed population)

Mixed population analyses include all studies other than those which include only participants with lobular breast cancer.

### Table 22: Clinical evidence profile (diagnostic accuracy) for FDG PET-CT for detecting any distant metastases (mixed population)

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 26[1,2] | Prospective and retrospective cohort studies | 4923 (2513 counting multiple interpretation studies only once) | 53.55 (28.89, 99.25) | 0.05 (0.03, 0.08) | Sensitivity 0.95 (0.93, 0.97) | Serious[3] | Serious[4] | Serious[5] | Not serious | VERY LOW |
| | | | | | Specificity 0.98 (0.97, 0.99) | Serious[3] | Not serious | Serious[5] | Not serious | LOW |

CI: confidence interval; LR: likelihood ratio.

1. Abd-Elkader 2020, Abo-Sheisha 2014, Aukema 2010, Balci 2012, Carkaci 2009, Catalano 2015, Choi 2012, Dirisamer 2010, Evangelista 2012, Gajjala 2018, Garg 2016, Goktas 2018, Groheux 2014, Ko 2020, Koolen 2011, Krammer 2015, Lee 2021, Melsaether 2016, Manohar 2012, Manohar 2013, Niikura 2011, Rager 2018, Riegger 2012, Shawky 2020, Vogsen 2021a, Vogsen 2021b

2. This analysis includes whole-body distant metastases or any site-specific distant metastases where whole-body distant metastases was not reported. Of these 26 studies, some contributed multiple results: 1 study reported on 3 metastatic sites, 1 study reported on 4 metastatic sites and 1 study reported on 5 metastatic sites from 2 different interpreters.

3. Downgraded once as ≥50% of the weighting of studies in a meta-analysis at moderate or high risk of bias as assessed by QUADAS-2

4. Downgraded once as <80% of point estimates are within the same range of test performance as determined by the clinical decision making thresholds, and point estimates are separated by 1 decision making threshold..

5. Downgraded once as population is indirect due to ≥50% of the weighting of studies in the meta-analysis having participants which did not fully represent the population specified in the protocol.

### Table 23: Clinical evidence profile (diagnostic accuracy) for FDG PET-CT for detecting whole-body distant metastases only (mixed population) (sensitivity analysis)

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 18[1] | Prospective and retrospective cohort studies | 1789 | 20.55 (14.24, 29.66) | 0.03 (0.01, 0.06) | Sensitivity 0.97 (0.94, 0.99) | Serious[2] | Not serious | Not serious | Not serious | MODERATE |
| | | | | | Specificity 0.95 (0.93, 0.97) | Serious[2] | Not serious | Not serious | Not serious | MODERATE |

CI: confidence interval; LR: likelihood ratio.

1. Abo-Sheisha 2014, Aukema 2010, Carkaci 2009, Choi 2012, Dirisamer 2010, Gajjala 2018, Garg 2016, Goktas 2018, Groheux 2014, Ko 2020, Koolen 2011, Krammer 2015, Manohar 2012, Manohar 2013, Nikkura 2011, Riegger 2012, Vogsen 2021a, Vogsen 2021b

2. Downgraded once as ≥50% of the weighting of studies in a meta-analysis at moderate or high risk of bias as assessed by QUADAS-2

**Table 24: Clinical evidence profile (diagnostic accuracy) for FDG PET-CT for detecting any distant metastases in studies that assessed both FDG-PET-CT and CECT (mixed population) (sensitivity analysis)**

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 4[1, 2] | Prospective and retrospective cohort studies | 488 (256 counting multiple interpretation studies only once) | 2105.30 (0.313, 14177918.7) | 0.036 (0.015, 0.088) | Sensitivity 0.96 (0.91, 0.99) | Very serious[3] | Serious[4] | Not serious | Not serious | VERY LOW |
| | | | | | Specificity 1.00 (0.24, 1.00) | Very serious[3] | Not serious | Not serious | Very serious[5] | VERY LOW |

This table includes only the 4 studies which presented results for both FDG PET-CT and CECT. The same people had both tests in all 4 studies.

1. Abd-Elkader 2020, Dirisamer 2010, Shawky 2020, Vogsen 2021a

2. Includes whole-body distant metastases or any site-specific distant metastasis where whole-body distant metastases was not reported. Of the 4 studies, 1 study reported on 3 metastatic sites and 1 study reported 4 metastatic sites.

3. Downgraded twice as ≥50% of the weighting of studies in a meta-analysis at high risk of bias as assessed by QUADAS-2

4. Downgraded once as <80% of point estimates are within the same range of test performance as determined by the clinical decision making thresholds, and point estimates are separated by 1 decision making threshold.

5. Downgraded twice as 95% CI crosses 2 decision making thresholds (for sensitivity, thresholds are 0.70 and 0.90; for specificity 0.60 and 0.80)

**Table 25: Clinical evidence profile (diagnostic accuracy) for FDG PET-CT for detecting bone metastasis (mixed population)**

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 8[1,2] | Prospective and retrospective cohort studies | 1001 | 337.29 (26.72, 4257.37) | 0.07 (0.04, 0.12) | Sensitivity 0.93 (0.88, 0.96) | Serious[3] | Serious[4] | Serious[5] | Serious[6] | VERY LOW |
| | | | | | Specificity 1.00 (0.97, 1.00) | Serious[3] | Not serious | Serious[5] | Not serious | LOW |

CI: confidence interval; LR: likelihood ratio.

1. Abd-Elkader 2020, Balci 2012, Catalano 2015, Groheux 2014, Melsaether 2016, Manohar 2012, Rager 2018, Shawky 2020

2. Includes 1 study that reported sclerotic bone metastasis and lytic bone metastasis separately and 1 study that had 2 interpreters.

3. Downgraded once as ≥50% of the weighting of studies in a meta-analysis at moderate or high risk of bias as assessed by QUADAS-2

4. Downgraded once as <80% of point estimates are within the same range of test performance as determined by the clinical decision making thresholds, and point estimates are separated by 1 decision making threshold.

5. Downgraded once as population is indirect due to ≥50% of the weighting of studies in the meta-analysis having participants which did not fully represent the population specified in the protocol.

6. Downgraded once as 95% CI crosses 1 decision making thresholds (for sensitivity, thresholds are 0.70 and 0.90; for specificity 0.60 and 0.80)

### Table 26: Clinical evidence profile (diagnostic accuracy) for FDG PET-CT for diagnosing visceral metastasis (mixed population)

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 7[1,2] | Prospective and retrospective cohort studies | 2248 | 127.44 (19.33, 840.09) | 0.09 (0.04, 0.17) | Sensitivity 0.91 (0.83, 0.96) | Serious[3] | Serious[4] | Serious[5] | Serious[6] | VERY LOW |
| | | | | | Specificity 1.00 (0.95, 1.00) | Serious[3] | Not serious | Serious[5] | Not serious | LOW |

CI: confidence interval; LR: likelihood ratio.

1. Abd-Elkader 2020, Dirisamer 2010, Evangelista 2012, Groheux 2014, Lee 2021, Melsaether 2016, Shawky 2020

2. Includes 1 study reporting on 3 metastatic sites and 1 study reporting on 4 metastatic sites from 2 different interpreters.

3. Downgraded once as ≥50% of the weighting of studies in a meta-analysis at moderate or high risk of bias as assessed by QUADAS-2

4. Downgraded once as <80% of point estimates are within the same range of test performance as determined by the clinical decision making thresholds, and point estimates are separated by 1 decision making threshold.

5. Downgraded once as population is indirect due to ≥50% of the weighting of studies in the meta-analysis having participants which did not fully represent the population specified in the protocol.

6. Downgraded once as 95% CI crosses 1 decision making thresholds (for sensitivity, thresholds are 0.70 and 0.90; for specificity 0.60 and 0.80)

## GRADE tables for FDG PET-CT (lobular breast cancer only)

### Table 27: Clinical evidence profile (diagnostic accuracy) for FDG PET-CT for detecting bone metastasis (lobular breast cancer only)

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 (Usmani et al., 2024) | Prospective and retrospective cohort studies | 21 | 5.00 (0.55, 45.39) | 0.71 (0.40, 1.28) | Sensitivity 0.33 (0.10, 0.70) | Serious[1] | Serious[2] | Not serious | Serious[3] | VERY LOW |
| | | | | | Specificity 0.93 (0.70, 0.99) | Serious[1] | Serious[2] | Not serious | Serious[3] | VERY LOW |

CI: confidence interval; LR: likelihood ratio.

1. Downgraded once as the study was at moderate risk of bias as assessed by QUADAS-2
2. Downgraded once for serious heterogeneity as only one study included in analysis
3. Downgraded once as 95% CI crosses 1 decision making thresholds (for sensitivity, thresholds are 0.70 and 0.90; for specificity 0.60 and 0.80)

## GRADE tables for CECT

All studies and analyses for CECT are mixed population. Mixed population analyses include all studies other than those which include only participants with lobular breast cancer.

### Table 28: Clinical evidence profile (diagnostic accuracy) for CECT for diagnosing any distant metastases

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 5[1,2] | Prospective and retrospective cohort studies | 532 | 21.20 (7.53, 59.68) | 0.20 (0.11, 0.38) | Sensitivity 0.80 (0.65, 0.89) | Very serious[3] | Very serious[4] | Not serious | Serious[5] | VERY LOW |
| | | | | | Specificity 0.96 (0.89, 0.98) | Very serious[3] | Not serious | Not serious | Not serious | LOW |

CI: confidence interval; LR: likelihood ratio.

1. Abd-Elkader 2020, Bruckmann 2021, Dirisamer 2010, Shawky 2020, Vogsen 2021a.

2. Includes whole-body distant metastases or any site-specific distant metastasis where whole-body distant metastases was not reported. Of the 5 studies, 1 study reported on 3 metastatic sites and 1 study reported 4 metastatic sites.

3. Downgraded twice as ≥50% of the weighting of studies in a meta-analysis at high risk of bias as assessed by QUADAS-2.

4. Downgraded twice as <80% of point estimates are within the same range of test performance as determined by the clinical decision making thresholds, and point estimates are separated by 2 decision making thresholds.

5. Downgraded once as 95% CI crosses 1 decision making threshold (for sensitivity, thresholds are 0.70 and 0.90).

**Table 29: Clinical evidence profile (diagnostic accuracy) for CECT for diagnosing whole-body distant metastases only (sensitivity analysis)**

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 (Dirisamer 2010) | Retrospective cohort | 52 | 14 (0.92, 211.14) | 0.35 (0.22, 0.54) | Sensitivity 0.67 (0.52, 0.79) | Very serious[1] | Serious[2] for sensitivity<br><br>Not serious for specificity | Not serious | Very serious[3] for sensitivity<br><br>Serious for specificity[4] | VERY LOW for sensitivity<br><br>VERY LOW for specificity |
| | | | | | Specificity 1.00 (0.72, 1.00) | | | | | |
| 1 (Vogsen 2021a) | Prospective cohort | 225 | 7.92 (5.28, 11.87) | 0.04 (0.01, 0.17) | Sensitivity 0.96 (0.87, 0.99) | | | | | |
| | | | | | Specificity 0.88 (0.82, 0.92) | | | | | |

CI: confidence interval; LR: likelihood ratio.

Meta-analysis was not possible as a minimum of 3 studies are needed for bivariate meta-analysis

1. Downgraded twice as ≥50% of the weighting of studies in a meta-analysis at high risk of bias as assessed by QUADAS-2.

2. Downgraded once as <80% of point estimates are within the same range of test performance as determined by the clinical decision making thresholds, and point estimates are separated by 1 decision making threshold.

3. Downgraded twice as 95% CI crosses 2 decision making thresholds (for sensitivity, thresholds are 0.70 and 0.90).

4. Downgraded once as 95% CI crosses 1 decision making threshold (for specificity, thresholds are 0.60 and 0.80).

**Table 30: Clinical evidence profile (diagnostic accuracy) for CECT for diagnosing any distant metastases in studies assessing both FDG PET-CT and CECT (sensitivity analysis)**

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 4[1,2] | Prospective and retrospective cohort studies | 488 (256 counting multiple interpretation studies only once) | Sensitivity 0.96 (0.91, 0.99) | 0.20 (0.11, 0.38) | Sensitivity 0.81 (0.64, 0.91) | Very serious[3] | Very serious[4] | Not serious | Very serious[5] | VERY LOW |
| | | | | | Specificity 0.95 (0.87, 0.99) | Very serious[3] | Not serious | Not serious | Not serious | LOW |

CI: confidence interval; LR: likelihood ratio.

1. Abd-Elkader 2020, Dirisamer 2010, Shawky 2020, Vogsen 2021a.

2. Includes whole-body distant metastases or any site-specific distant metastasis where whole-body distant metastases was not reported. Of the 4 studies, 1 study reported on 3 metastatic sites and 1 study reported 4 metastatic sites.

3. Downgraded twice as ≥50% of the weighting of studies in a meta-analysis at high risk of bias as assessed by QUADAS-2.

4. Downgraded twice as <80% of point estimates are within the same range of test performance as determined by the clinical decision making thresholds, and point estimates are separated by 2 decision making thresholds.

5. Downgraded twice as 95% CI crosses 2 decision making thresholds (for sensitivity, thresholds are 0.70 and 0.90).

## Table 31: Clinical evidence profile (diagnostic accuracy) for CECT for diagnosing bone metastasis

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 3[1,2] | Prospective and retrospective cohort studies | 255 | 89.83 (17.80, 453.35) | 0.17 (0.07, 0.40) | Sensitivity 0.83 (0.63, 0.93) | Very serious[3] | Serious[4] | Serious[5] | Very serious[6] | VERY LOW |
| | | | | | Specificity 0.99 (0.95, 0.99) | Very serious[3] | Not serious | Serious[5] | Not serious | VERY LOW |

CI: confidence interval; LR: likelihood ratio.

1. Abd-Elkader 2020, Bruckmann 2021, Shawky 2020.

2. Includes 1 study diagnosing sclerotic and lytic bone metastasis separately.

3. Downgraded twice as ≥50% of the weighting of studies in a meta-analysis at high risk of bias as assessed by QUADAS-2.

4. Downgraded once as <80% of point estimates are within the same range of test performance as determined by the clinical decision making thresholds, and point estimates are separated by 1 decision making threshold.

5. Downgraded once for population is indirect due to ≥50% of the weighting of studies in the meta-analysis having participants which did not fully represent the population specified in the protocol.

6. Downgraded twice as 95% CI crosses 2 decision making thresholds (for sensitivity, thresholds are 0.70 and 0.90).

### Table 32: Clinical evidence profile (diagnostic accuracy) for CECT for diagnosing visceral metastasis

| No of studies | Study design | Sample size | LR+ (95% CI) | LR – (95% CI) | Effect size (95% CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Certainty |
|---|---|---|---|---|---|---|---|---|---|---|
| 3[1,2] | Observational cohorts | 153 | 11.58 (3.09, 43.35) | 0.25 (0.08, 0.74) | Sensitivity 0.76 (0.44, 0.92) | Very serious[3] | Very serious[4] | Not serious | Very serious[5] | VERY LOW |
| | | | | | Specificity 0.93 (0.80, 0.98) | Very serious[3] | Not serious | Not serious | Serious[6] | VERY LOW |

CI: confidence interval; LR: likelihood ratio.

1. Abd-Elkader 2020, Dirisamer 2010, Shawky 2020.

2. Includes 1 study reporting on 3 metastatic sites.

3. Downgraded twice as ≥50% of the weighting of studies in a meta-analysis at high risk of bias as assessed by QUADAS-2.

4. Downgraded twice as <80% of point estimates are within the same range of test performance as determined by the clinical decision making thresholds, and point estimates are separated by 2 decision making threshold.

5. Downgraded twice as 95% CI crosses 2 decision making thresholds (for sensitivity, thresholds are 0.70 and 0.90).

6. Downgraded once as 95% CI crosses 1 decision making thresholds (for specificity, thresholds are 0.60 and 0.80).

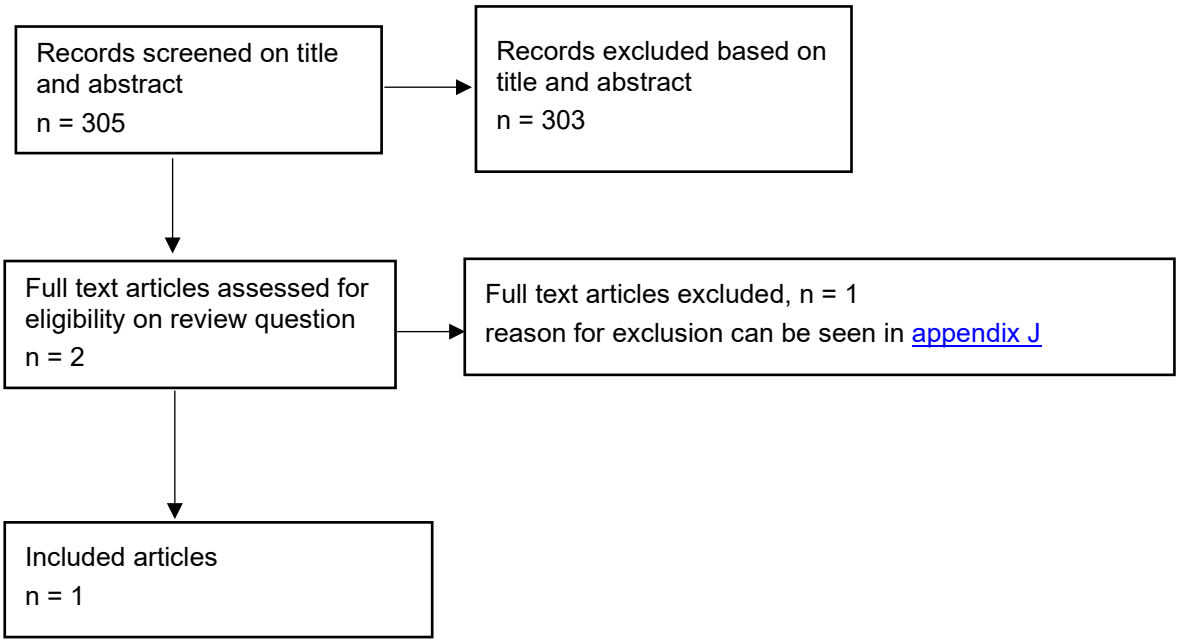
### Review B2

No studies were included in this review.

# Appendix G – Economic evidence study selection

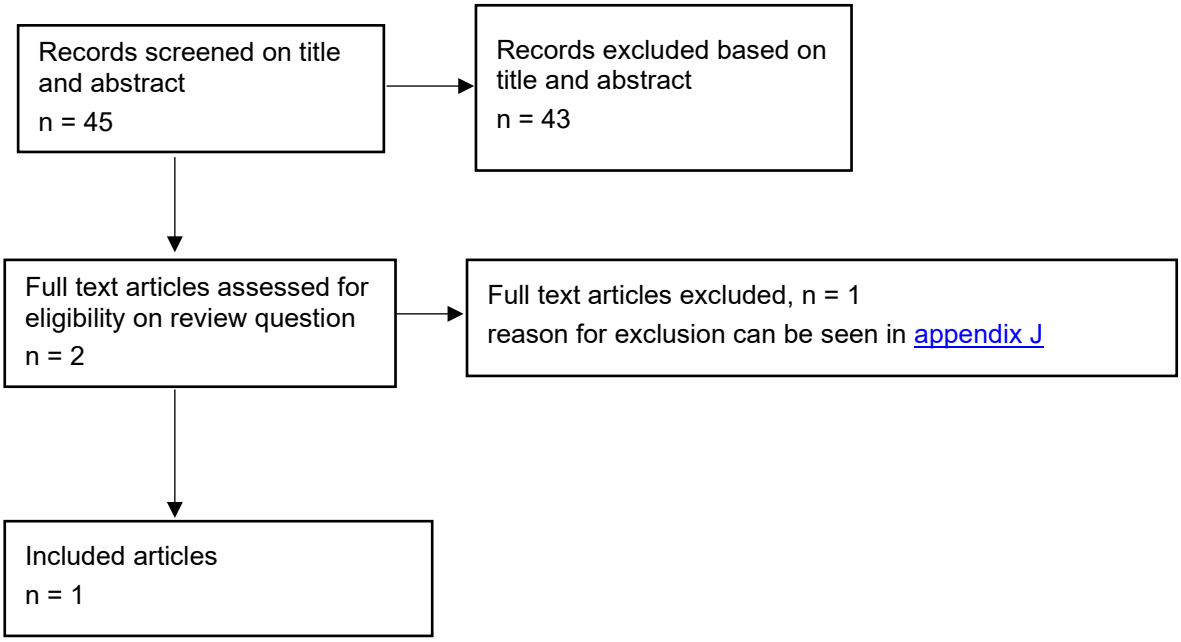
## Review B1

### Figure 22: PRISMA flow diagram for review B1 economic evidence



**Review B2**

**Figure 23: PRISMA flow diagram for review B2 economic evidence**



# Appendix H – Economic evidence tables

### Review B1

### Table 33: Economic evidence study extraction table: Auguste 2011

| Section | Details for Auguste, 2011 |
|---|---|
| **Study details** | **Economic analysis type:** Cost-utility<br>**Analysis design:** Decision Tree<br>**Country setting:** UK<br>**Perspective:** UK NHS+PSS<br>**Time horizon/Follow-up:** 1 year (costs), lifetime (QALYs)<br>**Discount rate per year:** Costs: NA (time horizon 1 year) Outcomes:NR |
| **Interventions** | **Intervention 1:** Conventional work-up (i.e. diagnostic package comprising ultrasound, radiography, CT, bone scintigraphy and measurement of serum tumour markers)<br>**Intervention 2:** PET-CT<br>**Intervention 3:** PET<br>**Intervention 4:** PET-CT as an adjunct to conventional work-up |
| **Population** | **Population:** Who had completed a course of treatment for primary breast cancer and undergoing diagnostic testing for distant recurrence.<br>**Baseline characteristics:** Starting age of model 50 years |
| **Costs included** | **Original currency & cost year:** 2007 UK Sterling<br>**Cost components incorporated:** Diagnostic tests, biopsy and treatment |
| **Outcomes included** | **Primary health outcome(s) in economic analysis:** QALYs<br>**Key events modelled /analysed:** Appropriate diagnosis and treatment |
| **Data Sources** | **Effectiveness data:** Systematic review and meta-analysis of 28 diagnostic accuracy studies published up to May 2009<br>**Baseline / epidemiological data:** NA<br>**Quality-of-life weights:** True positive: Obtained from oncology nurses using standard gamble technique.<br>True negatives and false positives: Taken from the general population (n=3,395) in the UK using the EuroQoL EQ-5D questionnaire and UK preference set to estimate a mean utility weight for the UK population.<br>False negatives: Assigned a utility value of zero (assumption) given assumptions around death.<br>**Costs and/or resource use:** NHS national schedule for reference costs 2002–3 (inflated to 2008 prices) |

| Section | Details for Auguste, 2011 |
|---|---|
| **Results: costs** | **Total costs (per patient):**<br>(1) Conventional work-up (i.e. diagnostic package comprising ultrasound, radiography, CT, bone scintigraphy and measurement of serum tumour markers) - £10,864<br>(2) PET-CT - £13,554<br>(3) PET -£12,807<br>(4) PET-CT as an adjunct to conventional work-up - £14,566<br>(95% CI: NR; p=NR) |
| **Results: health outcomes** | **QALYs (per patient):**<br>(1) Conventional work-up (i.e. diagnostic package comprising ultrasound, radiography, CT, bone scintigraphy and measurement of serum tumour markers) – 4.7826<br>(2) PET-CT – 4.8732<br>(3) PET -4.8490<br>(4) PET-CT as an adjunct to conventional work-up – 4.8972<br>(95% CI: NR; p=NR) |
| **Results: cost effectiveness** | **Incremental cost-effectiveness ratios (cost per QALY):**<br>2 vs 1: £31,000<br>3 vs 1: £29,300<br>4 vs 1: £42,100 |
| **Results: Uncertainty** | **Deterministic analysis:**<br>ICER for PET-CT versus conventional work-up of £29,700 per QALY.<br><br>When the sensitivity of PET-CT was increased to a value of 97%, the ICER for PET-CT versus PET fell to £27,800 per QALY.<br><br>The specificity of PET-CT was increased to a value of 100%, and the ICER for PET-CT versus PET was estimated at £30,800 per QALY.<br><br>The cost of PET-CT with a reduction of £26, which had the effect of reducing the ICER for PET-CT versus PET to an estimated ICER of £29,900 per QALY.<br><br>**Probabilistic analysis:**<br>Under WTP £20k per QALY, conventional work-up has the highest probability of being cost-effective.<br><br>When WTP >£40k per QALY,<br>PET-CT + conventional work-up becomes the preferred strategy with a high probability of cost-effectiveness. |

| Section | Details for Auguste, 2011 |
|---|---|
| | At WTP of £30k per QALY, there is considerable uncertainty regarding what would be considered the preferred strategy, and none of the strategies has over a 60% probability of being cost-effective.<br><br>Neither of the PET nor PET-CT strategies are cost-effective at a WTP of £20k per QALY |
| **Health inequalities assessment** | NR |
| **Comments** | **Source of funding:** The National Institute for Health Research Health Technology Assessment programme<br><br>Study has a time horizon for costs which may not capture all important differences. Conventional work-up, whilst largely CECT Scans also includes other diagnostic modalities. |
| **Rating: Applicability** | Partially applicable<br>Study takes a NHS+PSS perspective and reports outcomes in QALYs |
| **Rating: Quality/ limitations** | Potentially serious limitations<br>Time horizon for costs insufficient to capture all differences between interventions |

Abbreviations: Abbreviations: CECT: Contrast-enhanced computed tomography; ICER: Incremental cost-effectiveness ratio PET-CT: 2-deoxy-2-[18F] fluoro-D-glucose PET-CT positron emission tomography with integrated computed tomography; QALY: Quality adjusted life-year; Vs: Versus; WTP: Willingness-to-pay

### Review B2

### PET-CT versus CECT in people with biopsy-verified distant relapse or de novo metastatic breast cancer

### Table 34:Economic evidence study extraction table: Naghavi-Behzad, 2023

| Section | Details for Naghavi-Behzad, 2023 |
|---|---|
| **Study details** | **Economic analysis type:** Cost-effectiveness<br>**Analysis design:** Retrospective cohort analysis<br>**Country setting:** Denmark<br>**Perspective:** Danish healthcare system<br>**Time horizon/Follow-up:** Median follow-up: 30 months, range: 2-124 months<br>**Discount rate per year:** Costs: 0%; Outcomes: 0% |
| **Interventions** | **Intervention 1:** Contrast-enhanced computed tomography (CECT)<br>**Intervention 2:** 2-deoxy-2-[$^{18}$F]fluoro-D-glucose PET/CT positron emission tomography with integrated computed tomography (PET-CT)<br>**Intervention 3:** Any combination of the two modalities above |

| Section | Details for Naghavi-Behzad, 2023 |
|---|---|
| | The monitoring schedule was not reported for any of the interventions |
| **Population** | **Population:**<br>Biopsy-verified distant relapse or de novo metastatic breast cancer patients (biopsy verification of primary tumor or distant metastases along with disseminated disease at baseline scan) with available baseline scan and one or more follow-up scans.<br>**Baseline characteristics**<br>Sample size: CECT=144, PET-CT=83, combination of modalities=73<br>Baseline characteristics (age, length of diagnosis etc) not reported |
| **Costs included** | **Original currency & cost year:** 2019 Euros<br>**Cost components incorporated:** Hospital stays, outpatient visits, laboratory tests, imaging costs, treatment and palliative care |
| **Outcomes included** | **Primary health outcome(s) in economic analysis:** Life-years<br>**Key events modelled /analysed:** NA |
| **Data Sources** | **Effectiveness data:** Registry data of people treated at the Department of Nuclear Medicine and/or Radiology at Odense University Hospital (Denmark) between 1st January 2007 and 10th August 2019<br>**Baseline / epidemiological data:** NA<br>**Quality-of-life weights:** NA<br>**Costs and/or resource use:** Resource us taken from registry data. Costs assigned using Diagnosis Related Groups (DRG/DAGS) from the Danish reimbursement system |
| **Results: costs** | **Total costs (per patient):**<br>(1) CECT : £79,193±56,477<br>(2) PET-CT: £72,701±49,691<br>(3) Combined Modality: £143,601 130,193<br>Incremental (2-1): -£6,552<br>Incremental (3-1): £70,716<br>(95% CI: NR; p=<0.001) |
| **Results: health outcomes** | **Life- years (per patient):**<br>(1) CECT: 2.5 years<br>(2) PET-CT: 3.7 years<br>(3) Combined Modality: 4.5 years<br>Incremental (2-1): 1.2 years<br>Incremental (3-1): 2.0 years<br>(95% CI: NR; p=NR) |
| **Results: cost effectiveness** | **Incremental cost-effectiveness ratios:**<br>2 vs 1: Dominant (cost decreasing and survival increasing)<br>3 vs 2: £35,358 per life-year gained |
| **Results: Uncertainty** | Deterministic: PET-CT was cost-saving with increased survival when the analysis was restricted to the following sub-groups: |

| Section | Details for Naghavi-Behzad, 2023 |
|---|---|
| | • Patients not enrolled in clinical trials<br>• Diagnosed before 2009<br>• Oligometastatic disease<br>• ER+<br>• HER2 –<br>• De-novo metastatic breast cancer<br>• Performance status>2<br>• Performance status<2<br>ICERs for the following subgroups were:<br>Liver/lung metastases :£2,523 per life-year gained<br>ER+, HER-, non-oligometastatic: £1,589<br><br>Sensitivity analysis matching CT and PET-CT patients by performance status, age, years since diagnosis and number of involved organs:<br>All above groups PET-CT cost-saving and increase survival apart from:<br><br>Liver/lung metastases at baseline scan<br><br>ICER £6,732 per life year gained.<br><br>Sensitivity analyses not reported for combined modality<br><br>Probabilistic: NA |
| **Health inequalities assessment** | NR |
| **Comments** | **Source of funding:** Centre for Personalized Response Monitoring in Oncology (PREMIO) at Odense University Hospital (Denmark), the Dagmar Marshalls Fond (Denmark), and the University of Southern Denmark (Denmark)<br><br>Study is not randomised |
| **Rating: Applicability** | Partially applicable<br>Study takes a Danish healthcare system perspective. QALYs not reported.<br>3. |
| **Rating: Quality/ limitations** | Potentially serious limitations<br>Probabilistic sensitivity analyses not reported. Effectiveness data not from randomised sources, likely to be a high level of confounding |

Abbreviations: CECT: Contrast-enhanced computed tomography; ER+: Estrogen receptor-positive, HER-: human epidermal growth factor receptor 2 negative; ICER: Incremental cost-effectiveness ratio; NA: not applicable; NR: not reported; PET-CT: 2-deoxy-2-[18F]fluoro-D-glucose PET-CT positron emission tomography with integrated computed tomography; Vs: Versus

# Appendix I – Health economic model

## Economic analysis report for FDG PET-CT and contrast-enhanced CT for diagnosing and monitoring distant metastases

## 1. Introduction

People with suspected advanced breast cancer typically receive contrast enhanced computed tomography scan (CECT) to confirm diagnosis. Using CECT has been recognised as a standard procedure in the NHS over the last few decades. Currently, fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) is mostly being used in the diagnosis of de-novo breast cancer rather than monitoring although practice varies across the UK. The committee is interested whether wider use of FDG PET-CT, for both diagnosis and monitoring, would improve health outcomes and be an efficient use of NHS resources. The objective of this analysis was to examine whether using PET-CT compared to CECT is a cost-effective strategy in diagnosing and monitoring advanced breast cancer. This analysis considers FDG PET-CT as a replacement for CT in diagnosing and monitoring advanced breast cancer estimating incremental costs and quality-adjusted life years (QALYs) associated with changing approach.

## 2. Health economic modelling methods

### 2.1 Model overview

A de novo economic model was developed in Microsoft Excel to evaluate the cost-effectiveness of FDG PET-CT compared with CECT for people with suspected advanced breast cancer, from the perspective of the NHS and Personal Social Services (NHS+PSS) in England, in line with the NICE reference case for health interventions (see NICE's guidelines manual). Outcomes were measured in quality-adjusted life years (QALYs). Both costs and QALYs were discounted at an annual rate of 3.5%, as recommended by NICE's guidelines manual. The cost year of the analysis was 2024.

The model comprised two linked components addressing different decision questions:

- a decision-tree model capturing the short-term diagnostic phase (identification of advanced breast cancer and consequences of differing diagnostic test accuracy); and
- a Markov model capturing long-term monitoring, treatment, and survival outcomes for people with confirmed advanced breast cancer.

The lifetime time horizon allowed the model to capture all relevant downstream costs and QALY consequences of the initial diagnostic choice on subsequent disease monitoring and treatment. The method follows the standard assumptions outlined in the NICE reference case for interventions with health outcomes in an NHS setting.

## 2.2 Model population and setting

The population in the model is people with diagnosed breast cancer suspected of being advanced breast cancer receiving imaging for staging and subsequent monitoring in the UK NHS. The population is split into two cohorts for two clinically distinct populations:

- **Cohort 1:** Individuals with de-novo breast cancer suspected of being advanced breast cancer at time of first diagnosis.
- **Cohort 2:** Individuals with previously treated breast cancer which is suspected of having become advanced breast cancer.

This distinction was considered important because the diagnostic and subsequent treatment pathways differ between the two groups, which may influence both costs and outcomes. In particular:

- People with de novo disease would almost always undergo a confirmatory biopsy following a positive imaging result before initiating systemic therapy.
- For those with previously treated disease, a confirmatory biopsy may not always be clinically indicated, and treatment decisions may be based directly on imaging findings.

Consequently, the two cohorts may have different probabilities of receiving confirmatory biopsy, treatment initiation patterns, and subsequent management costs, which could affect the overall cost-effectiveness of FDG PET-CT compared with CECT. The NICE committee would therefore expect results to be presented separately for these subgroups to understand how diagnostic and therapeutic pathways impact the value of FDG PET-CT in each clinical context.

The age of the cohort was assumed to be 53 years, the average age reported in Seah 2014 used to inform survival estimates in the model. The study is discussed in detail below.

## 2.3 Model strategies

The economic analysis compared alternative imaging strategies for the diagnosis and monitoring of suspected metastatic breast cancer.

The following strategies were considered:

- CECT for diagnosis followed by monitoring with CECT
- FDG PET-CT for diagnosis followed by monitoring with FDG PET-CT
- CECT for diagnosis followed by monitoring with FDG PET-CT

These strategies reflect the pathways judged by the committee to be clinically plausible and relevant to current NHS practice. In clinical settings, the same imaging modality is typically used for both diagnosis and monitoring to enable consistent comparison of disease progression and treatment response. However, the committee also considered that a CT followed by FDG PET-CT sequence could represent a plausible escalation pathway in which a patient initially receives CECT but FDG PET-CT for subsequent monitoring when more detailed assessment is warranted.

The strategy of PET-CT for diagnosis followed by CECT for monitoring was not modelled, as the committee considered this switch to be clinically unrealistic. Once PET-CT has been used for baseline staging, subsequent monitoring with CECT would limit the ability to accurately assess treatment response due to differences in imaging resolution and quantification.

## 2.4 Model structure

The model is made up of two parts. A decision tree represents the initial diagnosis of advanced breast cancer, followed by a Markov model capturing the monitoring and treatment phases. This hybrid approach was selected because the short-term diagnostic decision (PET-CT vs CECT) determines entry into a disease and monitoring pathway that evolves over time. This is best represented by a Markov framework.

The model evaluated PET-CT compared with CECT for people with suspected advanced breast cancer undergoing imaging in the NHS (see Section 2.2 for population details). Both diagnostic strategies were modelled as one-off interventions at baseline; all subsequent management, monitoring and outcomes were simulated in the Markov component.

### Decision tree: diagnostic phase

In the diagnostic phase of the model, the cohort entered the decision tree, being imaged with either PET-CT or CECT.

The cohort represented people with clinical suspicion of advanced breast cancer, for example, based on new symptoms or abnormal findings on prior imaging. A proportion of this population was assumed to have true metastatic disease, while the remainder having their symptoms attributable to non-metastatic or unrelated conditions.

Each imaging modality (FDG PET-CT or CECT) could correctly or incorrectly classify disease status according to its diagnostic accuracy parameters (sensitivity and specificity). Consequently, patients could fall into one of four diagnostic outcomes: true positive, false positive, true negative, or false negative.

It was assumed that all imaging tests produced a definitive positive or negative result. Test failures and equivocal findings were not modelled, as no evidence was identified to inform their frequency and there was limited consensus among the committee on plausible values or differences between modalities.

For individuals with a positive imaging result, a proportion were assumed to undergo a confirmatory biopsy, which was modelled as having 100% accuracy and correcting any false positives to true negatives. The likelihood of receiving a biopsy varied between subgroups:

- people with de novo breast cancer were assumed to almost always undergo confirmatory biopsy,
- whereas in previously treated breast cancer, biopsy may not always be feasible or performed.

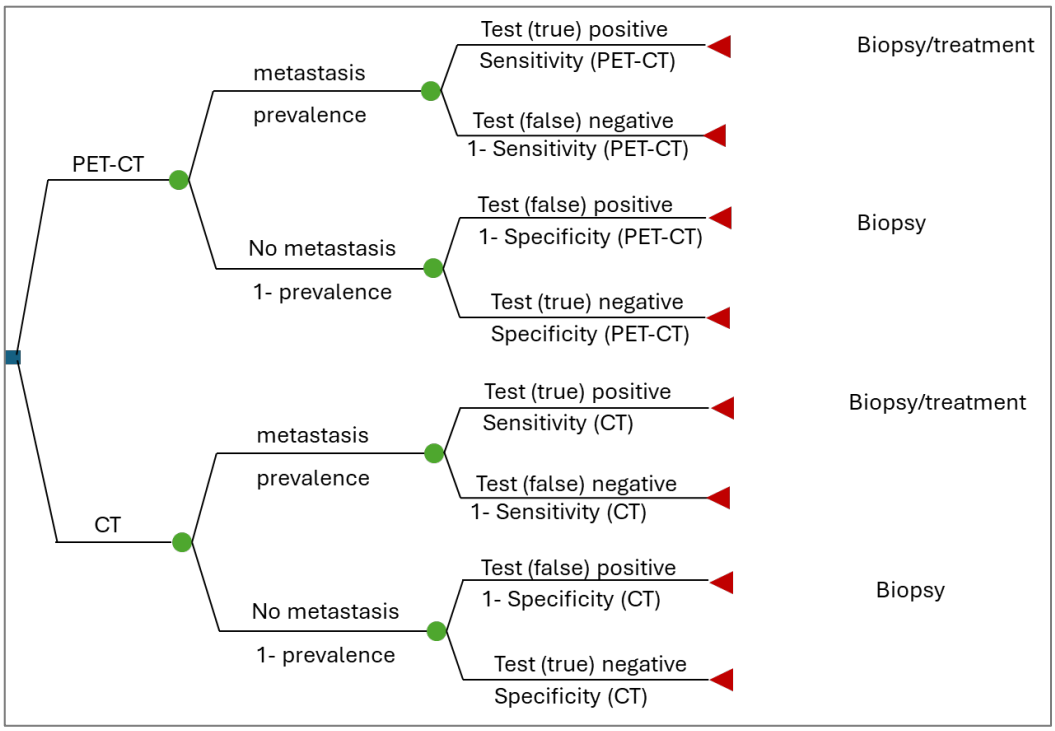
Each terminal node accrued the cost of imaging (and biopsy if applicable) and, where relevant, a transient disutility related to anxiety or inappropriate treatment. For false negative cases, it was assumed based on the committee consensus that persistent or worsening symptoms would lead to a repeat imaging assessment after one year, incurring an additional scan cost at that time point. All other diagnostic costs were assumed equal between imaging modalities and excluded.

Outputs from this stage determined the distribution of individuals entering the Markov model. These costs and utility detriments are made up of:

- **True positive:** Cost of scan plus cost of biopsy if applicable.
- **True negative:** Cost of scan.
- **False positive:** Cost of scan plus biopsy cost, where relevant. For false positives not corrected by biopsy, a temporary utility decrement related to anxiety was applied for one year, after which the diagnosis was assumed to be corrected. An additional scan cost (of the same modality) was applied at that time point to reflect re-imaging.
- **False Negative:** Cost of scan only. A repeat imaging assessment was assumed after one year, triggered by persistent or worsening symptoms, with the associated additional scan cost applied at that time point. No further treatment-related costs or QALY effects were modelled in this phase, as these were captured within the subsequent Markov model.

Other costs associated with diagnosis, for example cancer multi-disciplinary team meetings, additional tests to imaging etc were assumed to be equal between both modalities of imaging and were not included in the economic analysis. The decision tree schematic is shown in Figure 24.

**Figure 24: Decision tree schematic of diagnosis of metastatic disease**




**Markov model: treatment monitoring phase**

Only individuals with a true positive diagnosis entered the Markov model, which represented the monitoring and treatment phase of the disease pathway. The model comprised 5 living health states and one absorbing (dead) state, as follows:

- **Initial treatment – correct:** This state is for people receiving their first line of treatment. People remain in this state until their disease progresses/doesn't respond and that this is picked up on the imaging used during monitoring.
- **Initial treatment – incorrect:** This state is for people who have had disease progression or a lack of response which is not captured by the imaging scan used during monitoring.
- **Higher line treatment – correct:** This state is for who's metastatic disease has progressed or not responded to treatment, and this has been correctly identified during imaging.
- **Higher line treatment – incorrect:** This state is for individuals who's metastatic disease has responded to treatment but imaging modality used during monitoring has incorrectly identified that it has.
- **Best supportive care (BSC):** In this state people are no longer receiving active treatment for the tumour but will still receive treatments for pain, side-effects as well as psychological support.
- **Dead**: Absorbing state.

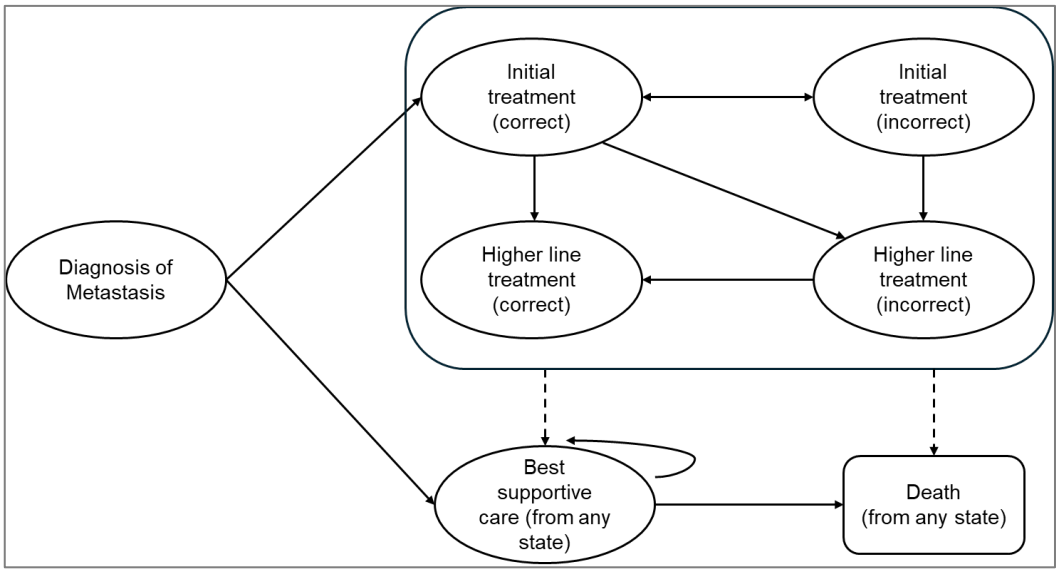
Each 3-month cycle reflected typical NHS follow-up and imaging intervals for metastatic breast cancer. Patients could move from any active-treatment state to BSC or death, depending on disease progression or mortality.

People may also discontinue treatment due to toxicity or other adverse events. These are not influenced by imaging modality, would be equal between modalities and have therefore been excluded from the model.

It was acknowledged that there were many more lines of treatment for people with metastatic disease. As the list of treatment options were almost identical between all the further lines and that no differential evidence on costs or utilities was identified for further lines this was compressed into the two higher-line Markov states so as not to overcomplicate the model.

At model start, individuals entered either the initial treatment state (where the tumours are actively treated) or the BSC state (if the diagnostic scan suggested that active treatment was not clinically appropriate or the individual decided against such treatment), depending on the diagnostic outcome from the decision tree. All other possible transitions are shown by arrows in Figure 25.

**Figure 25: Markov model schematic of monitoring metastatic disease**




The overall structure reflects the clinical pathway in the NHS, where imaging first establishes advanced breast cancer and is then used periodically to assess treatment response and progression. The linked decision-tree and Markov framework therefore captures both the short-term diagnostic consequences and the long-term clinical and economic implications of each imaging strategy.

### 2.4.1 Diagnostic accuracy

Diagnostic test accuracy estimates were taken from the accompanying systematic review and pairwise meta-analysis. The systematic review reported sensitivity and specificity for FDG PET-CT and CECT in people with invasive adenocarcinoma of the breast who have

suspected distant metastases (advanced breast cancer). This is the population considered in the model.

The systematic review reported diagnostic accuracy for assessing any metastases as well as distant metastases, bone metastases and visceral metastases. As the model did not split the population by suspected site of metastasis the values for any metastases was used to inform the model. The review is discussed in detail in the accompanying systematic review. Briefly 26 studies involving 4923 observations and 2513 individuals were identified for FDG PET-CT and 5 studies of 532 participants were identified for CECT. Estimated sensitivity and specificity values are reported in Table 35.

**Table 35 Diagnostic accuracy of PET-CT and CECT**

| | Effect estimate | Lower 95% CI | Higher 95% CI |
|---|---|---|---|
| **PET-CT** | | | |
| Sensitivity | 0.95 | 0.93 | 0.97 |
| Specificity | 0.98 | 0.97 | 0.99 |
| **CECT** | | | |
| Sensitivity | 0.8 | 0.65 | 0.89 |
| Specificity | 0.96 | 0.89 | 0.98 |

PET-CT has higher sensitivity than CECT identifying an additional 15 people for every 100 people with advanced breast cancer decreasing the total number of false negatives. PET-CT also has higher specificity compared to CECT reducing the number of false positives.

No diagnostic test accuracy data was identified for monitoring. In the absence of evidence, it was assumed that the sensitivity and specificity of PET-CT and CECT in monitoring of treatment response and disease progression was identical to that of diagnosis. Whilst both monitoring and diagnosis are trying to achieve slightly different aims (identification of disease versus changes in disease) it was considered similar enough that the diagnostic evidence could be confidently used in the absence of alternatives.

### 2.4.2 Baseline event rates

#### Prevalence of metastatic disease

Prevalence of metastatic breast cancer was derived from the studies included in the accompanying systematic review to inform the diagnostic test accuracy for ‘any metastases’ the value used to inform the diagnostic test accuracy in the model. Prevalence was estimated by calculating the total number of true positives and false negatives (those with metastatic disease) and dividing it by the total population reported above. This gave a prevalence estimate of 30.7%, which was used in the base-case analysis.

As this is a selected population of people with suspected metastatic disease, the prevalence is determined by the criteria used to define ‘suspected’. Studies that applied broader inclusion criteria were likely to report lower prevalence values, whereas studies using stricter definitions were likely to report higher prevalence. Prevalence in the included studies ranged

from 8.4% to 80.8%. Any estimates around prevalence would therefore be uncertain. Prevalence of advanced breast cancer by study is shown in Table 36.

**Table 36: Prevalence of advanced breast cancer by study**

| Study | Total number of people imaged | Prevalence |
|---|---|---|
| **Abo-Sheisha 2014** | 50 | 70% |
| **Aukema 2010** | 56 | 43% |
| **Carkaci 2009** | 41 | 46% |
| **Choi 2012** | 154 | 8% |
| **Dirisamar 2010** | 52 | 81% |
| **Dirisamar 2010** | 52 | 81% |
| **Gajjala 2018** | 61 | 33% |
| **Garg 2016** | 79 | 43% |
| **Goktas 2018** | 77 | 74% |
| **Ko 2020** | 195 | 14% |
| **Koolen 2011** | 154 | 13% |
| **Krammer 2015** | 101 | 16% |
| **Manohar 2013** | 43 | 23% |
| **Nikkura 2011** | 225 | 35% |
| **Riegger 2012** | 106 | 14% |
| **Vogsen 2021b** | 103 | 23% |

### Initial transition to best supportive care following positive diagnosis

The proportion of people moving straight to best supportive care (BSC) following a confirmed positive diagnosis of advanced breast cancer was informed by Smith 2025. This was a UK observational study of 4823 referrals from general practitioners to a pathway for people with non-specific symptoms between March 2017 and March 2023. Among these referrals, 8.2% of cancers identified were breast cancers, with just over half being stage III or IV disease. Across all cancers, 15.4% of patients received best supportive care as their initial treatment, and this estimate was used to inform the proportion of individuals entering the BSC state immediately after diagnosis in the economic model. No evidence was identified that was specific to breast cancer and thus this evidence from a general cancer population was used instead.

### Transition probabilities from treatment stages and to best supportive care

Transition probabilities between states were derived from Seah 2014. This study reported the average time spent on each line of treatment among people with advanced breast cancer. To estimate the probability of progression from first-line to higher-line treatment, the reported average duration on first-line therapy was converted into a 3-month transition probability, assuming a constant hazard of progression within each time 3-month cycle of the model. Whether an individual moved to the higher-line correct state or remained on initial treatment incorrect was based on the diagnostic accuracy of the monitoring modality.

Seah 2014 reported number of treatment lines and duration on each line for up to 5 lines of treatment. The model assumed that people would move to BSC after the fifth line of treatment had ended. To calculate the probability of progression to BSC the total time from initial treatment to the end of fifth-line treatment was converted into a 3-month probability again assuming that people had a constant hazard of progressing. We applied this probability equally to all Markov states other than death and BSC. Because Seah 2014 presented results by cancer subtype (HER2-positive, hormone-receptor-positive, and triple-negative), a weighted average across subtypes was calculated using the same proportional weights applied in the survival modelling. Calculations of 3-month transition probabilities are presented in Table 37.

**Table 37: Estimation of transition probabilities in the economic model**

| Subtype | Median duration of first-line treatment (months) | Median duration 5 lines of treatment (Months) | Probability progress off first-line treatment | Probability progress to BSC |
|---|---|---|---|---|
| HER2+ | 10.3 | 28.3 | 0.18 | 0.07 |
| HR+ | 6.8 | 19.9 | 0.26 | 0.10 |
| TNBC | 5.1 | 16.1 | 0.33 | 0.12 |
| Mean probability of progression (3-months) | | | 0.25 | 0.09 |

### 2.4.3 Mortality

The protocol for the accompanying systematic review of the clinical evidence listed overall survival as an outcome of interest. However, no evidence was found to inform differences in survival between imaging modalities (FDG PET-CT vs CECT) for people with advanced breast cancer.

The only evidence identified for survival by type of modality was Naghavi-Behzad 2022. This study informed survival in one previous economic evaluation of monitoring (Naghavi-Behzad 2023). This study estimated an increase in survival from using FDG PET-CT over CECT in the monitoring of advanced breast cancer of just over 1 year. However, the committee considered this effect size implausible based on clinical experience and judged the evidence to be at high risk of confounding. Because the study was observational and likely reflected differences in patient characteristics (for example, disease severity and treatment selection) by imaging modality rather than true causal effects.

Given the limited evidence around overall survival by modality of imaging and based on the committee's clinical opinion and consensus, the base-case made the assumption that overall survival was identical between the different diagnostic and monitoring strategies. Accordingly, differences in QALYs between FDG PET-CT and CECT were assumed to arise from more optimal treatment allocation and earlier correction of misclassification due to greater diagnostic accuracy, rather than a direct survival effect of the imaging modality.

An pragmatic targeted literature search of the data was undertaken to identify survival data for people with advanced breast cancer. Contemporaneous evidence was sought on survival,

given the rapid advances in treatment for advanced breast cancer over recent years. Although several recent studies were identified, most had limited follow-up, and would not capture long-term survival necessary for the model's lifetime horizon.

Therefore, survival estimates were derived from Seah 2014, which reported Kaplan–Meier curves for overall survival in 318 patients with metastatic breast cancer treated at a US medical centre between January 2014 and December 2017.

The study presented overall survival separately by three molecular sub-types (HER2+, HR+ and TNBC) for up to 100 months. The estimates by subtype were combined into a single Kaplan-Meier survival curve by weighting the overall estimates of survival at each time point by the proportion of patients in each subgroup as reported by the study and shown in Table 38.

**Table 38 Proportion of patients by cancer subtype**

| Subtype | Number | Proportion |
|---|---|---|
| **HER2+** | 96 | 47.1% |
| **HR+** | 49 | 24.0% |
| **TNBC** | 59 | 29.0% |

Given the assumption that overall survival was identical in all arms of the model the survival reported in the combined Kaplan-Meier curve was assumed to apply to all states in the model. Overall survival as estimated by the model is therefore identical to the input from this survival data. Thus, overall survival in the model reflects that observed in Seah 2014, with differences in modelled outcomes arising from downstream treatment and quality-of-life effects rather than differential mortality.

### 2.4.4 Utility data

#### Health related quality of life for decision tree (diagnosis)

Detriments to health-related quality of life (HRQoL) were only applied to people receiving either a false positive, false negative or a false positive which is corrected to a true negative by a negative biopsy are included in the diagnostic portion of the model. It was assumed that these 3 groups, who do not have advanced breast cancer would have identical HRQoL in future years other than any detriment associated with the diagnostic process. Therefore, there would be no impact on the incremental QALY beyond this stage. Trying to capture these QALYs would unnecessarily complicate the model.

#### Health related quality of life for Markov states (monitoring)

To express outcomes in the form of QALYs, the health states of the economic model (Initial treatment correct, initial treatment incorrect, higher line treatment correct, higher line treatment incorrect and BSC) must be linked to relevant utility values, which represent the health-related quality of life (HRQoL) associated with specific health states on a scale from 0 (representing death) to 1 (representing perfect health). Utility values are typically estimated using preference-based measures that capture individuals' valuations for the HRQoL experienced in the health states under consideration. QALYs are estimated by multiplying

the time spent in a specific health state by the health state utility value representing the HRQoL in that state. These disutilities reflected short-term anxiety, psychological distress, and the burden of diagnostic procedures. People with a true positive result entered the Markov model, where longer-term quality-of-life effects were captured through disease-specific utilities. As individuals without metastatic disease were assumed to have identical long-term quality of life following the diagnostic phase, no incremental QALY differences were modelled beyond this stage.

A review of NICE technology appraisals for interventions in advanced breast cancer and relevant to the Markov states for initial and higher line treatment was undertaken to identify suitable HRQoL estimates. This was considered an appropriate way to capture the HRQoL for those treatments as they were often measured using EQ-5D, are recently published and are relevant to a UK population. The technology appraisals however often redacted the utility values reported, had wide differences in the reported HRQoL between studies and rarely reported values for people receiving BSC. The RCTs underpinning the technology appraisals also had differing inclusion and exclusion criteria for participants. Using this approach to estimate utility values for the Markov states would have led to inconsistencies with values both for the treatments within the state and for comparability across states.

As a result, a pragmatic, non-systematic literature search was undertaken to identify studies which estimated utility values for all states included in the Markov model. We prioritised studies which used the EQ-5D scored with the UK population tariff and had estimates for large numbers of health states which matched or were sufficiently similar to those in the Markov model. Recent studies were prioritised over older ones given the large number of additional treatments that have become available in recent years.

The search identified one study, Claessens 2020, which estimated utility values by line of treatment, similar to the construction of the Markov model. The paper used the EQ-5D-3L with Dutch population tariffs to elicit HRQoL utilities in 92 patients with advanced breast cancer at one outpatient clinic in the Netherlands between October 2010 and May 2011. Patient and disease characteristics were taken from hospital records.

No studies were identified which reported utility values by line of treatment in a UK population scored using the UK population tariffs.

Utility values by line of treatment are reported in Table 39. The utility values for the initial treatment correct and initial treatment incorrect states were given the value for 1 line of treatment (0.586). The value for the higher line correct and higher line incorrect states were the mean of the values for 2,3 and ≥ 4 weighted by number of people.

No values were identified for BSC. The value for this state of the Markov model was taken from ≥ 4 lines cohort. It was hypothesised that a large proportion of people receiving BSC would have had multiple lines of treatment and this cohort would be the most representative of those reported.

The higher line treatment states report a higher HRQoL utility compared to the initial treatment states up to 4 lines or greater. The committee considered that earlier lines of treatment are more aggressive and toxicity and adverse events may be greater. Tolerability may also increase as treatment is received for a longer period of time.

The dead state was given a utility value equal to zero.

**Table 39 Utility values reported in Claessens 2020 by line of treatment**

| Number of lines of treatment | Number of people | Mean utility value | SD |
|---|---|---|---|
| **1** | 37 | 0.586 | 0.371 |
| **2** | 20 | 0.636 | 0.270 |
| **3** | 11 | 0.721 | 0.131 |
| **≥ 4** | 24 | 0.544 | 0.303 |
| **Mean 2,3 and ≥ 4** | 55 | 0.613 | |

**Detriment to utility from misdiagnosis**

The committee highlighted that beyond the utility detriments from being incorrectly diagnosed (either false positive or false negative) and receiving to suboptimal treatment that there would also be an impact on mood and anxiety that could significantly reduce the HRQoL of the individual. Capturing this impact on mood and anxiety would be difficult if not impossible to do in a contemporaneous cohort. By definition, a patient with a misdiagnosis would be unaware this is the case and therefore would be difficult to elicit health states around this.

The informal search of the quality-of-life evidence found no papers that reported such a value.

To estimate a QALY detriment for either a false positive or false negative associated with mood and anxiety we used the UK population tariffs from the EQ-5D and assumed that a responder would downgrade their response by 1 or 2 as a result of the misdiagnosis. Table 40 shows the reduction in utility from changing the response to this domain from “I am not anxious or depressed” to “I am moderately anxious or depressed”. In the base-case the larger detriment (-0.236) was applied based on committee consensus. to the utility scores. Deterministic sensitivity analysis assessed the impact of using the lower detriment (-0.071) and the difference between the two lowest responses (-0.165).

The utility decrement was applied for the duration of the misdiagnosis, which is until the diagnosis was corrected. For diagnostic-phase misdiagnoses, this was assumed to be one year for both false negatives and false positives not corrected by biopsy. For false positives followed by confirmatory biopsy, the duration was assumed to be 14 days, reflecting the estimated time required to receive biopsy results.

**Table 40 Change in utility as a result of change in response to EQ-5D anxiety/depression domain**

| EQ-5D domain for anxiety/depression | Reduction in utility value |
|---|---|
| **I am not anxious or depressed** | - |
| **I am moderately anxious or depressed** | -0.071 |
| **I am extremely anxious or depressed** | -0.236 |

### 2.4.5 Resource use and costs

**Intervention costs**

Imaging costs were obtained from the NHS cost collection 2023/24. It was assumed that imaging costs were identical for diagnostic and monitoring phases, as both would involve outpatient-based scans of two or more body regions. The costs used in the model are presented in Table 41.

**Table 41: National unit costs of imaging modalities in the model**

| Currency Code | Description | National average unit cost | Number of examinations |
|---|---|---|---|
| **RN02A** | Positron Emission Tomography with Computed Tomography (PET-CT) of Two or Three Areas, 19 years and over | £561.37 | 1,579 |
| **RN03A** | Positron Emission Tomography with Computed Tomography (PET-CT) of more than Three Areas, 19 years and over | £170.39 | 1,274 |
| **RD26Z** | Computerised Tomography Scan of Three Areas, with Contrast | £114.07 | 518,658 |

A weighted mean of the two FDG PET-CT cost categories (RN02A and RN03A) was used to represent the base-case FDG PET-CT unit cost (£386). The committee noted that the PET-CT cost estimate carried considerable uncertainty, so sensitivity analyses were undertaken using both the lower and higher PET-CT cost scenarios to test robustness.

The committee noted that the unit cost of FDG PET-CT identified from the 2023/24 NHS Cost Collection (£386 on average) was substantially lower than estimates reported in earlier studies and appraisals from around a decade ago.

This reduction is consistent with the maturing adoption of FDG PET-CT technology within the NHS.

When FDG PET-CT was first introduced, scanners were procured and operated by a limited number of NHS Trusts under capital-intensive contracts, with relatively low utilisation rates and restricted clinical indications. At that time, the high fixed costs of equipment and maintenance were spread across a small number of scans, resulting in high per-scan costs. In contrast, FDG PET-CT is now routinely used across multiple specialties, including oncology, cardiology, and neurology, enabling greater throughput and economies of scale in both staffing and equipment use. National commissioning arrangements and the entry of additional commercial suppliers have also increased competition and driven efficiency in service delivery, further reducing average unit costs. The lower reference cost used in this analysis therefore reflects the current, steady-state level of service provision, rather than the high marginal cost of early implementation observed in earlier economic evaluations.

Biopsy costs were also taken from NHS Cost Collection 2023/24 and are shown in Table 42. Costs for the 4 Markov states initial treatment correct, initial treatment incorrect, higher line correct and higher line incorrect were taken from Butnari 2025. This was a costing of cancer pathways from a UK NHS perspective, from 4596 across 9 cancer groups in the UK between April 2020 and September 2024. Although it reported for a range of cancers it disaggregated costs by cancer and stage including for breast cancer. 1075 people with breast cancer were identified in the dataset with 46 having advanced breast cancer (stage 4).

As disease is metastatic it could be present in any part of the body. Breast specific biopsy tariffs were therefore not appropriate. We therefore took a weighted average of a range of biopsies and used a weighted average as the base-case. All biopsies were assumed to be performed on an outpatient basis.

**Table 42: National unit costs of biopsy**

| Currency Code | Description | National average unit cost | Number of examinations |
|---|---|---|---|
| **YF05Z** | Percutaneous Biopsy of Abdominal Cavity | £371.58 | 4,998 |
| **YH31A** | Percutaneous Biopsy of Lesion of Bone, 19 years and over | £330.20 | 1,427 |
| **YH32A** | Percutaneous Biopsy of, Lesion of Muscle or Connective Tissue, 19 years and over | £425.02 | 125 |
| **YJ03Z** | Biopsy of Lesion of Breast and Associated Lymph Nodes | £801.19 | 1,063 |
| **YJ04Z** | Core Needle Biopsy of Axillary Lymph Nodes | £485.10 | 1,917 |
| **YJ09Z** | Vacuum Assisted Biopsy or Excision of Lesion of Breast | £608.92 | 2,228 |
| **YJ13Z** | Ultrasound Guided Core Needle Biopsy of Lesion of Breast | £557.77 | 56,306 |
| **YJ14Z** | Stereotactic Core Needle Biopsy of Lesion of Breast | £336.35 | 2,938 |
| **YL20A** | Percutaneous Needle Biopsy of Lesion of Kidney, 19 years and over | £298.42 | 260 |

**Costs of false diagnoses at diagnosis and the Markov model health states**

Costs for the 4 Markov states initial treatment correct, initial treatment incorrect, higher line correct and higher line incorrect were taken from Butnari 2025. This was a costing of cancer pathways from a UK NHS perspective, from 4596 across 9 cancer groups in the UK between April 2020 and September 2024. Although it reported for a range of cancers it disaggregated costs by cancer and stage including for breast cancer. 1075 people with breast cancer were identified in the dataset with 46 having advanced breast cancer (stage 4).

The study used the Somerset Cancer Registry, Hospital Episode Statistics (HES) and Patient Level-costing System (PLIC) to estimate the total cost of treatment pathways by stage of disease. Costs include personnel, pharmaceuticals, definitive treatment (chemotherapy, radiotherapy etc) and rehabilitation.

Table 43 shows the average cost per pathway estimated by Butnari 2025 and average length of time. These were adjusted to annual costs by dividing the average cost per pathway by the average length in days multiplied by 365.25. These were divided by 4 before being applied to the model to account for the 3-month cycle length used. The study also reported for stage 0 breast cancer. As it was unlikely that such people could be suspected of having advanced breast cancer these people were excluded from the costings.

**Table 43: Average cost per pathway and average length by stage of breast cancer**

| Stage | n | Average cost per pathway | length (days) | Yearly Cost |
|---|---|---|---|---|
| 1 | 423 | £11,405 | 196 | £ 21,253 |
| 2 | 265 | £20,642 | 196 | £ 38,468 |
| 3 | 167 | £23,792 | 278 | £ 31,259 |
| 4 | 46 | £35,143 | 278 | £ 46,173 |

A cost of a false negative diagnosis was estimated as the cost of stage 4 disease plus the difference in cost between the stage 4 disease and a weighted average of the other disease stages. False negatives were assumed to be identified after 1 year so the full yearly pathway cost was assumed.

A cost of a false positive diagnosis was assumed to be the cost of stage 4 disease plus the difference in cost between stage 1 and stage 2 disease. It was assumed that the difference in cost between stage 1 and stage 2 would capture the unnecessary treatments (such as surgery) that could result from incorrect diagnosis.

Yearly costs for the Markov states were calculated as follows:

- **Initial treatment correct:** This was assumed to be equal to the yearly cost for stage 4 cancer reported in Table 43.
- **Initial treatment incorrect:** This was equal to the stage 4 cost plus the estimated cost for a false negative.
- **Higher line treatment correct:** This was assumed to be equal to the yearly cost for stage 4 cancer reported in Table 43 . The cost is equal to the initial treatment costs but the treatments received are largely similar between the two groups.

- **Higher line incorrect:** This was equal to the stage 4 cost plus the additional cost for a false positive.

The costs for BSC were taken from Tappenden 2025. This was a Health Technology Assessment of tumour profiling tests to guide treatment decisions in early breast cancer. Although the population of interest was people with early breast cancer, as part of the lifetime horizon of the economic model, a cost for best supportive care was estimated.

No cost was applied to the dead state. All costs were reported at the most recent year for which inflation indices are available so no adjustment was made to the reported costs. The cost of each health state is reported in Table 44.

### Table 44: Costs of states included in the economic model

| State | Costs |
|---|---|
| False Positive | £17,630 |
| False negative | £17,215 |
| Initial treatment correct | £46,173 |
| Initial treatment incorrect | £63,388 |
| Higher line correct | £46,173 |
| Higher line incorrect | £63,803 |
| Best supportive care | £8,448 |
| Dead | £0 |

For the diagnostic portion of the model in the base-case no costs were assigned to false positives (not corrected by biopsy) and false negatives. This was likely to miss any costs from inappropriate treatment such as unnecessary surgery. A sensitivity analysis was therefore undertaken which applied these costs to these misdiagnoses. Any misdiagnosis was assumed to be corrected after 1 year.

## 2.5 Handling uncertainty

### Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was employed around the base-case model structure. Model input parameters were assigned probability distributions rather than expressed as point estimates (which is the approach adopted in a deterministic analysis). This allowed for a more comprehensive consideration of the uncertainty surrounding the input parameters and accounted for the non-linearity inherent in the economic model structure. As a result, more accurate estimates were produced than those generated by deterministic analysis, which relies solely on the mean value of each input parameter and disregards the associated uncertainty (Briggs 2006).

The type of distribution was determined with reference to the properties of data of that type. When possible, each distribution was parameterised using dispersion data from the source from which the value was obtained. When no such data were available, plausible ranges were applied based on committee advice and the usual properties of similar data.

## 2.6 Summary of model inputs

All parameters used in the model are summarised in Table 45, including details of the distributions and parameters used in probabilistic sensitivity analysis.

**Table 45.Model inputs (deterministic values and associated probability distributions)**

| Parameter | Point estimate | Probabilistic analysis | | Sources and notes |
|---|---|---|---|---|
| | | Distribution | Parameters | |
| **Prevalence of metastases** | 0.31 | Beta | α=476, β=1072 | |
| **Proportion each starting state following a positive diagnosis** | | | | |
| **BSC** | 0.15 | Dirichlet | | Smith 2025 |
| **Initial treatment (correct)** | 0.85 | Dirichlet | | |
| **CECT diagnostic accuracy** | | | | |
| **Sensitivity** | 0.80 | Beta | α=33, β=8 | clinical evidence review |
| **Specificity** | 0.96 | Beta | α=69, β=3 | clinical evidence review |
| **PET-CT diagnostic accuracy** | | | | |
| **Sensitivity** | 0.95 | Beta | α=432, β=23 | clinical evidence review |
| **Specificity** | 0.98 | Beta | α=737, β=15 | clinical evidence review |
| **Probability of progression** | | | | |
| **From any state to BSC** | 0.09 | Fixed | N/A | estimated from Seah 2014 |
| **No progression** | 0.75 | Fixed | N/A | estimated from Seah 2014 |
| **Costs** | | | | |
| **CECT Scan** | £114 | Fixed | N/A | NHS National Cost Collection |
| **FDG PET-CT Scan** | £387 | Gamma | α=4, β=99 | NHS National Cost Collection |
| **Biopsy** | £484 | Fixed | N/A | NHS National Cost Collection |
| **Initial treatment (correct)** | £46,173 | Fixed | N/A | estimated from Butnari 2025 |
| **Continued initial treatment (incorrect)** | £63,386 | Fixed | N/A | estimated from Butnari 2025 |
| **Advanced treatment (correct)** | £46,173 | Fixed | N/A | estimated from Butnari 2025 |

| | | | | |
|---|---|---|---|---|
| **Advanced treatment (incorrect)** | £63,802 | Fixed | N/A | estimated from Butnari 2025 |
| **BSC** | £15,000 | Fixed | N/A | |
| **Utility values** | | | | |
| **Disutility Biopsy** | 0.00 | Fixed | N/A | |
| **Disutility FP (Biopsy)** | -0.01 | Fixed | N/A | This value reflects the harm from a biopsy and short-term anxiety. |
| **Disutility FP (No biopsy)** | -0.24 | Fixed | N/A | This value reflects the harm from suboptimal treatment and anxiety from an incorrect positive diagnosis. |
| **Disutility FN** | -0.24 | Fixed | N/A | This value reflects the harm from incorrect treatment and anxiety from delayed diagnosis. |
| **Initial treatment (correct)** | 0.59 | Beta | α=7, β=5 | |
| **Continued initial treatment (incorrect)** | 0.35 | Beta | α=4, β=7 | |
| **Advanced treatment (correct)** | 0.61 | Beta | α=48, β=30 | |
| **Advanced treatment (incorrect)** | 0.38 | Beta | α=29, β=48 | |
| **Best supportive care** | 0.55 | Beta | α=16, β=13 | |
| **Death** | 0 | Fixed | | |

BSC, Best supportive care

## 2.7 Sensitivity analysis

Various sensitivity analyses were done to test the robustness of model assumptions. In these analyses, one or more inputs were changed at the same time, and the analysis was rerun to evaluate the impact on the results and whether the conclusions would change.

Scenario analyses were undertaken to explore the impact of alternative structural and behavioural assumptions on model results. Each scenario involved varying a single key parameter while holding all other inputs at their base-case values. The scenario analysis assessed the proportion of people receiving a confirmatory biopsy following a positive imaging result, reflecting clinical variation in biopsy practice among previously treated patients. A scenario analysis was also conducted to see how the prevalence of advanced breast cancer would change results. Scenario analyses were conducted deterministically, with incremental costs, QALYs, and ICERs reported relative to the base case.

### Cost effectiveness estimation and interpretation

To assess cost effectiveness, the incremental cost–effectiveness ratio (ICER) was estimated. The ICER represents the additional cost per additional unit of effectiveness (QALY) associated with one strategy relative to its comparators. The ICER was calculated by dividing the difference in total costs between 2 alternative strategies by the difference in their QALYs (see Table 46). If the ICER falls below a specified cost per QALY threshold, the assessed strategy is then considered cost effective relative to its comparator. A threshold of £20,000 per QALY has typically been used in analyses done for NICE guidelines (see NICE's guidelines manual).

### Table 46. ICER calculation

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where B is the assessed strategy and A is the comparator. Strategy B is cost effective if the ICER is less than the threshold.

Above a most plausible ICER of £20k per QALY gained, , decisions about the acceptability of the technology as an effective use of NHS resources specifically consider the following factors (see NICE's health technology evaluations manual):

- the degree of certainty and uncertainty around the ICER
- aspects that relate to uncaptured benefits and non-health factors
- aspects that relate to health inequalities.

A dominant strategy is one that results in higher QALYs and lower costs than its comparator. In such cases, the strategy is considered cost-effective without the need to calculate an ICER. Results are presented in two parts to reflect clinical practice. First, we report the diagnostic phase alone using ICER values (incremental costs and

QALYs per person tested) for FDG PET-CT versus CECT. Second, we report whole-pathway results (diagnosis + monitoring) using ICER values for each strategy compared with a CECT-only pathway. The whole-pathway strategies were: (1) CECT for diagnosis followed by monitoring with CECT, (2) FDG PET-CT for diagnosis followed by monitoring with FDG PET-CT, and (3) CECT for diagnosis followed by monitoring with FDG PET-CT. The probability of the best strategy being the most cost-effective option at a threshold of £20k per QALY is also provided, calculated as the proportion of iterations (out of the 1000 iterations run) in which the best strategy has had the highest net health benefit among all strategies considered in the analysis.

Finally, the cost–effectiveness acceptability curve (CEAC) is provided, which illustrates the probability that each imaging strategy is cost-effective at different willingness-to-pay thresholds. As the willingness-to-pay threshold increases, the CEAC indicates the proportion of simulations (from the probabilistic analysis) in which each strategy yields the highest net benefit.

### 2.4 Model validation

The economic model was developed by the guideline health economist in consultation with a health economics subgroup formed by members of the committee. The conceptual model, final model structure, and methods for identifying and selecting input parameters were presented to, and agreed by the committee, who also provided clinical validation. All inputs and model formulas were systematically checked. The model was tested for logical consistency by setting input parameters to null and extreme values to examine whether the results were plausible given the inputs and changed in the expected direction. The base-case results and results of sensitivity analysis were discussed with the committee to confirm their plausibility and support interpretation.

## 3. Results

### 3.1 Base-case deterministic analysis

The base-case results for both diagnostic and monitoring phases are presented in Table 47 and Table 48. Costs and outcomes are reported per tested person, with results expressed as mean total costs, QALYs and incremental cost-effectiveness ratios (ICERs).

**Table 47 Base-case deterministic results – diagnostic phase (de novo population)**

| Strategy | Absolute | | Incremental | | ICER |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| **CECT** | £ 257 | -0.015 | - | - | - |
| **FDG PET-CT** | £ 546 | -0.004 | £289 | 0.011 | £ 26,306 |

**Table 48 Base-case deterministic results – monitoring phase (diseased sub-cohort)**

| Strategy | Absolute | | Incremental | | ICER |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| **CECT** | £ 75,488 | 1.29 | - | - | - |
| **FDG PET-CT** | £ 75,657 | 1.44 | £168 | 0.148 | £1,139 |

Note: Convert per tested person

In the diagnostic phase, FDG PET-CT incurred higher costs (£546 vs £257 for CECT), reflecting its greater unit cost, but resulted in improved diagnostic accuracy and reduced QALY losses due to fewer misdiagnoses. The incremental gain of 0.011 QALYs per tested person produced an ICER of £26,306 per QALY gained.

In the monitoring phase, FDG PET-CT generated marginally higher costs (£52 more per tested person) and yielded 0.148 additional QALYs, resulting in an ICER of £1,139 per QALY gained.

**Combined diagnostic-to-monitoring strategies**

The two model components were combined to capture the complete diagnostic, monitoring and treatment pathway for individuals with advanced breast cancer. As only those diagnosed with metastases cohort were modelled in the Markov component results were adjusted to capture a cost per modelled person. The combined model, therefore, evaluated three linked imaging strategies as stated in session 2.3.

The base-case results for these combined strategies are presented in Table 49. Total per-person costs ranged from £23,659 for CECT–CECT to £24,001 for PET-CT–FDG PET-CT, with corresponding total QALYs of 0.38 to 0.44, respectively.

### Table 49 Base-case deterministic results for combined diagnostics-to-monitoring strategies

| Strategy | Absolute | | Incremental | | ICER |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| **CECT + CECT** | £23,454 | 0.38 | | | |
| **CECT + FDG PET-CT** | £23,506 | 0.43 | £ 52 | 0.05 | £1,139 |
| **FDG PET-CT+ FDG PET-CT** | £23,795 | 0.44 | £ 341 | 0.06 | £ 6,049 |

Relative to CECT+CECT, CECT+FDG PET-CT produced an incremental gain of 0.05 QALYs at an additional cost of £52 (ICER: £1,139 per QALY gained), while FDG PET-CT+FDG PET-CT achieved a QALY gain (0.06 QALYs) at an incremental cost of £341 (ICER: £6,049 per QALY gained)

This analysis captures the entire diagnosis-to-monitoring pathway, ensuring that both the short-term effects of diagnostic accuracy and the long-term consequences of monitoring precision are reflected.

Overall, FDG PET-CT–based strategies were associated with slightly higher total costs but improved health outcomes compared with CECT+CECT across the full diagnostic-to-monitoring pathway.

When the two model components were combined, both FDG PET-CT–based strategies generated greater health gains than CECT alone. This resulted in favourable ICERs well below the NICE threshold of £20k per QALY, indicating that FDG PET-CT could be a cost-effective option for diagnosing and monitoring advanced breast cancer under base-case assumptions.

#### Previously treated breast cancer cohort

The results for the diagnostic phase and the combined diagnostic–monitoring strategies in the previously treated breast cancer cohort are summarised Table 50 and Table 51.

In the diagnostic phase, FDG PET-CT remained more costly than CECT (£473 vs £190) but provided a small QALY gain of 0.013, resulting in an ICER of £22,198 per QALY gained (Table 50).

### Table 50 Subgroup analysis results for the previously diagnosed patients – diagnostic phase

| Strategy | Absolute | | Incremental | | ICER |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| **CECT** | £190 | -0.018 | | | |
| **FDG PET-CT** | £472 | -0.005 | £282 | 0.013 | £22,347 |

For the combined diagnosis-to-monitoring analysis, total per-person costs ranged from £23,388 for CECT–CECT to £23,721 for FDG PET-CT–FDG PET-CT, with corresponding QALYs of 0.38 to 0.44, respectively (Table 51). Relative to CT+CT,

CT+PET-CT produced an incremental gain of 0.05 QALYs at an additional cost of £52 (ICER: £1,140 per QALY gained), while FDG PET-CT–FDG PET-CT achieved a similar gain (0.06 QALYs) at an incremental cost of £333 (ICER: £5,753 per QALY gained).

**Table 51 Combined diagnostic-to-monitoring results – previously treated breast cancer cohort**

| Strategy | Absolute | | Incremental | | ICER |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| **CECT + CECT** | £ 23,338 | 0.38 | | | |
| **CECT + FDG PET-CT** | £ 23,439 | 0.43 | £ 52 | 0.05 | £1,140 |
| **FDG PET-CT+ FDG PET-CT** | £ 23,721 | 0.44 | £ 333 | 0.06 | £5,748 |

Overall, PET-CT–based strategies were more costly but consistently more effective than CECT+CECT. All resulting ICERs were below the threshold of £20k per QALY, the value at which NICE usually recommends interventions, indicating that PET-CT could be cost-effective in this cohort, particularly when both diagnostic and monitoring effects are considered together.

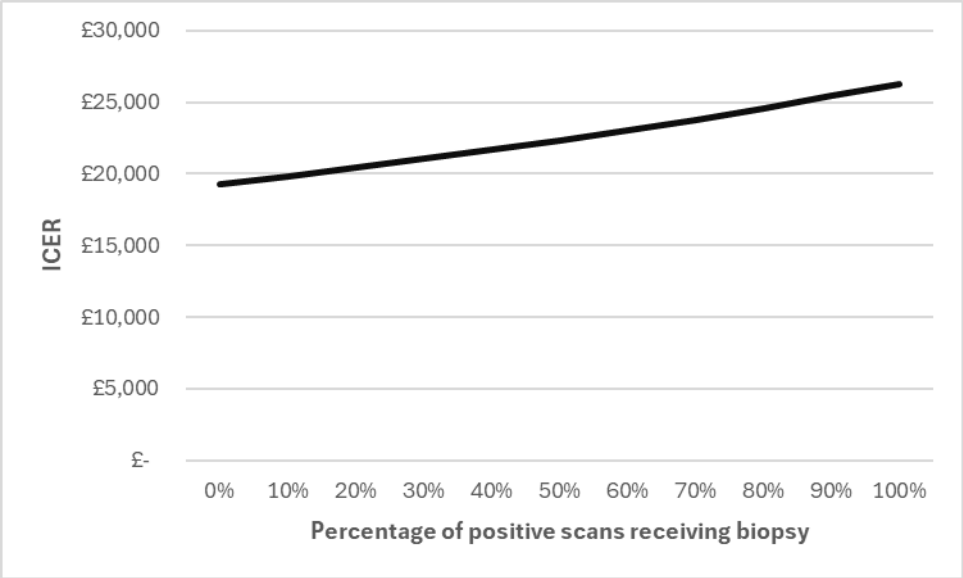
## 3.2 Deterministic sensitivity analyses

### Changes in percentage of positive scans receiving biopsy for the previously diagnosed cohort

Figure 26 shows the relationship between percentage of people receiving a confirmatory biopsy following a positive scan result and the ICER for the previously treated cohort in the diagnostic phase modelling.

As the proportion of confirmatory biopsies increases after imaging, the ICER also increases, reflecting that the cost and QALY gains from confirmatory biopsies do not outweigh the savings and health improvements from correcting false positives in the diagnostic portion of the model. Biopsies do deliver savings and QALY gains when they overturn false-positive imaging results (by avoiding inappropriate metastatic treatments and their harms). However, beyond that group, most extra biopsies fall on people already correctly classified, adding procedure costs (and small disutility) without meaningful additional benefit. In the analysis, biopsy rates below 13% led to an ICER below £20k per additional QALY.

**Figure 26 Relationship between ICER and percentage of people receiving biopsy after a positive scan for previously treated cohort**




**Changes in prevalence of advance breast cancer.**

Results of changing the prevalence of advanced breast cancer between the ranges reported in the included diagnostic accuracy studies and the prevalence needed for FDG PET-CT to be the most cost-effective option are reported in Table 52. FDG PET-CT becomes more cost-effective as prevalence increases, reflecting its greater diagnostic test accuracy in picking up advanced breast cancer. FDG PET-CT becomes cost-effective for previously diagnosed people at a prevalence of 34% slightly above the base-case estimate. For people with a de-novo diagnosis, FDG PET-CT becomes cost-effective at 42% within the range of prevalences reported in the diagnostic test accuracy studies.

**Table 52: ICER for FDG PET-CT vs CECT in diagnosis portion of model for different assumptions around prevalence.**

| | ICER for prevalence=8.4% | ICER for prevalence=80.3% | Prevalence above which ICER is below £20k per QALY |
|---|---|---|---|
| **De novo diagnosis** | £86,821 | £11,488 | 42% |
| **Previously diagnosed** | £52,131 | £10,332 | 36% |

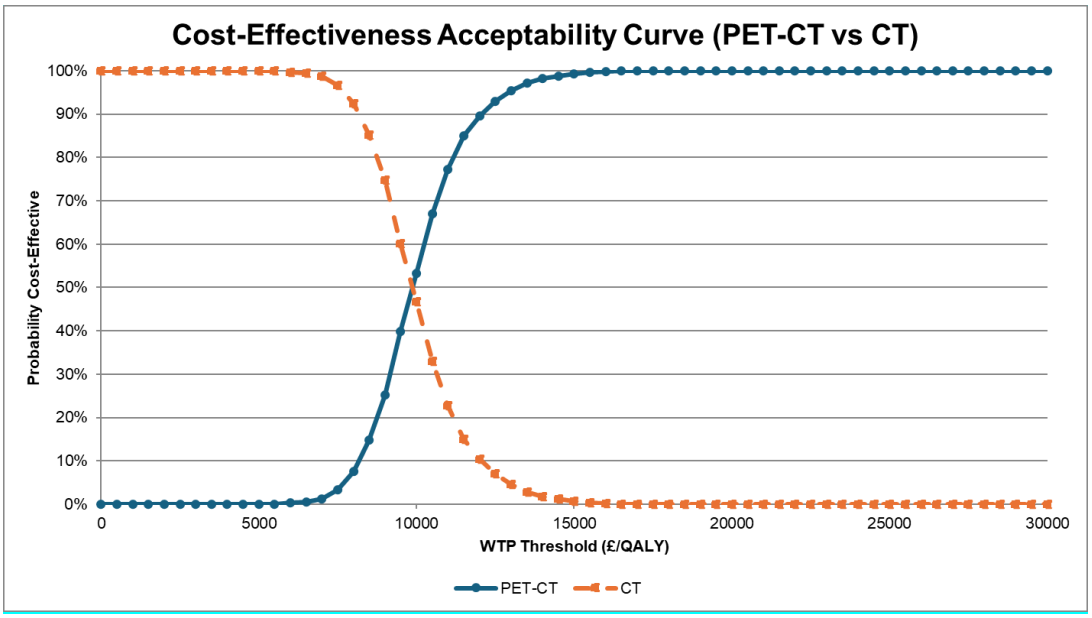
### 3.3 Probabilistic Sensitivity analysis

A probabilistic sensitivity analysis was conducted to test the robustness of the model results to parameter uncertainty and key structural assumptions.

Probabilistic sensitivity analysis (PSA) results are summarised in the cost-effectiveness acceptability curve (CEAC) (Figure 27)

At a willingness-to-pay (WTP) threshold of less than £6,000 per QALY, CECT is the cost-effective option. The probability that FDG PET-CT is cost-effective rises steeply thereafter, surpassing CT at approximately £9,000–£10,000 per QALY and reaching nearly 100% probability at thresholds above £15,000 per QALY. This indicates a high level of certainty that FDG PET-CT is cost-effective within the NICE reference threshold of £20k per QALY.

**Figure 27 Cost–effectiveness acceptability curve for PET-CT and CECT**




Overall, the results were robust to parameter uncertainty and insensitive to alternative structural assumptions. Although no evidence was identified to inform differences in treatment pathways and health outcomes between imaging modalities. This uncertainty will not be fully captured by the PSA.

While FDG PET-CT incurs higher upfront costs, its downstream benefits through improved diagnostic and monitoring accuracy translate into better health outcomes at an acceptable incremental cost, supporting the conclusion that FDG PET-CT could be a cost-effective imaging strategy for people with suspected metastatic breast cancer.

# 4. Discussion

## 4.1 Principal findings

The principal finding of this analysis is that FDG PET-CT represents a cost-effective imaging strategy compared with CECT for the diagnosis and monitoring of suspected metastatic breast cancer in the NHS setting under the base-case assumptions.

PET-CT was above the £20k per additional QALY when only diagnosis was considered although this model was only over a limited time-horizon. This result was sensitive to assumptions around prevalence with it being PET-CT being cost effective for values within the range identified by the clinical evidence review. When combined into a full diagnosis-to-treatment pathway, PET-CT–based strategies produced incremental cost-effectiveness ratios (ICERs) below the NICE threshold of £20k per QALY gained, indicating strong evidence of cost-effectiveness.

The diagnostic-only analysis showed a higher ICER (above £20k per additional QALY) because the benefits of improved diagnostic accuracy were limited to short-term quality-of-life effects. This result was only over a short-time horizon and did not capture all costs and benefits from the different imaging modalities. The decision and cost-effectiveness of the modality for monitoring (which the majority of individuals with a positive diagnosis would receive) is not exclusive of modality used at diagnosis. The cost effectiveness results from the diagnosis only part of the model should be interpreted with caution.

In the monitoring phase, PET-CT substantially improved the detection of disease progression and response to treatment, leading to greater QALY gains a small additional cost. This downstream benefit of more accurate monitoring offset the higher upfront diagnostic cost, resulting in overall ICERs below £20k per QALY gained across combined strategies (CT+FDG PET-CT and FDG PET-CT+FDG PET-CT).

Sensitivity analyses demonstrated that the model results were robust to variation in key parameters. Probabilistic sensitivity analysis confirmed the robustness of these findings, with FDG PET-CT being the most cost-effective strategy with near-100% probability at thresholds above £15,000 per QALY. Results were consistent across both de novo and previously treated subgroups, although the magnitude of benefit was smaller in the latter due to a lower likelihood of confirmatory biopsy following a positive result. Deterministic analyses showed that PET-CT became more cost-effective as the prevalence of metastatic disease increased, becoming cost-effective at around 34% for previously treated and 42% for de novo patients, while higher biopsy uptake after positive scans increased the ICER due to added biopsy costs. These results indicate that PET-CT's cost-effectiveness is most sensitive to disease prevalence and diagnostic follow-up practice, but remains robust across plausible parameter ranges, with its greatest value realised when both diagnostic and monitoring benefits are considered.

Overall, while FDG PET-CT involves higher upfront imaging costs, its better accuracy in diagnostic and monitoring pathway translate into better health outcomes at an acceptable incremental cost. These analyses suggest that the use of FDG PET-CT for both diagnosis and monitoring of advanced breast cancer could represent an efficient use of NHS resources although the robustness of this conclusion could be improved by better evidence around important inputs.

## 4.2 Strengths and limitations of the analysis

This analysis has several key strengths. First, it represents the first comprehensive economic evaluation of FDG PET-CT versus CT that jointly models both the diagnostic and monitoring phases of advanced breast cancer, capturing the full pathway from initial staging to ongoing disease management. The use of a linked decision tree–Markov model allowed short-term diagnostic decisions and long-term treatment outcomes to be analysed consistently within a single framework. The model structure closely reflects clinical practice in the NHS, where imaging results directly determine subsequent treatment pathways. Second, this analysis was informed by the most recent NHS cost data (2023/24) available during model development and evidence-based diagnostic accuracy inputs, ensuring it is relevant to current practice. Uncertainty was explored using probabilistic sensitivity analysis, and key assumptions, such as imaging costs, biopsy rates, and prevalence of metastases, were tested through deterministic sensitivity analyses. This transparent, stepwise approach strengthens confidence in the robustness of the results. Third, the model also explored clinically plausible strategy combinations (CECT–CECT, CECT–FDG PET-CT, and FDG PET-CT–FDG PET-CT), providing insight into the cost-effectiveness of potential escalation pathways rather than a single diagnostic substitution. Additionally, the analysis included two distinct patient subgroups—people with de novo disease and those with previously treated breast cancer—ensuring that results are relevant to different clinical contexts.

The results of the analysis concur with the only identified previously published economic evaluation on FDG PET-CT for diagnosis in advanced breast cancer (Auguste 2011) which showed FDG PET-CT not to be cost-effective for diagnosis. This model also had a short time horizon and cost differentials between PET-CT and CECT have significantly decreased in that time. The model also made assumptions around misdiagnoses that the committee did not believe to be plausible. This analysis updated the costs for FDG PET-CT and CECT and also found FDG PET-CT not to be cost-effective in the diagnosis part of the model. As discussed above this analysis also had a short time horizon and results should be interpreted with caution.

Several limitations should be acknowledged. The major weakness was that no clinical evidence was identified for differences in survival or other outcomes for monitoring with CECT or FDG PET-CT from the accompanying systematic review. The movement through treatment lines and resultant impact on health outcomes and survival were largely based on assumption. Identical values were used for test accuracy in both the diagnostic and monitoring portions of the model given the paucity of evidence for the later. The intent of imaging in diagnosis and monitoring differ with one concerned with monitoring disease and the other monitoring treatment response and disease progression. Whilst the committee considered that using these values was the appropriate it is plausible that accuracy could differ between the two stages of the model.

The model made the conservative estimate that there would be no difference in mortality between overall survival between different imaging modalities. This goes against the only previous economic evaluation identified for this topic (Naghavi-Behzad 2023) which found that monitoring with FDG PET-CT both improved overall survival and was cost saving. The committee did not find the outcome estimates from that study plausible and highlighted significant confounding as a result of the observational nature of the study.

The model assumed no difference in overall survival between imaging modalities due to a lack of comparative evidence, meaning QALY gains were driven solely by diagnostic and monitoring accuracy. The model simplified aspects of the care pathway, such as the assumption that false negatives would be corrected after one year via repeat imaging, and that false positives uncorrected by biopsy would be resolved after one year. In reality, misdiagnoses may be corrected at anytime or not all depending on ongoing symptoms and future diagnostic testing Utility estimates for treatment phases were drawn from non-recent, international sources, which may not perfectly reflect UK patient preferences, although EQ-5D values were applied consistent with the NICE reference case.

While FDG PET-CT costs were based on recent NHS reference costs data, the committee noted some residual uncertainty about true service-level costs, particularly regarding contracting arrangements for providing FDG PET-CT. The lower FDG PET-CT cost compared with earlier appraisals reflects the mature integration of FDG PET-CT services within the NHS, with higher utilisation rates, shared use across specialties, and greater market competition reducing average per-scan costs.

Long-term outcomes for patients receiving modern systemic therapies were extrapolated from older survival data, reflecting a necessary compromise between recency and data completeness.

Overall, these limitations are unlikely to materially affect the direction of results. The analysis provides a robust, evidence-based, and policy-relevant assessment of the relative value of FDG PET-CT compared with CT for the diagnosis and monitoring of advanced breast cancer in the NHS.

## 5. **Conclusion**

FDG PET-CT could be a cost-effective imaging modality for people suspected of having advanced breast cancer. Results of the model are positive for a number of alternative assumptions. However, the model is particularly sensitive to parameters around which there is significant uncertainty including prevalence of advanced breast cancer in those suspected of having the disease, the diagnostic test accuracy of both imaging modalities for monitoring and the impact on health outcomes of improved diagnostic test accuracy. Stronger evidence around these parameters would increase the robustness of any conclusions drawn from the model.

# Appendix J – Excluded studies

## Review B1

The systematic reviews by Shen et al., 2025 and Xia et al., 2023 included studies that did not meet the inclusion criteria in our protocol. A list of these studies with the reason for exclusion can be seen in the evidence tables for Shen et al., 2025 and Xia et al., 2023 (appendix D).

## Effectiveness and diagnostic studies (n = 78)

| Study | Reason for exclusion |
|---|---|
| Abe, Koichiro, Sasaki, Masayuki, Kuwabara, Yasuo et al. (2005) Comparison of 18FDG-PET with 99mTc-HMDP scintigraphy for the detection of bone metastases in patients with breast cancer. Annals of nuclear medicine 19(7): 573-9 | - Study does not contain any relevant index tests<br>*Index test is 18FDG-PET without CT* |
| Alberini, Jean-Louis, Lerebours, Florence, Wartski, Myriam et al. (2009) 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging in the staging and prognosis of inflammatory breast cancer. Cancer 115(21): 5038-47 | - Reference standard in study does not match that specified in protocol<br>*PET-CT compared to other imaging modalities* |
| Bhoriwal, Sandeep, Deo, S V S, Kumar, Rakesh et al. (2021) A Prospective Study Comparing the Role of 18 FDG PET-CT with Contrast-Enhanced Computed Tomography and Tc99m Bone Scan for Staging Locally Advanced Breast Cancer. Indian journal of surgical oncology 12(2): 266-271 | - Outcome to be predicted does not match that specified in the protocol<br>*Results include axillary metastasis* |
| Bin, Ji, Wenjia, Li, Wan, Wang et al. (2025) Comparison of 18F-FDG PET/CT and 18F-FAPI PET/CT in Systemic Staging of Newly Diagnosed Breast Cancer. Academic radiology 32(1): 50-57 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Study could not obtain true-negative findings of 18F-PET-CT for metastatic disease; therefore, specificity of 18F-PET-CT for assessment of distant metastases could not be calculated* |
| Bitencourt, Almir Galvao Vieira, Andrade, Wesley Pereira, da Cunha, Rodrigo Rodrigues et al. (2017) Detection of distant metastases in patients with locally advanced breast cancer: role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography and | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Reports sensitivity but no specificity data* |

| Study | Reason for exclusion |
|---|---|
| conventional imaging with computed tomography scans. Radiologia brasileira 50(4): 211-215 | |
| Bonnin, D., Ladoire, S., Briot, N. et al. (2023) Performance of [18F]FDG-PET/CT Imaging in First Recurrence of Invasive Lobular Carcinoma. Journal of Clinical Medicine 12(8): 2916 | - Study published before included systematic review for the outcome reported<br>*Outcome: any distant metastases; systematic review: Shen et al., 2025* |
| Botsikas, Diomidis, Bagetakos, Ilias, Picarra, Marlise et al. (2019) What is the diagnostic performance of 18-FDG-PET/MR compared to PET/CT for the N- and M- staging of breast cancer?. European radiology 29(4): 1787-1798 | - Study does not contain any relevant index tests<br>*PET-CT of upper abdomen and thorax only* |
| Buus, Thomas Winther, Rasmussen, Finn, Nellemann, Hanne Marie et al. (2021) Comparison of contrast-enhanced CT, dual-layer detector spectral CT, and whole-body MRI in suspected metastatic breast cancer: a prospective diagnostic accuracy study. European radiology 31(12): 8838-8849 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Does not report FP NF TP TN data, reports overall sensitivity and specificity* |
| Caglar, M, Kupik, O, Karabulut, E et al. (2016) Detection of bone metastases in breast cancer patients in the PET/CT era: Do we still need the bone scan?. Revista espanola de medicina nuclear e imagen molecular 35(1): 3-11 | - Study published before included systematic review for the outcome reported<br>*Outcome: bone metastasis; systematic review: Xia et al., 2023* |
| Campone, M., Rauscher, A., Faivre-Chauvet, A. et al. (2015) Pretargeted immuno-PET with an anti-carcinoembryonic antigen (CEA) bispecific antibody (BsMAb) and a 68Ga-labeled hapten-peptide compared to conventional imaging and FDG-PET in metastatic breast cancer patients (BC): First results. Cancer Research 75(9) | - Conference abstract |
| Capitanio, Selene, Bongioanni, Francesca, Piccardo, Arnoldo et al. (2016) Comparisons between glucose analogue 2-deoxy-2-((18)F)fluoro-D-glucose and (18)F-sodium fluoride positron emission tomography/computed tomography in breast cancer patients with bone lesions. World journal of radiology 8(2): 200-9 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Does not report FP NF TP TN data, reports overall sensitivity and specificity* |

| Study | Reason for exclusion |
|---|---|
| Catalano, Onofrio Antonio, Daye, Dania, Signore, Alberto et al. (2017) Staging performance of whole-body DWI, PET/CT and PET/MRI in invasive ductal carcinoma of the breast. International journal of oncology 51(1): 281-288 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Not enough data reported to calculate sensitivity and specificity* |
| Champion, L., Brain, E., Giraudet, A.-L. et al. (2011) Breast cancer recurrence diagnosis suspected on tumor marker rising. Cancer 117(8): 1621 | - Study published before included systematic review for the outcome reported<br>*Outcome: any distant metastases; systematic review: Shen et al., 2025* |
| Chen, Zhenying, Fu, Fangmeng, Li, Fang et al. (2018) Comparison of [99mTc]3PRGD2 Imaging and [18F]FDG PET/CT in Breast Cancer and Expression of Integrin alphavbeta3 in Breast Cancer Vascular Endothelial Cells. Molecular imaging and biology 20(5): 846-856 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*No sensitivity or specificity data for distant metastatic lesions reported; also population with suspected breast cancer* |
| Chung, Hannah L, Shin, Kyungmin, Sun, Jia et al. (2021) Extra-axillary nodal metastases in breast cancer: comparison of ultrasound, MRI, PET/CT, and CT. Clinical imaging 79: 113-118 | - Reference standard in study does not match that specified in protocol<br>*Ultrasound as reference standard* |
| Cochet, Alexandre, Dygai-Cochet, Inna, Riedinger, Jean-Marc et al. (2014) 18F-FDG PET/CT provides powerful prognostic stratification in the primary staging of large breast cancer when compared with conventional explorations. European journal of nuclear medicine and molecular imaging 41(3): 428-37 | - End point does not match that specified in the protocol<br>*Study focused on staging rather than diagnostic accuracy. No diagnostic accuracy measures reported and therefore unable to obtain 2x2 data.* |
| Damle, Nishikant Avinash, Bal, Chandrasekhar, Bandopadhyaya, G P et al. (2013) The role of 18F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and 99mTc-MDP bone scan. Japanese journal of radiology 31(4): 262-9 | - Reference standard in study does not match that specified in protocol<br>*FDG PET-CT was the reference standard rather than assessment tool* |
| Davidson, Tima, Shehade, Nagham, Nissan, Ella et al. (2021) PET/CT in breast cancer staging is useful for evaluation of axillary lymph node and distant metastases. Surgical oncology 38: 101567 | - Not possible to calculate a contingency table from the data specified in the protocol |

| Study | Reason for exclusion |
|---|---|
| Dayes, Ian S, Metser, Ur, Hodgson, Nicole et al. (2023) Impact of 18F-Labeled Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography Versus Conventional Staging in Patients With Locally Advanced Breast Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 41(23): 3909-3916 | - Population does not have suspected metastases<br>*Study excluded people with clinical suspicion of metastatic disease* |
| de Mooij, Cornelis Maarten, Sunen, Ines, Mitea, Cristina et al. (2020) Diagnostic performance of PET/computed tomography versus PET/MRI and diffusion-weighted imaging in the N- and M-staging of breast cancer patients. Nuclear medicine communications 41(10): 995-1004 | - Systematic review used as source of primary studies<br>*More recent SR available. Inconsistencies across included studies - 1 study had PET-CT as reference standard and 1 study had imaging covering less than neck, thorax, abdomen and pelvis.* |
| Demir, S.S.; Aktas, G.E.; Yenici, F.U. (2017) A lesion based and sub-regional comparison of FDG PET/CT and MDP bone scintigraphy in detection of bone metastasis in breast cancer. Current Medical Imaging Reviews 13(4): 422 | - Outcome to be predicted does not match that specified in the protocol<br>*Lesion-based analysis* |
| Dondi, Francesco, Albano, Domenico, Giubbini, Raffaele et al. (2022) 18F-FDG PET/CT for the evaluation of male breast cancer: a systematic review. Nuclear medicine communications 43(2): 123-128 | - Systematic review used as source of primary studies<br>*No reference standard. Review assessed staging and re-staging of Male breast cancer and results were not compared with a reference standard.* |
| Evangelista, L., Cuppari, L., Burei, M. et al. (2019) Head-to-head comparison between 18F-FDG PET/CT and PET/MRI in breast cancer. Clinical and Translational Imaging 7(2): 99 | - Systematic review used as source of primary studies<br>*More recent systematic review available and review quality not adequate because QUADAS-2 was not used for risk of bias assessment* |
| Fueger, Barbara J, Weber, Wolfgang A, Quon, Andrew et al. (2005) Performance of 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography and integrated PET/CT in restaged breast cancer patients. Molecular imaging and biology 7(5): 369-76 | - Outcome to be predicted does not match that specified in the protocol<br>*Study looked at absence or presence of cancer not at distant metastases* |
| Gallowitsch, HJ, Kresnik, E, Gasser, J et al. (2003) F-18 fluorodeoxyglucose positron-emission tomography in the diagnosis of tumor recurrence and | - Study published before 2005 |

| Study | Reason for exclusion |
|---|---|
| metastases in the follow-up of patients with breast carcinoma: a comparison to conventional imaging. Investigative radiology 38(5): 250-6 | |
| Gao, Haiyan, Chen, Jie, Yang, Zhichuan et al. (2024) Comparative Study of [18F]AlF-LNC1007, [18F]FDG, and [18F]AlF-NOTA-FAPI-04 PET/CT in Breast Cancer Diagnosis: A Methodological Exploration and Analytical Insight. ACS applied materials & interfaces 16(49): 67523-67531 | - Outcome to be predicted does not match that specified in the protocol<br>*Diagnostic test accuracy was reported by lesion without complete data on patient-based analysis* |
| Garami, Z, Hascsi, Z, Varga, J et al. (2012) The value of 18-FDG PET/CT in early-stage breast cancer compared to traditional diagnostic modalities with an emphasis on changes in disease stage designation and treatment plan. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 38(1): 31-7 | - Reference standard in study does not match that specified in protocol<br>*Reference standard was not clearly stated; PET-CT indicated distant metastases in 8 people and confirmation of distant metastases was done only in these people* |
| Gerke, Oke, Naghavi-Behzad, Mohammad, Nygaard, Sofie Tind et al. (2025) Diagnosing Bone Metastases in Breast Cancer: A Systematic Review and Network Meta-Analysis on Diagnostic Test Accuracy Studies of 2-[18F]FDG-PET/CT, 18F-NaF-PET/CT, MRI, Contrast-Enhanced CT, and Bone Scintigraphy. Seminars in nuclear medicine 55(1): 137-151 | - Systematic review used as source of primary studies |
| Groheux, David, Giacchetti, Sylvie, Delord, Marc et al. (2013) 18F-FDG PET/CT in staging patients with locally advanced or inflammatory breast cancer: comparison to conventional staging. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 54(1): 5-11 | - Reference standard in study does not match that specified in protocol<br>*Bone scans and CT-scans were used as reference standards* |
| Guglielmo, Priscilla, Mazzola, Rosario, Darwish, Shadya Sara et al. (2025) Head-to-Head comparison of [18F]FES and [18F]FDG PET/CT in breast cancer patients: has a new era come?. European journal of nuclear medicine and molecular imaging | - Systematic review used as source of primary studies<br>*Systematic review does not meet inclusion criteria for this review. Modified CASP checklist used for critical appraisal and not all included studies had a reference standard. Primary studies meeting the inclusion criteria have been included individually in this review* |

| Study | Reason for exclusion |
|---|---|
| Guo, Wei, Xu, Weizhi, Meng, Tinghua et al. (2025) FAP-targeted PET/CT imaging in patients with breast cancer from a prospective bi-center study: insights into diagnosis and clinic management. European journal of nuclear medicine and molecular imaging | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Specificity was not evaluated in the study* |
| Guo, Xiaoyi, Liu, Jiayue, Lin, Shiyu et al. (2025) Detectability of Al 18 F-NOTA-HER2-BCH PET for Nodal Metastases in Patients With HER2-Positive Breast Cancer. Clinical nuclear medicine 50(5): 381-387 | - Outcome to be predicted does not match that specified in the protocol<br>*Diagnostic test accuracy was reported for combined regional nodal metastasis and distant nonregional nodal metastasis* |
| Hahn, Steffen, Heusner, Till, Kummel, Sherko et al. (2011) Comparison of FDG-PET/CT and bone scintigraphy for detection of bone metastases in breast cancer. Acta radiologica (Stockholm, Sweden : 1987) 52(9): 1009-14 | - Reference standard in study does not match that specified in protocol<br>*Bone scan was used as reference standard* |
| Hansen, Jeanette Ansholm, Naghavi-Behzad, Mohammad, Gerke, Oke et al. (2021) Diagnosis of bone metastases in breast cancer: Lesion-based sensitivity of dual-time-point FDG-PET/CT compared to low-dose CT and bone scintigraphy. PloS one 16(11): e0260066 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Reports sensitivity data but not specificity data* |
| Haug, Alexander Robert, Schmidt, Gerwin Paul, Klingenstein, Annemarie et al. (2007) F-18-fluoro-2-deoxyglucose positron emission tomography/computed tomography in the follow-up of breast cancer with elevated levels of tumor markers. Journal of computer assisted tomography 31(4): 629-34 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Reports data for lesions and not individuals so unable to calculate* |
| Heusner, Till A, Kuemmel, Sherko, Umutlu, Lale et al. (2008) Breast cancer staging in a single session: whole-body PET/CT mammography. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 49(8): 1215-22 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*No data for specificity and sensitivity for distant metastases - only reported for primary and axilla* |
| Hildebrandt, Malene Grubbe, Gerke, Oke, Baun, Christina et al. (2016) [18F]Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)/Computed Tomography (CT) in Suspected Recurrent Breast Cancer: A | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Reports FP and FN but does not report TP or TN for PET-CT as it gives an overall number of confirmed metastasis from all scanning methods used* |

| Study | Reason for exclusion |
|---|---|
| Prospective Comparative Study of Dual-Time-Point FDG-PET/CT, Contrast-Enhanced CT, and Bone Scintigraphy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34(16): 1889-97 | |
| Hong, Shikai; Li, Junhong; Wang, Shengying (2013) 18FDG PET-CT for diagnosis of distant metastases in breast cancer patients. A meta-analysis. Surgical oncology 22(2): 139-43 | - Systematic review used as source of primary studies<br>*More recent systematic review available and review quality not adequate because QUADAS-2 was not used for risk of bias assessment. Meta-analysis of 8 primary studies to be checked* |
| Houssami, N and Costelloe, C M (2012) Imaging bone metastases in breast cancer: evidence on comparative test accuracy. Annals of oncology : official journal of the European Society for Medical Oncology 23(4): 834-43 | - Systematic review used as source of primary studies<br>*Includes only 2 studies on PET-CT, one of which sensitivity and specificity could not be calculated. Other included studies had index tests as FDG-PET or SPECT* |
| Hu, Hongyu, Hu, Xianwen, Liang, Zhigang et al. (2024) Diagnostic performance of 18F-FDG PET/CT vs. 18F-NaF PET/CT in breast cancer with bone metastases: An indirect comparative meta-analysis. Oncology letters 28(5): 546 | - Systematic review used as source of primary studies<br>*Lesion- and patient-based data combined in meta-analysis, and one of the included studies had MRI follow-up as reference standard (not adequate as per protocol)* |
| Hyland, C.J., Varghese, F., Yau, C. et al. (2019) The use of 18F-FDG PET/CT as an initial staging procedure for stage II-III breast cancer reduces false positives, costs, and time to treatment: A multicenter value analysis in the I-SPY2 trial. Cancer Research 79(4) | - Conference abstract<br>*IS confirmed that this is a conference abstract. FT not ordered* |
| Hyland, Colby J, Varghese, Flora, Yau, Christina et al. (2020) Use of 18F-FDG PET/CT as an Initial Staging Procedure for Stage II-III Breast Cancer: A Multicenter Value Analysis. Journal of the National Comprehensive Cancer Network : JNCCN 18(11): 1510-1517 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Authors state unable to determine FP rate due to nature of study* |
| Knip, Jelijn J, Iqbal, Ramsha, Bonjer, Emma C et al. (2025) The Diagnostic Accuracy of 18F-FDG PET and 18F-FES PET for Staging Grade 1-2 Estrogen Receptor-Positive Breast Cancer. Radiology 314(3): e241850 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Reports TP and FP per individual but reports FN on lesions rather and individuals* |
| Komek, Halil, Can, Canan, Guzel, Yunus et al. (2021) 68Ga-FAPI-04 | - Not possible to calculate a contingency table from the data specified in the protocol |

| Study | Reason for exclusion |
|---|---|
| PET/CT, a new step in breast cancer imaging: a comparative pilot study with the 18F-FDG PET/CT. Annals of nuclear medicine 35(6): 744-752 | *Does not report FP NF TP TN data for distant metastases* |
| Koolen, B.B., Van Der Leij, F., Vogel, W.V. et al. (2012) Value of 18F-FDG PET/CT for primary tumor visualization and staging in T1 breast cancer patients. European Journal of Surgical Oncology 38(9): 812-813 | - Conference abstract |
| Koolen, Bas B, van der Leij, Femke, Vogel, Wouter V et al. (2014) Accuracy of 18F-FDG PET/CT for primary tumor visualization and staging in T1 breast cancer. Acta oncologica (Stockholm, Sweden) 53(1): 50-7 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Only reports sensitivity and specificity for axillary. Not enough data reported for distant* |
| Mahner, S, Schirrmacher, S, Brenner, W et al. (2008) Comparison between positron emission tomography using 2-[fluorine-18]fluoro-2-deoxy-D-glucose, conventional imaging and computed tomography for staging of breast cancer. Annals of oncology : official journal of the European Society for Medical Oncology 19(7): 1249-1254 | - Assessment tool does not match that specified in the protocol<br>*Compares FDG-PET to CT. Does not use PET-CT* |
| Medina-Ornelas, Sevastian, Garcia-Perez, Franciso, Estrada-Lobato, Enrique et al. (2020) 68Ga-PSMA PET/CT in the evaluation of locally advanced and metastatic breast cancer, a single center experience. American journal of nuclear medicine and molecular imaging 10(3): 135-142 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Combines axillary with distant metastases to determine sensitivity and specificity* |
| Mittal, Bagwant Rai, Manohar, Kuruva, Kashyap, Raghava et al. (2011) The role of (18)F-FDG PET/CT in initial staging of patients with locally advanced breast carcinoma with an emphasis on M staging. Hellenic journal of nuclear medicine 14(2): 135-9 | - End point does not match that specified in the protocol<br>*Only reports TP data* |
| Morris, Patrick G, Lynch, Colleen, Feeney, John N et al. (2010) Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. Journal of clinical oncology : official journal of the | - End point does not match that specified in the protocol<br>*Not DTA- Compares BSc with PET-CT. No specificity and sensitivity data reported* |

| Study | Reason for exclusion |
|---|---|
| American Society of Clinical Oncology 28(19): 3154-9 | |
| Nakai, Takako, Okuyama, Chio, Kubota, Takao et al. (2005) Pitfalls of FDG-PET for the diagnosis of osteoblastic bone metastases in patients with breast cancer. European journal of nuclear medicine and molecular imaging 32(11): 1253-8 | - Study does not contain any relevant index tests<br>*Index test is FDG-PET without CT* |
| Niikura, Naoki, Hashimoto, Jun, Kazama, Toshiki et al. (2016) Diagnostic performance of (18)F-fluorodeoxyglucose PET/CT and bone scintigraphy in breast cancer patients with suspected bone metastasis. Breast cancer (Tokyo, Japan) 23(4): 662-7 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Reports only true positive data* |
| Noh, Hee Yeon, Ahn, Su Joa, Nam, Sang Yu et al. (2022) Comparison of Diagnostic Performance and Confidence between Contrast-Enhanced Computed Tomography Scan and Non-Contrast-Enhanced Computed Tomography Plus Abdomen Ultrasound for Hepatic Metastasis in Patients with Breast Cancer. Journal of medical ultrasound 30(2): 116-124 | - Study does not contain any relevant index tests<br>*Contrast-enhanced CT was limited to the abdomen and pelvis* |
| Palaniswamy, Shanmuga Sundaram and Subramanyam, Padma (2024) Diagnostic performance of simultaneous PET-MR versus PET-CT in oncology with an overview on clinical utility and referral pattern of PET-MR: a single institutional study. Nuclear medicine communications 45(12): 1022-1032 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Diagnostic test accuracy was reported combining data for people with breast cancer and people with lung cancer* |
| Port, Elisa Rush, Yeung, Henry, Gonen, Mithat et al. (2006) 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography scanning affects surgical management in selected patients with high-risk, operable breast carcinoma. Annals of surgical oncology 13(5): 677-84 | - Reference standard in study does not match that specified in protocol<br>*Reference standard was not clearly stated; confirmation of distant metastases was done in people with metastases on both PET-CT and CT* |
| Pritchard, Kathleen I, Julian, Jim A, Holloway, Claire M B et al. (2012) Prospective study of 2-[18F]fluorodeoxyglucose positron emission tomography in the assessment of regional nodal spread of disease in patients with breast cancer: an Ontario | - Outcome to be predicted does not match that specified in the protocol<br>*Distant metastases were incidental findings* |

| Study | Reason for exclusion |
|---|---|
| clinical oncology group study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30(12): 1274-9 | |
| Rezk, Mahmoud, Nasr, Ibrahim, Ali, Ismail et al. (2019) Comparative Study between 18F FDG-PET/CT and Whole Body MRI DWIBS in Assessment of Recurrent Breast Cancer (Prospective, Comparative, Cross-sectional Study Design). Indian journal of nuclear medicine : IJNM : the official journal of the Society of Nuclear Medicine, India 34(1): 1-9 | - Outcome to be predicted does not match that specified in the protocol<br>*Data reported as the number of lesions with metastasis without reporting the overall number of people with metastasis* |
| Rong, Jian, Wang, Siyang, Ding, Qiue et al. (2013) Comparison of 18 FDG PET-CT and bone scintigraphy for detection of bone metastases in breast cancer patients. A meta-analysis. Surgical oncology 22(2): 86-91 | - Systematic review used as source of primary studies<br>*More recent systematic review available and review quality not adequate because QUADAS-2 was not used for risk of bias assessment* |
| Roop, Mohan J, Singh, Baljinder, Singh, Harmandeep et al. (2017) Incremental Value of Cocktail 18F-FDG and 18F-NaF PET/CT Over 18F-FDG PET/CT Alone for Characterization of Skeletal Metastases in Breast Cancer. Clinical nuclear medicine 42(5): 335-340 | - Not a relevant study design<br>*Comparative study without data on diagnostic test accuracy* |
| Rousseau, Caroline, Goldenberg, David M, Colombie, Mathilde et al. (2020) Initial Clinical Results of a Novel Immuno-PET Theranostic Probe in Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 61(8): 1205-1211 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Specificity was not reported; all participants had confirmed metastasis* |
| Sahin, Ertan, Zincirkeser, Sabri, Akcan, Abdullah Baris et al. (2014) Is (99m)Tc-MDP whole body bone scintigraphy adjuvant to (18)F-FDG-PET for the detection of skeletal metastases?. Journal of B.U.ON. : official journal of the Balkan Union of Oncology 19(1): 291-6 | - Outcome to be predicted does not match that specified in the protocol<br>*Reports data per lesion not per patient* |
| Sawicki, Lino M, Grueneisen, Johannes, Schaarschmidt, Benedikt M et al. (2016) Evaluation of 18F-FDG PET/MRI, 18F-FDG PET/CT, MRI, and CT in whole-body staging of recurrent breast cancer. | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Study reports true positives at patient-based level data without reporting any other relevant* |

| Study | Reason for exclusion |
|---|---|
| European journal of radiology 85(2): 459-65 | *measures (for example: sensitivity or specificity) to calculate 2x2 table* |
| Schmidt, Gerwin P, Baur-Melnyk, Andrea, Haug, Alexander et al. (2008) Comprehensive imaging of tumor recurrence in breast cancer patients using whole-body MRI at 1.5 and 3 T compared to FDG-PET-CT. European journal of radiology 65(1): 47-58 | - Outcome to be predicted does not match that specified in the protocol<br>*Data reported as the number of lesions with metastasis without reporting the overall number of people with metastasis* |
| Sugihara, Tsutomu, Koizumi, Mitsuru, Koyama, Masamichi et al. (2017) Bone metastases from breast cancer: associations between morphologic CT patterns and glycolytic activity on PET and bone scintigraphy as well as explorative search for influential factors. Annals of nuclear medicine 31(10): 719-725 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Only reports sensitivity (specificity could not be calculated, FDG PET-CT only reported for people with confirmed metastasis)* |
| Sun, Zhe, Yi, Yu Li, Liu, Yu et al. (2015) Comparison of whole-body PET/PET-CT and conventional imaging procedures for distant metastasis staging in patients with breast cancer: a meta-analysis. European journal of gynaecological oncology 36(6): 672-6 | - Systematic review used as source of primary studies<br>*Newer systematic review available and review quality not adequate as used QUADAS for quality appraisal rather than QUADAS-2* |
| Suárez, M, Pérez-Castejón, MJ, Jiménez, A et al. (2002) Early diagnosis of recurrent breast cancer with FDG-PET in patients with progressive elevation of serum tumor markers. The quarterly journal of nuclear medicine : official publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR) 46(2): 113-21 | - Study published before 2005 |
| Taneja, Sangeeta, Jena, Amarnath, Goel, Reema et al. (2014) Simultaneous whole-body 18F-FDG PET-MRI in primary staging of breast cancer: a pilot study. European journal of radiology 83(12): 2231-2239 | - Not possible to calculate a contingency table from the data specified in the protocol<br>*Diagnostic test accuracy data was not reported separately for FDG PET-CT* |
| Teke, Fatma, Teke, Memik, Inal, Ali et al. (2015) Significance of hormone receptor status in comparison of 18F - FDG-PET/CT and 99mTc-MDP bone scintigraphy for evaluating bone metastases in patients with breast cancer: single center experience. Asian | - Outcome to be predicted does not match that specified in the protocol<br>*Data reported as the number of lesions with metastasis without reporting the overall number of people with metastasis* |

| Study | Reason for exclusion |
|---|---|
| Pacific journal of cancer prevention : APJCP 16(1): 387-91 | |
| van Uden, D J P, Prins, M W, Siesling, S et al. (2020) [18F]FDG PET/CT in the staging of inflammatory breast cancer: A systematic review. Critical reviews in oncology/hematology 151: 102943 | - Systematic review used as source of primary studies<br>*Only included patients with inflammatory breast cancer. Primary studies meeting the inclusion criteria have been included individually in this review* |
| Vogsen, M., Jensen, J.D., Christensen, I.Y. et al. (2020) FDG-PET/CT in high-risk primary breast cancer: A prospective study of stage migration and clinical impact. Annals of Oncology 31: 340 | - Conference abstract |
| Vogsen, M., Jensen, J.D., Christensen, I.Y. et al. (2020) FDG-PET/CT in high-risk primary breast cancer: A prospective study of stage migration and clinical impact. Annals of Oncology 31: 340 | - Duplicate reference |
| Wang, Y.-Z.; Zhang, L.; Lei, J.-Q. (2013) Value of dual phase 18FDG-PET/CT and single phase 18FDG-PET/CT in diagnosis of breast cancer: Meta-analysis. Chinese Journal of Medical Imaging Technology 29(3): 415-419 | - Study not reported in English<br>*Chinese* |
| Yang, Wei T, Le-Petross, Huong T, Macapinlac, Homer et al. (2008) Inflammatory breast cancer: PET/CT, MRI, mammography, and sonography findings. Breast cancer research and treatment 109(3): 417-26 | - Outcome to be predicted does not match that specified in the protocol<br>*Distant metastases reported in combination with axillary node and supraclavicular node metastases* |
| Yilmaz, Burcak, Dag, Sedef, Ergul, Nurhan et al. (2019) The ability of pre-treatment F-18 FDG PET/CT metabolic parameters for predicting axillary lymph node and distant metastasis and overall survival. Nuclear medicine communications 40(11): 1112-1121 | - Outcome to be predicted does not match that specified in the protocol<br>*Study reported diagnostic accuracy for various parameters used for measuring FDG uptake including SUVmax-T and SUVmax-LN, which do not reflect how metastases are measured in clinical practice.* |
| Yoon, Seok-Ho, Kim, Ku Sang, Kang, Seok Yun et al. (2013) Usefulness of (18)F-fluoride PET/CT in Breast Cancer Patients with Osteosclerotic Bone Metastases. Nuclear medicine and molecular imaging 47(1): 27-35 | - BACKUP STUDY POT - slightly indirect reference standard<br>*Reference standard included FDG PET-CT in 8 of the 9 participants* |
| Zamanian, Maryam; Treglia, Giorgio; Abedi, Iraj (2023) Diagnostic Accuracy | - Reference standard in study does not match that specified in protocol |

| Study | Reason for exclusion |
|---|---|
| of PET with Different Radiotracers versus Bone Scintigraphy for Detecting Bone Metastases of Breast Cancer: A Systematic Review and a Meta-Analysis. Journal of imaging 9(12) | *Systematic review but reference standards included CT/MRI scans, physical examination, bone scan blood tests, PET CT etc.* |
| Zhang, J., Xiong, J., Wang, M. et al. (2024) Comparison of the diagnostic value of 68Ga-FAPI and 18F-FDG PET/CT in breast cancer: a systematic review. Clinical and Translational Imaging 12(6): 787 | - Systematic review used as source of primary studies<br>*Systematic review focused on assessing primary breast lesion rather than distant metastases. 2 included studies reported on distant metastases at patient-level and were assessed individually for inclusion* |
| Zhang, Xuemei; Wu, Fengyu; Han, Ping (2014) The role of (18)F-FDG PET/CT in the diagnosis of breast cancer and lymph nodes metastases and micrometastases may be limited. Hellenic journal of nuclear medicine 17(3): 177-83 | - Outcome to be predicted does not match that specified in the protocol<br>*Study reports on axillary lymph nodes metastasis* |

### Cost-effectiveness studies (n=1)

| Study | Reason for exclusion |
|---|---|
| Fatima, N., Zaman, U., Ahmed, A., Zaman, S., Khan, K., & uz Zaman, M. (2024). Impact of 18FDG PET/CT on Clinical Management, Cost Effectiveness, and Radiation Exposure in Newly Diagnosed Breast Cancer Patients. *Asian Pacific Journal of Cancer Prevention: APJCP*, *25*(10), 3577. | - Population outside of protocol |

### Review B2

### Effectiveness studies (n=1)

| Study | Reason for exclusion |
|---|---|
| Escalona, S, Blasco, JA, Reza, MM et al. (2010) A systematic review of FDG-PET in breast cancer. Medical oncology (Northwood, London, England) 27(1): 114-29 | - Systematic review did not meet inclusion criteria in protocol and did not have any relevant studies to include |

## Cost-effectiveness studies (n=1)

| Study | Reason for exclusion |
|---|---|
| Meng Y, Ward S, Cooper K, Harnan S, Wyld L. Cost-effectiveness of MRI and PET imaging for the evaluation of axillary lymph node metastases in early stage breast cancer. Eur J Surg Oncol. 2011 Jan;37(1):40-6. doi: 10.1016/j.ejso.2010.10.001. Epub 2010 Nov 27. PMID: 21115232. | - Comparator of MRI not included in interventions of interest |

# Appendix K– Research recommendations – full details

## K1.1 Research recommendation - Review B1

In adults with lobular breast cancer and suspected metastatic disease, what is the diagnostic accuracy and cost effectiveness of different imaging modalities [such as whole-body MRI, fibroblast activation protein inhibitor (FAPI) PET-CT and 18F-fluoroestradiol (FES) PET-CT] for detecting distant metastases?

### K1.1.1 Why this is important

Invasive lobular cancer makes up about 15% of breast cancers and is the most common type after invasive ductal carcinoma. There was evidence from 1 small retrospective cohort study (n=21 participants) showing that FDG PET-CT was not sensitive for detecting metastases (bone metastases were the target condition in the study). The committee agreed that although the study on lobular breast cancer was small, it was still clinically relevant because FDG uptake in lobular breast cancer is often low, therefore, FDG PET-CT may not always be useful for identifying metastases in people with lobular breast cancer.

The committee noted that although FDG PET-CT showed low uptake for people with lobular breast cancer, there were no studies to show the diagnostic accuracy of CECT in the same population. But from their knowledge and practice, CECT is not likely to perform better than FDG PET-CT for diagnosing metastases in people with lobular breast cancer. The committee conclusions were for both bone and visceral metastases, but lobular breast cancer most commonly spreads to the bone.

The committee were aware of 2 other tracers used with PET-CT: fibroblast activation protein inhibitor (FAPI) and 18F-Fluoroestradiol (FES). However, they were also aware that there might not be available evidence and that it was important to promote research for evidence generation. The committee mentioned that other imaging modalities are more likely to be used in practice for people with lobular breast cancer such as whole-body MRI but evidence is also uncertain for this type of imaging. Therefore all imaging modalities were included in this question.

Tumour biology influences how well different imaging techniques detect metastases. If tumour biology also varies by individual characteristics – such as socioeconomic status or ethnicity – then these factors become important to examine in any research comparing imaging techniques. The impact of these characteristics, which are also related to health inequalities, on tumour biology is not yet fully understood. Ensuring these subgroups are included in analyses would help generate evidence that is both methodologically robust and relevant to reducing health inequalities.

### K1.1.2 Rationale for research recommendation

**Table 53: Rationale for research recommendation**

| | |
|---|---|
| Importance to ‘patients’ or the population | An effective imaging approach could limit inappropriate management for people with non-metastatic breast cancer such as offering non-curative treatments and potentially missing the time when the cancer may have been cured. Effective imaging |

| | |
|---|---|
| | could also limit inappropriate interventions for people with metastatic breast cancer such as surgery. |
| Relevance to NICE guidance | There is lack of data comparing different imaging modalities to detect distant metastases in people with lobular breast cancer. Research to address this could lead to separate recommendations about the best imaging modalities to use for people with lobular breast cancer. |
| Relevance to the NHS | There is a lack of evidence on which imaging modality is best to detect distant metastases in people with lobular breast cancer. Therefore, it would be helpful if clinicians had evidence-based guidance to help them to choose the best imaging modality in this population. An effective imaging approach would also have downstream effects on treatment and on disease progression. New tracers for use with PET-CT may improve the accuracy of diagnosing metastases in people with lobular breast cancer, but more research is needed to investigate this. |
| National priorities | Low |
| Current evidence base | Lack of data comparing different imaging modalities to detect distant metastases in people with lobular breast cancer. |
| Equality considerations | None known |

### K1.1.3 Modified PICO table

### Table 54: Modified PICO table

| | |
|---|---|
| Population | Adults (18 and over) with lobular breast cancer who have suspected distant metastases (M1) |
| Index tests | Any diagnostic imaging test, for example:<br>• Whole-body MRI<br>• FAPI PET-CT<br>• FES PET-CT |
| Reference standard | • Histopathology from surgery or biopsy confirming metastasis<br>• Clinical follow-up involving expert decision making with support of imaging (other than the index tests alone) and / or histological data |
| Outcomes | • Sensitivity and specificity<br>• Positive and negative likelihood ratios |
| Study design | • Diagnostic accuracy cross-sectional studies and cohort studies |
| Timeframe | Short term |
| Additional information | Subgroup analysis by characteristics which may impact tumour biology, such as socioeconomic status and ethnicity, should be performed where possible. |