National Institute for Health and Care Excellence

Final

Addendum to Clinical Guideline 81, Advanced Breast Cancer

Clinical Guideline Addendum 81.2

Methods, evidence and recommendations

August 2017

Final

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

Contents

Clinical guidelines update

The NICE clinical guidelines update team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found via appendix B.

1 Summary section

1.1 Update information

The NICE guideline on advanced breast cancer (NICE clinical guideline CG81) was reviewed in November 2015 as part of NICE's routine surveillance programme to decide whether it required updating. 2 new studies (1 which was a pooled analysis of individual patient data from 2 prospective studies and the other a prospective cohort study) were identified examining discordance between primary and recurrent breast cancer in terms of oestrogen receptor (ER), human epidermal growth factor receptor 2 (HER-2) and progesterone receptor (PR) status. The 2 studies found there could be discordance in receptor status between the primary tumour and metastases, which led to altered management in 14.2–20% of cases.

The topic experts agreed with the need to reassess receptor status on disease recurrence. They noted that the Breast Cancer Quality Standard (QS) already states that people with recurrent disease (if clinically appropriate) have the ER and HER-2 status of the tumour assessed.

It appears that the QS statement is supported by the evidence from the current surveillance review. However it was recognised that the QS doesn't align with the current recommendations in the clinical guideline – which state that, if disease recurs, further biopsy just to reassess ER and HER-2 status should not be done. This area should therefore be reviewed to see if the clinical guideline needs to be updated in light of the new evidence. The existing quality standard will be reviewed in light of the guideline update.

The review question that the committee considered was:

1. In patients (women and men) with advanced breast cancer[a] and ER/PR/HER-2 status known in primary tumour, does receptor status change on disease recurrence at any site?

The original guideline can be found here.

The full surveillance report can be found here.

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

[a] Advanced breast cancer defined as invasive adenocarcinoma of the breast of clinical stage 4 (i.e. with known metastatic disease).

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

1.23 Recommendations

1. On recurrence, consider reassessing oestrogen receptor (ER) and human epidermal growth factor 2 receptor (HER-2) status if a change in receptor status will lead to a change in management. [2017]

Replaced recommendation:

1.1.6 Patients with tumours of known oestrogen receptor (ER) status whose disease recurs should not have a further biopsy just to reassess ER status. [2009]

1.1.7 Patients with tumours of known human epidermal growth factor receptor 2 (HER-2) status whose disease recurs should not have a further biopsy just to reassess HER-2 status. [2009]

Deleted recommendations:

1.1.8 Assess ER and HER-2 status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis. In the absence of tumour tissue from the primary tumour, and if feasible, obtain a biopsy of a metastasis to assess ER and HER-2 status. [2009]

1.34 Patient-centred care

This guideline offers best practice advice on the care of patients (men and women) with advanced breast tumour and ER/PR /HER-2 status known at first diagnosis.

People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

NICE has also produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

1.4 Methods

This update was developed based on the process and methods described in Developing NICE guidelines: the manual.

2 Evidence review and recommendations

2.1 Introduction

The NICE guideline on advanced breast cancer (NICE clinical guideline CG81) was reviewed in November 2015 as part of NICE's routine surveillance programme to decide whether it required updating. 2 new studies (1 which was a pooled analysis of individual patient data from 2 prospective studies and the other a prospective cohort study) were identified that examined discordance between primary and recurrent breast cancer in terms of oestrogen (ER), human epidermal growth factor receptor 2 (HER-2) and progesterone (PR) receptor status. The 2 studies found there could be discordance in receptor status between the primary tumour and metastases, which led to altered management in 14.2–20% of cases.

2.2 Review question

In patients (women and men) with advanced breast cancer[b] and ER/PR/HER-2 status known in the primary tumour, does receptor status change on disease recurrence at any site?

It became apparent during the course of this update that the above review question carried forward from the original guideline should contain more than whether the receptor status can change on recurrence – specifically, it should consider whether it is worth re-biopsying patients with loco-regional or distant recurrence. This depends on the likelihood of change in receptor status, the direction of change, the cost and benefits of alternative treatments and the cost impact, especially if a patient switches from HER-2 negative to HER-2 positive for which there are tailored management options. Hence, the review question answered in this update (and to be carried forward in any future updates) was:

What is the clinical and cost effectiveness of retesting receptor status on disease recurrence in patients with advanced breast cancer?

The evidence search that was run for this update was not re-run after the review question was revised. This was because it was not anticipated that any additional relevant evidence would be identified, because the committee noted that there are unlikely to be randomised controlled trials in this area. The studies identified in the update searches provided sufficient material in terms of the outcomes prioritised by the topic experts.

2.3 Clinical evidence review

A systematic search was conducted (see appendix D) which identified 7,240 articles. The titles and abstracts were screened and 79 articles were identified as potentially relevant (including 17 studies from the original guideline). Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 20 were excluded as they did not meet the criteria and 59 studies met the criteria and were included.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

[b] Advanced breast cancer defined as invasive adenocarcinoma of the breast of clinical stage 4 (i.e. with known metastatic disease).

2.3.11 Methods

For a summary of the review protocol and methods, please refer to Appendix C:

The committee agreed at the first committee meeting that studies assessing change in receptor status in locoregional metastases only should not be considered for inclusion for the following reasons.

- surgery is often the standard of care so this information would not help with 'change in treatment' outcome.
- locoregional metastases routinely are biopsied in clinical practice at the moment

It was, however, decided as a post-hoc analysis that data relating to a change in direction of HER-2 status needed to be extracted to feed into the health economic model. For breast cancer, it is known that ER/PR/HER-2 status may differ between primary and recurrent tumours. Of these markers, a change in HER-2 status has the largest impact on change in management, as HER-2-positive tumours are indicated for treatment with trastuzumab, which makes treatment of HER-2-positive cancer substantially more expensive. This data was extracted as a post-hoc analysis for both the locoregional and distant subgroups. For results of this post-hoc analysis, please see Appendix I:Appendix I:

Overall summary of evidence

The 59 included studies covered recurrences in the following regions:

- Distant metastases only: 19 new studies plus 6 studies from original guideline - 25 included studies in total.
- Mixed locoregional and distant metastases: 28 new studies, 2 studies from the original guideline – 30 included studies in total.
- Both distant metastases and mixed locoregional and distant metastases: 2 new studies, 2 studies from the original guideline – 4 included studies in total.

Overall, the quality of the evidence was very low. Typical reasons for downgrading included baseline demographics being poorly reported (and therefore it not being possible to assess how homogenous the populations were), not all eligible patients having tissues samples for both primary tumour and recurrence, and it not being possible for imprecision to be quantitatively assessed.

For a summary of included studies please see Table 1 (for the full evidence tables and full GRADE profiles please see Appendix G: and G.2.34).

1 **Table 1: Summary of included studies examining distant recurrences**

Study reference	Study population and time between primary diagnosis and recurrence	Method used to analyse receptor status	Outcomes reported	Comments
Aurilio 2013	• Breast cancer patients with suspected bone metastases. • Median (range): 4.2 (0 – 18.9) years	• Immunohistchemical analysis • Fluorescence in situ hybridisation	• Change in ER, PR and HER-2 receptor expression between the two samples • Change in management	• Biopsy site: pelvic bones, sternum, vertebral bodies, ribs, skull, upper and lower limbs.
Andersen 1988	• Randomly selected patients with ipsilateral lymph node metastases • Range: 0 to 92 months	• 3 layer immunoperoxidase technique	• Change in ER receptor expression between the two samples	• Biopsy site: lymph node
Curigliano 2011	• Diagnosis of primary, unilateral breast cancer with development of liver recurrent disease. • Median (range): 3.4 years (0 – 18).	• Immunohistchemical analysis • Fluorescence in situ hybridisation	• Change in ER, PR and HER-2 receptor expression between the two samples • Change in management	• Biopsy site: liver
Duchnoswka 2012	• Unilateral breast cancer cases with synchronous or metachronous excised brain metastases. • Mean 3 years (no SD).	• Immunohistchemical analysis • Fluorescence in situ hybridisation	• Change in ER, PR and HER-2 receptor expression between the two samples	• Biopsy site: brain
Fabi 2011	• Invasive breast cancer between 1999 – 2007 and underwent biopsies to pathologically confirm presence of metastasis during follow-up. • Mean (range): 45.4 months (1 – 94)	• Immunohistochemical analysis, • Silver in situ hybridization , • Fluorescence in situ hybridisation	• Change in HER-2 receptor expression between the two samples	• Biopsy site: visceral disease non -visceral disease
Gancberg 2002	• Patients with samples from primary tumour and distant metastases.	• Immunohistchemical analysis • Fluorescence in situ hybridisation	• Change in HER-2 receptor expression between the two samples	• Bone, soft tissue, liver, lung or bronchus or pleura, stomach or duodenum or

Study reference	Study population and time between primary diagnosis and recurrence	Method used to analyse receptor status	Outcomes reported	Comments
	• Range : 1 months – 18 years			biliary tract or peritoneum, ovary, brain and other (not reported)
Hilton 2011	• Histologically confirmed breast cancer and radiological evidence of at least one bone metastasis that was amenable to CT-guided biopsy. • Time interval not reported.	• Not reported	• Change in ER/PR receptor expression between the two samples	• Biopsy site: bone
Hoefnagel 2010	• Metachronous non-bone distant metastases. • Time interval not reported.	• Immunohistochemical analysis	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site Brain , lung, liver, skin, gastro-intestinal
Idirisinghe 2010	• Primary breast carcinoma with subsequent histologically proven local recurrences and distant metastases. • Mean (range) : 46.1 months (0.7 – 175.4)	• Immunohistochemical analysis	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site: bone, skin, brain, lung, pleura, omentum, pericardium, ovary, intestine, adrenal gland, and liver.
Jensen 2012	• Patients with biopsies from distant metastases and paired samples • Median time from primary surgery to biopsy: 59 months (range: 8 – 323 months)	• Immunohistochemical analysis • Fluorescence In situ hybridisation • Chromogenic In situ hybridisation	• Change in HER-2 and ER receptor expression between the two samples	• CNS, bones, liver, skin, lungs, pleural effusion. abdomen (other than liver), lymph nodes chest, lymph nodes contralateral, other
Karagoz Ozen 2014	• Histological evidence of breast cancer. • Time interval not reported.	• Immunohistochemical analysis	• Change in ER/PR/HER-2 receptor expression between the two samples • Change in management	• Biopsy site: not reported
Lorincz 2006	• Bone metastatic samples of breast cancer	• Immunohistochemistry	• Change in HER-2 receptor expression between the two samples	• Biopsy site: Bone

Study reference	Study population and time between primary diagnosis and recurrence	Method used to analyse receptor status	Outcomes reported	Comments
	• Time interval not reported			
Lower 2005	• Patients with metastatic breast cancer. Median interval not reported.	• Not reported	• Change in ER/PR receptor expression between the two samples	• Biopsy site : local, lymph node; bone, lung, brain, liver, orbit, ovary, skin, colon, pancreas
Okita 2013	• Patients diagnosed with breast cancer and underwent surgical removal of brain metastases between 2010 – 2012. • Median overall survival – 6.5 yrs,	• HercepTest • Fluorescence in situ hybridization	• Change in ER/PR/HER-2 receptor expression between the two samples • Change in tumour type	• Biopsy site: breast and brain
Omoto 2010	• Patients diagnosed as having breast cancer and who underwent breast surgery and developed metachronous brain metastasis. • Mean : 44.5 months	• Histopathologic examination.	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biospy site: brain
Regitnig 2004	• Samples from primary tumour and distant metastases. • Mean (range): 45.5 months (2 – 103).	• Fluorescence in situ hybridisation • ELISA	• Change in HER-2 receptor expression between the two samples	• Biopsy site: Bone/bone marrow, skin other than ipsilateral breast, brain, lung or pleura , liver, pancreas, stomach, kidney, peritoneum and cervical lymph node.
Santinelli 2008	• metachronous breast cancer metastases (locoregional and distant). • Median interval not reported.	• Immunohistochemical analysis • Fluorescence in situ hybridisation	• Change in HER-2 receptor expression between the two samples	• Biopsy site: Bone, cervical, CNS , colon, liver,, lung, ovary, peritoneum, pleura, retroperitoneum , skin, stomach

Study reference	Study population and time between primary diagnosis and recurrence	Method used to analyse receptor status	Outcomes reported	Comments
Shen 2015	• Patients undergoing craniotomy for breast cancer brain metastasis. • Median (range): 46 months (0 – 266).	• Immunohistochemical analysis • Fluorescence in situ hybridisation	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site: brain
Shiino 2016	• Patients who underwent surgery for primary breast cancer between 1985 and 2013 in the database of the Department of Breast Surgery in the National Cancer Centre Hospital. • Time interval not reported.	• Immunohistochemical analysis	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site : Breast, chest wall, regional lymph node, lung, bone, liver, brain, distant lymph node, other metastatic sites
Shimizu 2000	• Patients who had undergone radical surgery for primary tumours and surgical resection of asynchronous metastatic lesions. • Mean (range) 19 months (5 – 104)	• Immunohistochemical analysis • Sandwich enzyme immunoassay	• Change in ER/PR/HER-2 receptor expression between the two samples	• Site not reported
Simmons 2009	• Suspected clinical or radiological recurrence. • Median (IQR range): 2.4 years (1.2 – 6.5).	• Immunohistochemical analysis • Fluorescence in situ hybridisation	• Change in ER/PR/HER-2 receptor expression between the two samples • Change in management	• Biopsy site: one, Soft tissue (not surgically curable) , Pleural effusion, Liver, Lung , CSF
Tapia 2007	• Availability of matched samples from primary tumour and distant metastases. • Median (range): 66 months (0 – 254)	• Fluorescence in situ hybridisation	• Change in HER-2 receptor expression between the two samples	• Biopsy site: Ascites, liver, lung, distant lymph nodes, pericardium, pleura, skin/soft tissue and central nervous system.
Vincent-Salomon 2002	• Availability of matched samples from primary	• Immunohistochemical analysis	• Change in HER-2 receptor expression between the two samples	• Biopsy site: liver, lung

Study reference	Study population and time between primary diagnosis and recurrence	Method used to analyse receptor status	Outcomes reported	Comments
	tumour and distant metastases. • Mean (range): 6.5 years (1 – 19).	• Fluorescence in situ hybridization (FISH).		
Wu 2008	• Patients with metastatic breast cancer. Time interval not reported.	• Immunohistochemical analysis • Fluorescence in situ hybridization (FISH).	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site - bone, liver
Yang 2014	• Patients who underwent biopsy or surgical resection of suspected recurrent breast cancer. • Time interval not reported.	• Immunohistochemical analysis • Fluorescence in situ hybridization (FISH).	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biposy site: distant soft tissue, lung, bone, liver, ovary, serous membranes, cutaneous lesions, gastrointestinal, renal
Zidan 2005	• Metastatic breast cancer with paired tumour samples available and suitable for immunohistochemistry analysis. • Median (range): 3.5 years (1 – 12).	• Immunohistochemical analysis • Fluorescence in-situ hybridisation	• Change in HER-2 receptor expression between the two samples • Change in management	• Biopsy site: one, skin/soft tissue, liver ,lung, pleura

Table 2: Summary of included studies examining mixed locoregional and distant metastases

Study reference (including study design)	Study population	Method used to analyse receptor status	Outcomes reported	Comments
Amir 2012	• Women with recurrent or progressive metastatic breast cancer and availability of archival primary tumour. • Median (range): 35 months (0 – 274).	• Fluorescence in situ hybridisation	• Change in ER/PR/HER-2 receptor expression between the two samples • Change in management • Adverse events	• Biopsy site: Lymph node (25), cutaneous (24), bone (20), liver (19), soft tissue (10), bone marrow (9), paracentesis (7), lung (5), central nervous system (2)

Study reference (including study design)	Study population	Method used to analyse receptor status	Outcomes reported	Comments
Andersen 1988	• Randomly selected patients with ipsilateral lymph node metastases • Randomly selected patients with at least one simultaneous or sequential biopsy from distant metastases • Range: 0 to 92 months	• 3 layer immunoperoxidase technique	• Change in ER receptor expression between the two samples	• Biopsy sites: ipsilateral lymph node and sites outside the ipsilateral mammary region, ipsilateral axilla or ipsilateral periclavicular region.
Arapantoni-Dadioti 2012	• Consecutive metachronous breast cancer metastases and local recurrences along with their primary tumours • Time interval not reported	• Immunohistochemistry	• Change in ER/PR/HER-2 receptor expression between the two samples	• Lymph nodes, other local recurrence. Skin, stomach, small bowel, large bowel, liver, thyroid gland, soft tissues, bone marrow, omentum, bones, lung, ovary.
Bogina 2011	• Breast cancer with histological samples of local recurrence/distant metastases and primary tumour samples on file. • Mean (range): 73.6 months (6 – 216 months)	• Immunochemistry • Silver in-situ hybridisation	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site : • Locoregional recurrence - Breast, axilla, homolateral clavicular nodes, Metasynchronous distant metastases - liver, lung pleura, bone, skin, ovary, peritoneum, stomach, duodenum, thyroid, cervix and node, Synchronous distant metastases – colon, bone, node, brain.
Chan 2012	• Patients seen from 1999 to 2009 with primary breast cancer and who had biopsy of a local or distant recurrence.	• In-situ hybridisation	• Change in HER-2 receptor expression between the two samples	• Biopsy site: breast, lymph nodes, chest wall, skin, bone, liver, brain, lung, others

Study reference (including study design)	Study population	Method used to analyse receptor status	Outcomes reported	Comments
Chang 2011	• Patients with HR and HER-2 results available from primary and metastatic tumours. Median time interval not reported.	• Immunohistochemistry (IHC).	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site: Liver, lung, lymph node, bone, others.
Dieci 2013	• Patients who underwent biopsy or surgical resection of suspected recurrent breast cancer. • Mean time 68 months (range 0.5 – 238 months)	• Histological sampling, details not reported	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site: distant metastases 63%, locoregional soft tissues or lymph nodes 37%
Dieci 2014	• Consecutive cases of patients who underwent biopsy or surgical resection of suspected recurrent breast cancer • Time interval not reported	• Immunohistochemistry	• Change in ER receptor expression between the two samples	• Distant (75%), Locoregional (25%)
Falck 2010	• Cohort of patients treated with adjuvant tamoxifen for 2 years. • Time interval not reported.	• Unclear – embedded in paraffin blocks.	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site : primary tumour (breast), one from corresponding lymph node
Gomez-Fernandez 2008	• Presence of local recurrence and/or distant metastases • Distant metastases occurred up to 21 years after the primary diagnosis. Locoregional recurrence occurred from 2 months to 7 years later.	• Immunohistochemistry	• Change in ER receptor expression between the two samples	• Chest wall, skin, ipsilateral breast, bone, brain, female genital tract, gastrointestinal tract, kidney, liver, lung, gallbladder, serosal surfaces

Study reference (including study design)	Study population	Method used to analyse receptor status	Outcomes reported	Comments
Gong 2005	• Known HER-2 status from primary tumours and paired metastatic tumours. • Time interval not reported.	• Flourescence in situ hybridisation	• Change in HER-2 receptor expression between the two samples	• Biopsy site: Locoregional - axillary lymph node, soft tissue chest, supraclavicular lymph node, Distant – Lung, liver, pleura, bone.
Gong 2011	• Identified metastatic breast carcinomas between 2003 and 2008. • Median 61 months (range 1.5 – 275 months)	• Immunohistochemical staining	• Change in ER receptor expression between the two samples	• Biopsy site: locoregional: axillary lymph node, supraclavicular lymph node, infraclavicular lymph node, Ipsilateral anterior chest wall. Distant metastases: lung, liver, effusion fluid, bone, distant lymph node, distant soft tissue, other visceral organs.
Guarneri 2008	• Diagnosis of breast cancer with available samples from primary tumour and metastatic site. Median (range) : Locoregional 42.8 months (7.2 – 197.4) : Distant 54.2 months (7.4 – 308.2)	• Immunohistochemistry • Fluorescence in situ hybridisation	• Change in ER/PR/HER-2 receptor expression between the two samples	• Patients with stage IV disease at diagnosis were included only in cases when sampling of metastases was performed on metachronous lesions. • Biopsy site : locoregional soft tissues, liver, central nervous system, bone, pleura, distant soft tissues, stomach/colon/peritoneum) ,bronchus, and bone marrow.
Holdaway 1983	• Serial receptor measurements over a five year period.	• Unclear, dextran-charcoal assay used	• Change in ER/PR receptor expression between the two samples	• Biopsy site : ipsilateral axillary lymph nodes, ipsilateral supraclavicular lymph nodes, contralateral lymph nodes, locoregional chest wall, skin metastases beyond chest,

Study reference (including study design)	Study population	Method used to analyse receptor status	Outcomes reported	Comments
				opposite breast and visceral sites
Kamby 1989	• Patients with primary locally advanced breast cancer or with distant metastases at the time of initial diagnosis were also included. • Median 27 months (25-75%: 11-50 months)	• Immunohistochemistry	• Change in ER receptor expression between the two samples	• Biopsy site: Bone, Liver, regional lymph nodes
Kuukasjarvi 1996	• Primary breast carcinomas and matched asynchronous recurrent tumours • Median (range): 25 (3 to 228)	• Immunohistochemistry	• Change in ER and PR receptor expression between the two samples	• Biopsy site: supraclavicular, pelvis, bone marrow, lung , distant soft tissues, abdominal cavity
Lindstrom 2012	• Diagnosis of local or systemic breast cancer relapse from January 1997 to December 2007 • Time interval not reported	• Immunohistochemical/immunocytochemical methods	• Change in ER, PR and HER-2 receptor expression between the two samples	• Biopsy site: Local and systemic relapse (specific sites not reported)
Lower 2005	• Patients with metastatic breast cancer. Median interval not reported.	• Not reported	• Change in ER/PR receptor expression between the two samples •	• Biopsy site : local, lymph node; bone, lung, brain, liver, orbit, ovary, skin, colon, pancreas
Macfarlane 2012	• Diagnosis of breast cancer and a biopsy-proven local, regional, or distant relapse. Median (range) : 35 months (4–149).	• Not reported	• Change in ER/HER-2 receptor expression between the two samples	• Biopsy site : Locoregional (34), regional (99), distant (27)

Study reference (including study design)	Study population	Method used to analyse receptor status	Outcomes reported	Comments
Masood 2000	• Metastatic breast cancer • Time interval not reported	• Immunohistochemistry	• Change in HER-2 receptor expression between the two samples	• Biopsy site: lymph node, skin, liver, spleen, lung, bone
Mobbs 1987	• Primary and secondary breast carcinoma specimens from patients undergoing breast surgery • Time interval not reported	• Receptor assays using cytosol preparation	• Change in ER, PR receptor expression between the two samples	• Biopsy site: lymph nodes, chest wall, breast tissue, mastectomy scar, muscle of the back, abdominal wall, lung, neck muscle, peritoneum
Niehans 1993	• Tumour tissue obtained at autopsy from two to five metastatic organ sites in patients who died with metastatic breast carcinoma.	• Formalin-fixed, paraffin-embedded tissue	• Change in HER-2 receptor expression between the two samples	• Biopsy site : Breast, lung, liver, lymph node, skin, ovary, central nervous system, adrenal, stomach, bowel, contralateral breast, kidney, spleen, omentum and heart •
Nishimura 2011	• Patients from whom the lesion was resected either by surgery or biopsy and evaluated by immunostaining. • Time interval not reported	• Immunostaining	• Change in ER/PR/HER-2 receptor expression between the two samples	• Chest wall, In-breast, Regional lymph node, Lung, Bone, Brain, Ovary, Distant skin.
Sari 2011	• Female patients having biopsy-proven recurrent breast carcinoma. Time interval not reported.	• Immunohistochemical analysis • Fluorescence in situ hybridisation	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site : Locoregional disease, Distant soft tissue, Liver, Serous membranes, Lung, Bone, Ovary, Brain, Other
Shiino 2016	• Patients who underwent surgery for primary breast cancer between 1985 and 2013 in the database of the Department of Breast	• Immunohistochemical analysis	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site : Breast, chest wall, regional lymph node, lung, bone, liver, brain, distant lymph node, other metastatic sites

Study reference (including study design)	Study population	Method used to analyse receptor status	Outcomes reported	Comments
	Surgery in the National Cancer Centre Hospital. • Time interval not reported.			
Saedi 2012	• Patients with primary tumours and recurrent sites of breast cancer • Time interval: mean (SD) : 23.54 months (19.17)	• Immunohistochemistry	• Change in ER/PR receptor expression between the two samples	• Locoregional (26), bone (4), lung (2), brain (2), liver (1).
Sekido 2003	• Asynchronous metastatic/recurrent breast cancer tumours • Time interval not reported	• Immunohistochemistry/FISH	• Change in ER/PR/HER-2 receptor expression between the two samples	• Chest wall, Skin, Lung, Lymph node
Spataro 1992	• Breast cancer patients with availability of ER assay from both primary tumour and from a biopsy-accessible relapse site. Median: 22 months (2 – 122)	• Not reported	• Change in ER receptor expression between the two samples	• Biopsy site : Breast, regional and breast, distant soft tissue, contra-lateral breast, bone, visceral.
Soomro 2014	• Female patients having biopsy-proven recurrent breast carcinoma. Mean (SD) : 2.3 years (1.9)	• Immunohistochemistry • Fluorescence In Situ Hybridization	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site: breast
Tanner 2001	• Breast cancer patients with tumor samples available from untreated primary tumoursand later clinically manifested metastatic tumour deposits. Time interval not reported.	• Immunostaining and in situ hybridisation	• Change in HER-2 receptor expression between the two samples	• Local or regional and were hematogeneously-spread distant metastases (no other details reported).
Thompson 2010	• Patients with a formalin fixed paraffin-embedded (FFPE) tumour sample	• Fixed paraffin-embedded (FFPE)	• Change in ER/PR/HER-2 receptor expression between the two samples	• Biopsy site: Unclear, states: locoregional 64.2%, distant

Study reference (including study design)	Study population	Method used to analyse receptor status	Outcomes reported	Comments
	available from both the primary cancer and the recurrence. Mean 8 years (93.2 months).			soft tissues 11.7%, other distant metastasis 24.1%.
Wilking 2011	• Breast cancer patients with relapse • Time interval not reported	• Immunohistochemistry, immunocytochemistry and fluorescent in situ hybridisation	• Change in HER-2 receptor expression between the two samples	• Bone/bone marrow, liver, local recurrence, lung or pleura, axillary lymph nodes, skin, supra clavicular lymph nodes, and other sites

1

2.41 Health economic evidence review

2.4.12 Methods

3 Evidence of cost effectiveness

4 The Committee is required to make decisions based on the best available evidence of both
5 clinical and cost effectiveness. Guideline recommendations should be based on the expected
6 costs of the different options in relation to their expected health benefits rather than the total
7 implementation cost.

8 Evidence on cost effectiveness related to the key clinical issues being addressed in the
9 guideline update was sought. The health economist undertook a systematic review of the
10 published economic literature.

11 Economic literature search

12 A systematic literature search was undertaken to identify health economic evidence within
13 published literature relevant to the review questions. The evidence was identified by
14 conducting a broad search in the NHS Economic Evaluation Database (NHS EED) and the
15 Health Technology Assessment database (HTA). The search also included Medline and
16 Embase databases using an economic filter. Studies published in languages other than
17 English were not reviewed. The health economic search strategies are detailed in Appendix
18 J.

19 The health economist also sought out relevant studies identified by the surveillance review or
20 Committee members.

21 Economic literature review

22 The health economist:

23 • Identified potentially relevant studies for each review question from the economic search
24 results by reviewing titles and abstracts. Full papers were then obtained.
25 • Reviewed full papers against pre-specified inclusion and exclusion criteria to identify
26 relevant studies.
27 • Critically appraised relevant studies using the economic evaluations checklist as specified
28 in *Developing NICE Guidelines: the manual*.
29 • Generated summaries of the evidence in economic evidence profiles.

30 Inclusion and Exclusion criteria

31 Full economic evaluations (studies comparing costs and health consequences of alternative
32 courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence
33 analyses) and comparative costing studies that address the review question in the relevant
34 population were considered potentially includable as economic evidence.

35 Studies that only reported burden of disease or cost of illness were excluded. Literature
36 reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and
37 studies not in English were excluded.

38 Remaining studies were prioritised for inclusion based on their relative applicability to the
39 development of this guideline and the study limitations. For example, if a high quality, directly
40 applicable UK analysis was available, then other less relevant studies may not have been

included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix L).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual*.

Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, new economic analysis was undertaken by the health economist.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case as far as possible
- The Committee was involved in the design of the model, selection of inputs and interpretation of results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available, Committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was quality assured by another health economist within NICE's Centre for Clinical Practice.

Full methods for the cost-effectiveness analysis conducted for this guideline are described in the Economic Modelling section.

Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*. As the evaluation in this analysis was a cost consequences analysis rather than a cost utility analysis, outputs were reported in terms of incremental cost per breast cancer case prevented, rather than the incremental cost per QALY. Therefore, results were not directly comparable to a £20,000 per QALY threshold. However, the analysis did present results in terms of the QALY gain required per breast cancer case averted in order for each intervention to be cost effective at a £20,000 threshold. This allowed committee members to assess the likely cost effectiveness of interventions according to their experience of the disease area.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review, and de novo modelling was not feasible or prioritised, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

2.4.2 Results of the economic literature review

The search returned 1659 articles, four of which were ordered after screening of based on title and abstract. All four were excluded on screening of full text. The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix L.

Appendix M: contains a list of excluded studies and the reason for their exclusion.

2.4.3 Economic modelling

2.4.3.1 Introduction

For breast cancer, the evidence review for this update showed that ER/PR/HER-2 status may differ between primary and recurrent tumours. Of these markers, a change in HER-2 status has the largest impact on change in management, as HER-2-positive tumours are responsive to treatment with trastuzumab, and other therapies such as pertuzumab and trastuzumab emtansine. The objective of this simple analysis is to estimate the cost effectiveness of testing HER-2 status in recurrent breast cancer for both locoregional and distant metastatic tumours, compared to no testing. Cost effectiveness of changes in ER and PR status were not assessed explicitly, as differences in treatments (and resulting costs) are primarily determined by HER-2 status.

2.4.3.2 Methods

2.4.3.2.1 Model structure

For each recurrent tumour type (locoregional and distant metastatic), decision trees were constructed for two subpopulations: patients with a HER-2-positive primary tumour and patients with a HER-2-negative primary tumour, shown in Figure 1 and **Error! Reference source not found.**. For each tree, in the 'test HER-2 status' arm, all patients diagnosed with a HER-2-positive tumour were treated with trastuzumab, while patients with HER-2-negative tumours did not receive trastuzumab. The assumption was made that HER-2 status testing is 100% accurate in the model. In the 'do not test HER-2 status arm' patients were treated according to their primary tumour status – patients with a HER-2-positive primary tumour were all treated with trastuzumab, and vice versa.

To calculate cost effectiveness, costs and QALY outcomes comparing treatment of HER-2-positive tumours with and without trastuzumab from the literature and relevant technology appraisals were appended to the terminal nodes of the decision tree. For patients with HER-2-negative tumours it was assumed that treatment costs were equivalent to those of patients with HER-2-positive tumours (dependent on whether patients received trastuzumab or not). Conversely, it was assumed that patients with HER-2-negative tumours had the same number of QALYs whether they received trastuzumab or not.

Figure 1: Decision tree for patients with HER-2-positive primary tumour

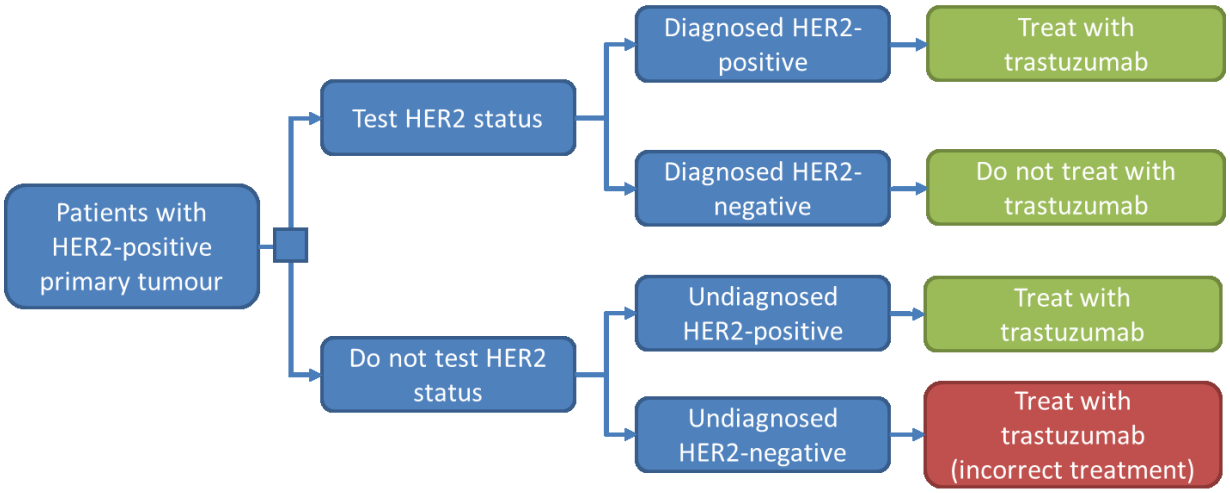
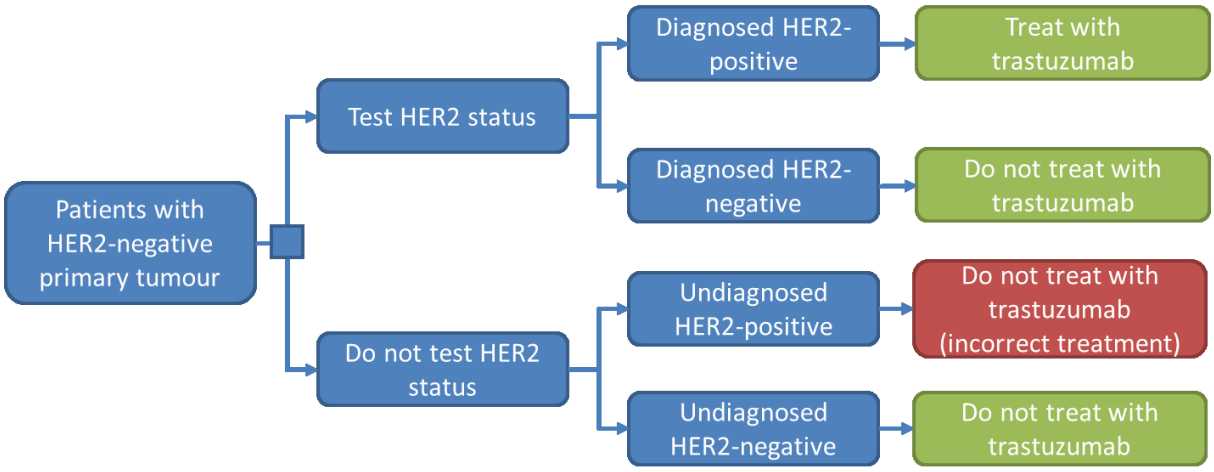
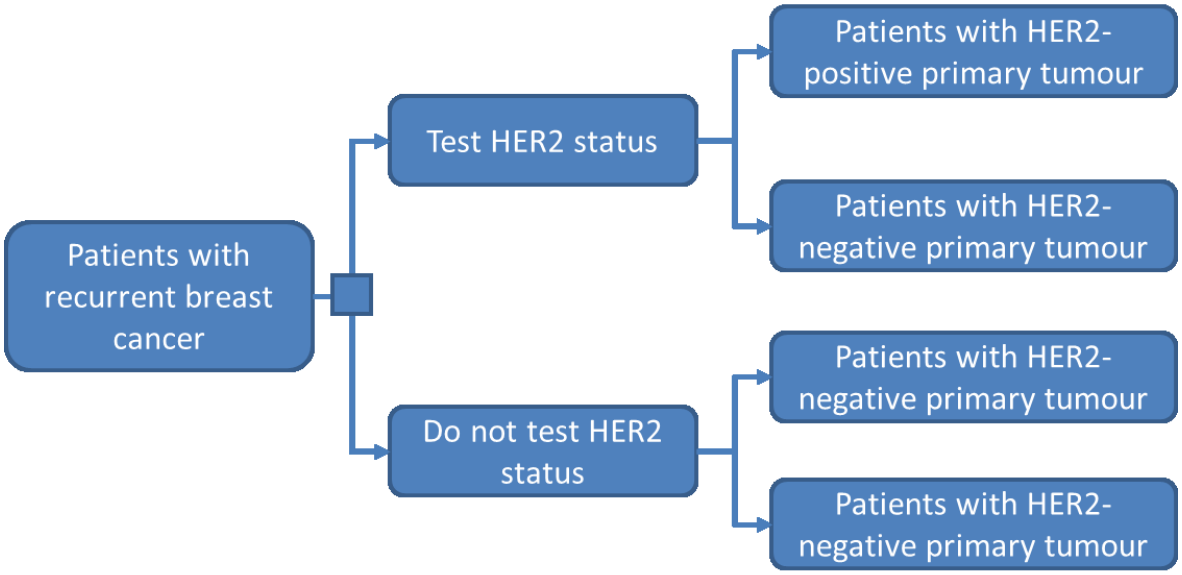


Figure 2: Decision tree for patients with HER-2-negative primary tumour



For each recurrent tumour type, a third decision tree (shown in Figure 3) was constructed to calculate the overall cost effectiveness of HER-2 testing for the entire population (both patients with HER-2-positive and HER-2-negative primary tumours) by combining the outputs of the first two decision trees.

Figure 3: Decision tree for all patients (HER-2-positive and HER-2-negative primary tumour)



In order to assess the overall cost effectiveness of HER-2 status testing across patients with either type of recurrent cancer, results were also combined using an estimate of the relative proportion of patients with locoregional and distant metastatic breast cancer.

2.4.3.2.27 Probabilities

Probabilities used to inform the model are shown in Table 2. These values were calculated via meta-analyses of values from studies included in the clinical literature review, using all studies which reported data on HER-2 status for locoregional and distant metastatic populations separately. This was achieved using a Bayesian predictive distribution calculated via WinBUGS software, consistent with the advice in the NICE DSU Technical Support Document 5 (Dias et al, 2011). A predictive distribution captures uncertainty by producing estimates of unobserved future observations and therefore generally produces wider confidence intervals than a posterior distribution.

To assess the overall cost effectiveness of HER-2 status testing across patients with either type of recurrent cancer, an estimate of 56% for the proportion of patients with locoregional cancer was derived from studies included in the clinical review which included both locoregional and distant metastatic cancers, and reported the number of patients with each type of cancer. This was again achieved via a meta-analysis using a Bayesian predictive distribution.

Table 2: Probabilities used to inform decision trees

	Locoregional metastases (95% CIs)	Distant metastases (95% CIs)
Proportion of patients with HER-2-positive primary tumour	34.2% (4.3%-82.1%)	26.9% (8.6%-54.5%)
Probability of recurrent tumour being HER-2-positive, given primary tumour is HER-2-negative	8.5% (0.5%-35.3%)	9.4% (1.5%-28%)
Probability of recurrent tumour being HER-2-negative, given primary tumour is HER-2-positive	13.1% (<0.1%-79.0%)	20.4% (4.7%-49.6%)

2.4.3.2.31 *Costs of biopsy and HER-2 testing*

Costs of biopsy for distant metastatic cancer and HER-2 tests are displayed in Table 3. The cost of biopsy was calculated by taking an average of costs of biopsy procedures for common distant metastasis locations from the NHS National Schedule of Reference costs 2015-16 (percutaneous biopsy of lesion of pleura, percutaneous biopsy of lesion of lung or mediastinum, percutaneous transvascular biopsy of lesion of liver, percutaneous punch biopsy of lesion of liver [19 years and over], and image guided biopsy of lesion of bone). The cost of biopsy was not included for locoregional breast cancer, as patients are generally biopsied as standard practice for reasons other than assessing HER-2 status.

The assumption was made that (for both locoregional and distant metastatic cancer) HER-2 status is tested by immunohistochemistry (IHC) in the first instance, with 25% of patients requiring fluorescence in situ hybridisation (FISH) as a confirmatory test.

Table 3: Costs of biopsy and HER-2 status tests

Category	Cost	Source
Biopsy of distant metastases	£885	NHS National Schedule of Reference Costs 2015-16*
Immunohistochemistry (IHC)	£35	TA107 manufacturer's submission
Fluorescence in situ hybridisation (FISH)	£120	Price charged for FISH at University College London

*Calculated from a simple mean of percutaneous biopsy of lesion of pleura, percutaneous biopsy of lesion of lung or mediastinum, percutaneous transvascular biopsy of lesion of liver, percutaneous punch biopsy of lesion of liver (19 years and over), and image guided biopsy of lesion of bone

2.4.3.2.47 *Costs and QALYs of breast cancer treatment*

For distant metastatic cancer, discounted lifetime costs and QALYs of treatment with and without trastuzamab combination therapy were taken from the manufacturer's submission for TA34 (guidance on the use of trastuzumab for the treatment of advanced breast cancer). These values are shown in Table 4, along with life years for each strategy, for reference purposes.

Table 4: Costs, QALYs, and life years for treatment of advanced HER-2 positive breast cancer with and without trastuzumab combination therapy from manufacturer's submission for TA34

	Cost	QALYs	Life years
Treatment without trastuzumab	£10,904	0.27	0.55
Treatment with trastuzumab	£28,574	0.76	1.87

For locoregional cancer, costs and QALYs of treatment with and without trastuzumab were taken from an economic evaluation of trastuzumab for early stage breast cancer (Hall et al, 2010). These values are shown in Table 5 (again, along with life years for reference purposes).

Table 5: Costs, QALYs, and life years for treatment of early HER-2 positive breast cancer with and without trastuzumab from Hall et al (2010). NB – only

incremental costs and QALYs were available, but this does not affect the ICERs produced by the model

	Cost	QALYs	Life years
Treatment without trastuzumab	£0	0	0
Treatment with trastuzumab	£12,629	0.49	0.60

2.4.3.2.5 Sensitivity analysis

For both populations (distant metastatic and locoregional cancer) deterministic sensitivity analyses were conducted for the following scenarios:

- Proportion of patients changing HER-2 status: Since the studies identified in the clinical review reported widely varying proportions of patients with a change in HER-2 status, sensitivity analyses were carried out in which these proportions were first halved and then doubled relative to the base case (for both patients with a HER-2-negative and a HER-2-positive primary tumour) in order to test the cost-effectiveness of testing HER-2 status under extreme scenarios. In addition, threshold analyses were carried out to quantify the proportion of patients changing status required for testing patients with a HER-2-positive primary tumour to no longer be cost saving.
- Cost of HER-2 status testing: In order to reflect that some centres use dual-colour dual-hapten brightfield in situ hybridisation (DDISH) testing, rather than FISH, as a confirmatory test, an analysis in which a plausible lower bound cost of £90 for DDISH was conducted

The following sensitivity analyses were conducted for the distant metastatic population:

- Cost of biopsy: Since biopsy costs vary greatly according to the location of metastasis, sensitivity analyses were carried out in which the midpoint between the lowest value and the mean (£779), and the highest value and the mean (£1,068) were used for the cost of biopsy.
- No biopsy cost: The cost of biopsy was removed, to represent a scenario in which patients with distant metastatic cancer are biopsied by default.
- Biopsy cost halved: The cost of biopsy was set to a value of £443, in order to reflect a scenario in which half of patients with distant metastatic cancer are biopsied by default.

For the locoregional population a sensitivity analysis was conducted in which cost and QALY outcomes of TA34 (for advanced breast cancer) were used instead of the Hall et al (2010) values for early breast cancer.

2.4.3.3 Results

2.4.3.3.1 Distant metastatic cancer

Cost effectiveness results for patients with distant metastatic breast cancer are shown in **Error! Reference source not found.**. These results show that, for patients with a HER-2-positive primary tumour, HER-2 testing dominates no testing. This is because the cost of HER-2 testing is more than offset by the cost saving of preventing patients with HER-2-negative tumours from unnecessarily being treated with trastuzamab. However, testing patients with a HER-2-negative primary tumour results in an ICER of £56,116/QALY, as this strategy is associated with both the additional cost of testing for HER-2 status, as well as treating patients with HER-2-positive tumours with trastuzamab. The ICER for testing all patients' HER-2 status is somewhat lower – £34,992/QALY – due to costs being partially offset by the savings from patients with HER-2-positive primary tumours.

Table 6: Cost effectiveness results for patients with distant metastatic cancer

Patient group	Incremental cost (HER-2 testing versus no testing)	Incremental QALYs (HER-2 testing versus no testing)	ICER (HER-2 testing versus no testing)
HER-2-positive primary tumour	-£2,669	0	HER-2 testing dominates no testing
HER-2-negative primary tumour	£2,611	0.04	£56,116
All patients	£1,190	0.03	£34,992

2.4.3.3.22 Locoregional cancer

Results for patients with locoregional recurrent breast cancer are shown **Error! Reference source not found.**, using treatment costs and QALYs from TA34 and Hall et al (2010), respectively. Both sets of results show that testing HER-2 status in patients with a HER-2-positive primary tumour dominates no testing, due to cost savings from prevention of treating HER-2-negative tumours with trastuzamab. ICERs for testing HER-2 status in patients with HER-2-negative primary tumours are considerably lower than those of the distant metastatic cancer population (£27,387/QALY). This is primarily due to biopsy costs not being included for locoregional cancer patients (due to biopsies being carried out routinely in this population for reasons other than assessing HER-2 status). ICERs of the locoregional cancer population overall (£7,602/QALY) are similarly lower than those of the distant metastatic population, and indicate that testing HER-2 status is likely to be cost effective if the population is considered as a whole.

Table 7: Cost effectiveness results for patients with locoregional cancer

Patient group	Incremental cost (HER-2 testing versus no testing)	Incremental QALYs (HER-2 testing versus no testing)	ICER (HER-2 testing versus no testing)
HER-2-positive primary tumour	-£1,583	0	HER-2 testing dominates no testing
HER-2-negative primary tumour	£1,140	0.04	£27,387
All patients	£208	0.03	£7,602

2.4.3.3.36 Combined population

Table 8 shows the cost effectiveness results for distant metastatic and locoregional populations combined. As in the individual subpopulations, testing patients with a HER-2-positive primary tumour dominates no testing. Testing patients with a HER-2-negative primary tumour results in an ICER of £41,501 compared to no testing, while testing for the whole population with recurrent breast cancer has an ICER of £21,058.

Table 8: Cost effectiveness results for distant metastatic and locoregional populations combined

Patient group	Incremental cost (HER-2 testing versus no testing)	Incremental QALYs (HER-2 testing versus no testing)	ICER (HER-2 testing versus no testing)
HER-2-positive primary tumour	-£1,995	0	HER-2 testing dominates no testing
HER-2-negative primary tumour	£1,822	0.04	£41,501
All patients	£638	0.03	£21,058

2.4.3.3.41 Sensitivity analysis

Sensitivity analysis results for patients with distant metastatic cancer are shown in Table 9, and results for patients with locoregional cancer are shown in Table 10. Sensitivity analysis results for the two populations combined are shown in Table 11.

For patients with distant metastatic cancer, results show that retesting receptor status in patients with a HER-2-positive primary tumour remains dominant over no testing in all scenarios. Contrastingly, the ICER of retesting in patients with a HER-2-negative tumour varies quite considerably in a number of scenarios. Specifically, the ICER is considerably reduced when the cost of biopsy is removed or halved, showing that retesting HER-2 status is substantially more cost effective if patients are already receiving a biopsy as a matter of standard procedure. The ICER is also sensitive to variation in the proportion of patients changing HER-2 status. Changing the cost of biopsy to plausible lower and upper bounds also affects the ICER, but to a lesser degree. Results are relatively insensitive to a change in the cost of FISH.

For patients with locoregional cancer, results are most sensitive to using cost and QALY outcomes from TA34 (advanced breast cancer) rather than from Hall et al (2010). This results in a substantial increase in the ICER of retesting in patients with a HER-2-negative primary tumour to £37,239/QALY, although retesting in patients with a HER-2-positive primary tumour remains dominant over no testing. Comparatively, results are insensitive to variations in the proportion of patients changing HER-2 status and the cost of FISH.

Table 9: Sensitivity analysis results for patients with distant metastatic cancer

Scenario	ICER for HER-2-positive primary tumour	ICER for HER-2-negative primary tumour	ICER for all patients
Base case	HER-2 testing dominates no testing	£56,116	£34,992
Proportion of patients changing HER-2 status halved	HER-2 testing dominates no testing	£76,536	£62,934
Proportion of patients changing HER-2 status doubled	HER-2 testing dominates no testing	£45,907	£21,022
Cost of FISH set to £90	HER-2 testing dominates no testing	£55,955	£34,772
Cost of biopsy set to £779	HER-2 testing dominates no testing	£53,831	£31,864
Cost of biopsy set to £1,068	HER-2 testing dominates no testing	£60,054	£40,380
No cost of biopsy	HER-2 testing dominates no testing	£37,094	£8,962
Cost of biopsy halved	HER-2 testing dominates no testing	£46,605	£21,977

Table 10: Sensitivity analysis results for patients with locoregional cancer

Scenario	ICER for HER-2-positive primary tumour	ICER for HER-2-negative primary tumour	ICER for all patients
Base case	HER-2 testing dominates no testing	£27,387	£7,602

Scenario	ICER for HER-2-positive primary tumour	ICER for HER-2-negative primary tumour	ICER for all patients
Proportion of patients changing HER-2 status halved	HER-2 testing dominates no testing	£28,948	£9,975
Proportion of patients changing HER-2 status doubled	HER-2 testing dominates no testing	£26,607	£6,415
Cost of FISH set to £70	HER-2 testing dominates no testing	£27,087	£7,146
Cost and QALY outcomes used from TA34	HER-2 testing dominates no testing	£37,239	£9,572

Table 11: Sensitivity analysis results for distant metastatic and locoregional populations combined

Scenario	ICER for HER-2-positive primary tumour	ICER for HER-2-negative primary tumour	ICER for all patients
Base case	HER-2 testing dominates no testing	£41,501	£21,058
Proportion of patients changing HER-2 status halved	HER-2 testing dominates no testing	£52,327	£35,993
Proportion of patients changing HER-2 status doubled	HER-2 testing dominates no testing	£36,088	£13,591
Cost of FISH set to £90	HER-2 testing dominates no testing	£41,331	£20,811
Cost of biopsy set to £779	HER-2 testing dominates no testing	£40,378	£19,522
Cost of biopsy set to £1,068	HER-2 testing dominates no testing	£43,436	£23,705
No cost of biopsy	HER-2 testing dominates no testing	£32,156	£8,270
Cost of biopsy halved	HER-2 testing dominates no testing	£36,829	£14,664

Threshold analysis of the proportion of patients changing HER-2 status showed that, for retesting to no longer dominate no testing in patients with a HER-2-positive primary tumour, the proportion changing from HER-2-positive to HER-2-negative status would have to be below 5.4% for patients with distant metastases, and below 3.7% for patients with locoregional recurrence. Since these values are very substantially lower than the estimates used in the base case, this reinforces the robustness of the cost effectiveness of retesting receptor status in patients with a HER-2-positive primary tumour.

2.4.3.41 Discussion

In patients with locoregional recurrent breast cancer results indicate that, for the population as a whole and for the subgroup of patients with HER-2-positive primary tumours, testing HER-2 status is likely to be cost effective, as ICERs are well below £20,000/QALY for results using both sets of cost and QALY outputs. For the subgroup of patients with HER-2-negative

primary tumours, the ICER is considerably higher (£27,387), due to additional costs of HER-2 status testing and of treating the identified HER-2-positive patients with trastuzumab. However, it should be noted that this value is not substantially higher than the ICER for treating patients with known HER-2-positive status (£25,826/QALY). Therefore, considering that NICE recommends trastuzumab in TA107 and TA34, and therefore considers it to be a cost effective treatment for early and advanced breast cancer, it is also likely that testing HER-2 status in locoregionally recurrent cancer is also cost-effective.

In patients with distant metastatic cancer, base case results show that ICERs for both the population as a whole and for the subgroup of patients with HER-2-negative primary tumour are considerably higher than those for locoregionally recurrent cancer (£34,992 and £56,116, respectively). This is largely due to the additional cost of biopsy, as patients with distant metastatic cancer are not routinely biopsied, and the higher ICER for trastuzumab in patients with advanced breast cancer (around £35,700/QALY). It should be noted, however, that this analysis potentially overestimates ICERs for the distant metastatic population, as the appraisal committee for TA34 noted that the manufacturer's submission likely underestimates the QALY gains produced by trastuzumab due to underestimation of the survival benefit provided by trastuzumab (although an alternative ICER was not provided).

Sensitivity analysis results show that ICERs for distant metastatic patients with a HER-2-negative primary tumour are particularly sensitive to changes in the proportion of patients changing HER-2 status. However, ICERs are not changed to a degree that is likely to affect decision making. Furthermore, threshold analysis has shown that the proportion of patients changing HER-2 status would have to be substantially lower for retesting to no longer dominate no testing in patients with a HER-2-positive primary tumour, demonstrating that the cost effectiveness of retesting in these patients is robust. Removing the cost of biopsy for the distant metastatic cancer subgroup results in a substantially lower ICER of £37,094. While this value is still higher than the conventional NICE upper threshold for cost effectiveness, the same consideration applies as with the equivalent locoregional population: since the ICER for trastuzumab in TA34 is around £35,700/QALY, if the treatment is accepted to be cost effective it is highly likely that retesting in this population is also cost effective for patients who would receive a biopsy regardless of intention to test HER-2 status.

Sensitivity analyses in patients with locoregional cancer show that ICERs are relatively stable, with the exception of the scenario in which costs and QALY outcomes from TA34 are used in place of the Hall et al (2010) values, which produces an ICER of £37,239 for patients with a HER-2-negative primary tumour. For this result, the previous argument applies that if trastuzumab is considered cost effective at an ICER of £35,700/QALY, it is also likely that testing HER-2 status is also cost effective, even in this conservative scenario.

Finally, the scenario combining results for both locoregional and distant metastatic cancer shows that considering the entire population produces an ICER of £21,058 for HER-2 testing, compared to no testing. This indicates that, if this perspective is taken, HER-2 testing is likely to be cost effective, as the ICER is lower than that of treating patients with confirmed HER-2-positive status with trastuzumab compared to treatment without trastuzumab.

It should be noted that this model simplifies clinical reality in a number of key ways. First, in practice, other treatments besides trastuzumab are provided to patients with HER-2-positive breast cancer, such as pertuzumab and trastuzumab emtansine. Due to these treatments being compared to trastuzumab, rather than to no treatment, in the relevant technology appraisals, including them in the economic analysis was not practical. However, it is reasonable to assume that including these treatments in the analysis would increase the mean cost of treatment for HER-2 positive patients due to the extra drug cost, and therefore increase the overall cost of testing patients with a HER-2-negative primary tumour. The effect on ICERs is less clear, but given an ICER of £23,467 for pertuzumab and trastuzumab compared to trastuzumab alone (evidence review group's base case ICER for TA424) and an ICER of £166,400 for trastuzumab emtansine after treatment with trastuzumab (evidence

review group's base case ICER for TA371), it is likely that including these treatments in the analysis would respectively slightly lower and substantially increase the ICER for testing HER-2-negative patients.

Second, it is likely that, in reality, HER-2-negative patients treated as if they were HER-2 positive would not have identical QALY outcomes to appropriately treated HER-2-negative patients. This is because of the toxicity associated with trastuzumab, and also due to those patients foregoing other management options specific to their disease status. Third, a substantial proportion of patients with distant metastatic cancer are biopsied independently of the intention of testing HER-2 status in practice, meaning that the model underestimates the cost effectiveness of retesting receptor status in patients with distant metastatic cancer, although, as noted above, even if all patients receive a biopsy as standard practice the ICER is still only reduced to £37,094/QALY. Fourth, the analysis does not consider the quality of life decrement or risks associated with biopsy procedures, although, due to the short duration of biopsy, the effect on total QALYs is unlikely to be substantial.

In summary, despite the limitations of the analysis, it is likely that testing of HER-2 status is cost effective in patients with locoregionally recurrent breast cancer, providing that these patients are biopsied as part of routine practice. For patients with distant metastatic breast cancer, testing HER-2 status in patients with HER-2-positive primary tumours is also likely to be cost effective, although the cost effectiveness of testing in patients with HER-2-negative primary tumours, and for the population as a whole is ambiguous. The key driver of this difference is the additional cost of biopsy associated with distant metastatic cancer, and the lower cost effectiveness of treating patients with distant metastatic cancer with trastuzumab.

2.4.43 Unit costs

Basic unit costs related to this review question are detailed in Table 12.

Table 12: Unit costs

Code	Description	Unit cost
YJ01Z	Bilateral Core Needle Biopsy of Lesions of Breasts	£380.13
YJ02Z	Unilateral Core Needle Biopsy of Lesion of Breast	£302.92
YJ03Z	Core Needle Biopsy of Lesion of Breast and Associated Lymph Nodes	£534.09
YJ04Z	Core Needle Biopsy of Axillary Lymph Nodes	£1,523.50
YJ05Z	Bilateral Fine Needle Aspiration of Lesions of Breasts	£239.07
YJ06Z	Unilateral Fine Needle Aspiration of Lesion of Breast	£234.24
YJ07Z	Fine Needle Aspiration of Lesion of Breast and Associated Lymph Nodes	£368.76
YJ08Z	Fine Needle Aspiration Cytology of Axillary Lymph Nodes	£283.87
YJ09Z	Vacuum Assisted Biopsy of Lesion of Breast	£251.35
YJ10Z	Wire Guided Biopsy of Lesion of Breast	£608.02
FZ52Z	Diagnostic Colonoscopy with Biopsy, 19 years and over	£604.02
FZ55Z	Diagnostic Flexible Sigmoidoscopy with Biopsy, 19 years and over	£480.76
FZ61Z	Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over	£469.18
FZ64A	Combined Upper and Lower Gastrointestinal Tract Diagnostic Endoscopic Procedures with Biopsy, 19 years and over	£680.70
GB10Z	Diagnostic Endoscopic Retrograde Cholangiopancreatography, with Biopsy or Cytology	£942.52
GB12Z	Endoscopic Ultrasound Examination, of Hepatobiliary or Pancreatic Duct, with Biopsy or Cytology	£751.15
MA32Z	Diagnostic Hysteroscopy with Biopsy	£507.97

Code	Description	Unit cost
MA37Z	Transvaginal Ultrasound with Biopsy	£217.88
MA39Z	Diagnostic Colposcopy with Biopsy	£219.21
YD02Z	Percutaneous Biopsy of Lesion of Pleura	£881.21
YD03Z	Percutaneous Biopsy of Lesion of, Lung or Mediastinum	£781.52
YG10Z	Percutaneous Transvascular Biopsy of Lesion of Liver	£1,385.17
YG11A	Percutaneous Punch Biopsy of Lesion of Liver, 19 years and over	£716.83
YH10Z	Image Guided Biopsy of Extradural Spinal Lesion	£1,256.78
YH31Z	Image Guided Biopsy of Lesion of Bone	£1,118.08
YH32Z	Image Guided Biopsy of, Lesion of Muscle or Connective Tissue	£1,452.61
YL20A	Percutaneous Needle Biopsy of Lesion of Kidney, 19 years and over	£920.70

2.51 Evidence statements

2.5.12 Clinical evidence statement

59 studies examined changes in receptor expression between primary tumour and recurrent samples.

For the studies assessing distant recurrences, the median change in ER (19 studies, n=1,496), PR (17 studies, n=1,302) and HER-2 (23 studies, n=1,687) receptor expression was 18.1% (range: 0 to 55.6%), 30.6% (range: 4.17 to 48.6%) and 8.8% (range: 0to 22.5%) respectively. The evidence was of very low quality.

1 study (n=107) reported on change in management in those with ER discordance (59.1%), 2 studies (n=144) reported change in management in those with HER-2 discordance (50 to 66.7%), 2 studies (n=284) reported change in management in those with ER/PR/HER-2 discordance (12.1% to 25%) and 1 study (n=58) reported change in management in those with ER and/or PR discordance (40.7%). The evidence was of very low quality.

1 study (n=9) reported on complications of biopsy of distant metastases - 1 of 9 subjects developed a haematoma in the left iliac biopsy site.

For the studies assessing mixed locoregional and distant recurrences, the median change in ER (26 studies, n=3,890), PR (19 studies, n=1,979) and HER-2 (23 studies, n=1,398) receptor expression was 20.1% (range: 3.2 to 53.6); 26.1% (16.3 to 54.2) and 9.9% (0 to 22.4) respectively. One additional study (n=35) reported a change in ER or PR receptor expression of 31.4%. The evidence was of very low quality.

3 studies (n=489) reported on change in management in those with ER/PR/HER-2 discordance (17.5% to 20.5%). The evidence was of very low quality.

1 study (n=94) reported on complications of biopsy of mixed locoregional/distant metastases – one out of 83 subjects had a case of bleeding from a punch biopsy which led to admission.

No evidence was identified for any of the other outcomes.

2.5.26 Health economic evidence statements

No evidence was identified in the health economic literature.

Results of the novel economic analysis showed that, for the entire population with recurrent breast cancer, testing HER-2 status is associated with an ICER of £21,058. For patient subpopulations the analysis showed that, in patients with a HER-2-positive primary tumour, testing HER-2 status dominates no testing, as it results in a cost saving from unnecessarily

treating HER-2-negative tumours with trastuzumab. For patients with a HER-2-negative primary tumour, testing HER-2 status results in an ICER of £56,116 for patients with distant metastatic cancer and an ICER of £27,387 for patients with locoregional cancer (under conservative assumptions). ICERs for patients with distant metastatic cancer are higher than those for locoregional cancer due to biopsies being carried out as routine practice for the latter group of patients, and trastuzumab being relatively more cost effective for patients with early stage breast cancer. This evaluation was assessed as being directly applicable to the decision problem, but was categorised as having potentially serious limitations, due to relying on costs and QALYs from previously published analyses, the low quality of data used to populate the model, and a large number of assumptions inherent in the analysis.

2.61 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The majority of papers were concerned with identifying the proportion of people with a change in receptor status between the two samples, but few studies reported on change in management and only one reported on adverse events related to biopsy rate of status change, but did not address quality of life. No evidence was available for the outcomes of quality of life, change in tumour type or survival/progression to recurrence. The committee agreed that change in management was the critical outcome as the clinical context has changed since the original guideline was published. More tailored approaches to pharmaceutical management based on receptor status are now available. The opportunity to change to a more appropriate strategy, or to stop treatment based on new biopsy results, has considerable implications for both the patient and the NHS. For the patient, appropriately targeted treatment should be associated with gains in patient related outcomes such as survival and response rates, and also reduced side effects from drugs that might have previously been given, but which wouldn't have benefitted the patient, as they wouldn't have an anti-tumour action. For the NHS, change to more appropriate management would be expected to result in better use of NHS resources by making more effective use of cost-effective treatments. The committee noted that some of the included papers also reported on the proportion of people whose re-biopsy indicated that the tumour was benign. This would have an enormous impact on the quality of life of the patient in terms of reassurance and reduction in anxiety. This would also benefit the NHS in stopping unnecessary treatments that are associated with serious adverse effects. The topic experts noted that tests for PR status are not currently commissioned, and clinical opinion is that change in PR receptor status, if confirmed, would very rarely change management.
Trade-off between benefits and harms	The committee noted that current practice in most UK healthcare settings is to perform a routine biopsy for locoregional recurrence, as patients may require surgery and further management. For distant metastases, it was noted that practice varies and not all patients will receive a routine biopsy. It was agreed that the majority of patients are likely to want to be re-tested if this improves management, but those who had a traumatic experience at previous biopsy may want to avoid further biopsy. The committee noted that knowing receptor status on disease recurrence can be important as it may alter the clinical management of the disease. It agreed that it was important that a caveat be added that receptor status only be re-assessed if there is the potential to change the way the disease is managed. In certain groups of people, where a clinician is confident that a

	Committee discussions
	different test result would not result in a change of management, neither the costs of the biopsy nor the potential harms of biopsy to the individual could be justified. Knowing receptor status is important because HER-2 positive breast cancers are often responsive to trastuzumab, as outlined in TA34 guidance. However, it was noted that trastuzumab is often given with chemotherapy and/or other drugs including pertuzumab. Additionally, trastuzumab may not be suitable for all patients, especially those with poor cardiac function. Taking this into consideration, the committee agreed that knowing HER-2 status on suspected recurrence can prolong life with further treatment in people found to be HER-2 positive on recurrence, and avoid incorrect treatments and their associated potentially serious adverse effects in people found to be HER-2 negative on recurrence. They also agreed there has been an increase in treatments targeted based on ER status, and therefore reassessment of this would also have the possibility to positively affect people's treatment. The committee formulated a recommendation to consider reassessment of receptor status on suspected disease recurrence in a person with breast cancer, where biopsy will change management. The committee noted the lack of evidence for adverse events of a biopsy and relied on their experience to fill this gap. Potential harms of core biopsy include a need for general anaesthesia (and potential associated surgical complications) with biopsy on some sites. The committee agreed that, provided management would be likely to change, the benefits of an accurate diagnosis outweighed the potential harms of biopsy because it will ensure the patient enters the correct treatment pathway. The committee agreed that there was no evidence presented that progesterone re-testing would lead to improvements in management, nor was there clinical consensus that it would, and therefore it was agreed to be appropriate not to make any recommendations in this area. Additionally, the committee agreed it was appropriate to delete the recommendation from the old guideline to assess ER and HER-2 status in people who were not assessed at the time of first diagnosis. This was because the overwhelming majority of people will now be tested at diagnosis, and in those who aren't it would be standard practice to test on recurrence, and therefore there was no need for specific guidance in this area.
Trade-off between net health benefits and resource use	The committee discussed the results of the de novo economic analysis conducted for the update. It was noted that results indicate that retesting receptor status in all patients with a HER-2-positive primary tumour is likely to be cost saving, with at least equivalent health outcomes to a strategy of no retesting, due to preventing patients with HER-2-negative recurrent cancer from being unnecessarily treated with trastuzumab. It was also noted that the ICER for retesting receptor status in patients with locoregional cancer and who had a HER-2-negative primary tumour was only marginally higher than the ICER for treating patients with known HER-2-positive status with trastuzumab. Therefore, given that NICE considers trastuzumab to be a cost effective treatment for both early and advanced HER-2-positive breast cancer (it is recommended in TA107 and TA34), it is also likely that retesting receptor status in these patients is a cost effective strategy. The committee noted that retesting status in patients with distant metastatic cancer who had a HER-2-negative primary tumour is associated with a relatively high ICER of £56,116/QALY, due to the additional cost of biopsy in these patients, as well as trastuzumab treatment being less cost effective for advanced breast cancer. The committee discussed a number of limitations with the economic analysis and with the underlying clinical evidence. Firstly, it was noted that the cost and QALY outcomes for trastuzumab used to populate the model

	Committee discussions
	are relatively dated and, in clinical practice, other treatments are also used to treat HER-2-positive recurrent cancer. Specifically, the majority of patients are treated with pertuzumab as an adjunct to trastuzumab, and some patients are treated with trastuzumab emtansine following treatment with trastuzumab. The cost effectiveness of these treatments, and the potential effect on model outcomes, was discussed. Treating HER-2-positive patients with pertuzumab is likely to increase the cost effectiveness of retesting receptor status, whereas trastuzumab emtansine is likely to substantially decrease cost effectiveness (although it should be noted that this treatment is not recommended by NICE). This is because the ICERs of these two treatments (in addition to or following trastuzumab treatment) are likely to be, respectively, lower and higher than the ICER of treating HER-2-positive breast cancer with trastuzumab alone. Therefore, including these treatments in the analysis would also shift the ICER of testing patients with a HER-2-negative primary tumour down or up respectively. Secondly, it was noted that the assumption that patients with HER-2-negative cancer accrue the same number of QALYs regardless of treatment with or without trastuzumab is potentially unrealistic. The committee felt that, in reality, these patients would likely experience a reduction in quality of life due to the toxicity associated with trastuzumab and adjuvant treatment. Furthermore, patients whose HER-2 status changes from positive to negative could potentially miss out on treatments specific to HER-2-negative cancer if they are not retested, and therefore experience a further QALY loss. This indicates that the model is potentially underestimating the cost effectiveness of receptor status testing in patients with a HER-2-positive primary tumour, although this is unlikely to affect decision making, as testing already dominates no testing in the base case. Thirdly, the studies identified in the clinical review display high variability in estimates of the proportion of patients changing HER-2 status between primary and recurrent cancer. However, sensitivity analyses carried out on the model show that, even when the proportion of patients changing HER-2 status is halved or doubled, retesting patients with a HER-2-positive primary tumour still remains a dominant strategy, and there is little effect on the ICER of retesting in patients with locoregional recurrence and a HER-2-negative primary tumour. Contrastingly, the ICER of retesting in patients with distant metastatic cancer and a HER-2-negative primary tumour was sensitive to variation in the proportion of patients changing status. Fourthly, the committee noted that, in practice, a substantial proportion of patients with distant metastatic recurrence are biopsied independently of the intention of testing HER-2 status. For these patients, the cost effectiveness of retesting receptor status would be substantially reduced, to an extent that the ICER would likely be only marginally higher than that of trastuzumab for patients with HER-2 status. Therefore, as with the equivalent locoregional population, retesting is likely to be cost effective in these patients if trastuzumab is generally accepted to be a cost effective treatment. Finally, the committee discussed that, on occasion, clinicians may treat patients with a HER-2-positive primary tumour and HER-2-negative metastases with trastuzumab, on the assumption that metastases at other sites were HER-2-positive. Furthermore, some metastases sites may be difficult to validate – for example if only a small sample is available, or if metastases are in the bone.

	Committee discussions
	The committee acknowledged that, although the model base case results indicate that retesting HER-2 receptor status is likely to be more cost effective in some patient subgroups than others, the level of uncertainty in the modelling results and the complexity of clinical reality indicated that nuancing recommendations according to primary tumour status and stage of recurrent cancer was not appropriate. The committee concluded that the clinical reality is sufficiently complex that clinician's judgement should play a key role in determining whether retesting HER-2 status is appropriate, and therefore opted to make a recommendation that retesting should be considered in all patients with recurrent breast cancer, where the result could change management. Based on an incidence rate of 1,876 cases of recurrent breast cancer per year, and an overall incremental cost of £638 for retesting HER-2 status across all patients, implementing the recommendation for the entire population would incur a significant resource impact of around £1,196,000 per year. However, in practice, this figure is likely to be lower, as a considerable proportion of patients with distant metastatic cancer are currently biopsied as a matter of routine practice. Making the assumption that 50% of patients with distant metastatic cancer are biopsied regardless of the intention to test HER-2 status gives an annual resource impact of around £833,000 per year.
Quality of evidence	The committee agreed that the quality of the clinical evidence was very low. Many of the studies were carried out on an opportunistic basis (using autopsy findings, routinely collected data or as part of a wider project) and overall there was very poor reporting of baseline demographic characteristics beyond age. For the outcome of change in receptor status, there were fairly consistent findings across the studies with median proportions of change in ER and HER-2 consistent with the previous review in CG81. Imprecision was not quantitatively assessed as the committee were not able to define the percentage change in receptor expression that would be considered as clinically significant. The use of medians as the primary summary measure also means it is difficult to formally evaluate the level of variability in the data. However, with the overall quality of the data consistently assessed as very low, this is unlikely to have made a difference to the recommendations made. The committee raised applicability concerns with regard to older trials from 1995 and before. This is because many of these trials did not mandate that a re-biopsy is necessary. Additionally, many of these trials based HER-2 receptor status testing on the immunohistochemistry (IHC) criteria, and receptor status testing has progressed since this with the use of FISH and D-DISH.
Other considerations	The committee noted that the following exclusion criteria specified in the protocol may not be entirely appropriate for this evidence review question: "Women and men with invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 (this will be covered by the NICE guideline on 'Early breast cancer: diagnosis and treatment) unless it is a stage 1/2/3 disease that has recurred and become stage 4". This is because stage of cancer may not be defined at primary sample and all adenocarcinoma has the potential to become metastatic. However, the committee were aware that no evidence was excluded on this basis and therefore this will have made no difference to the overall conclusions of the review. The committee made a post-hoc decision to not review the clinical studies looking at locoregional disease recurrence or metastases as surgery is often the standard of care

	Committee discussions
	so this information would not help with 'change in treatment' outcome. Topic experts also noted that locoregional metastases are routinely biopsied in clinical practice at the moment so any recommendation to biopsy these instances will not have any impact of clinical practice. **Equalities impact** The committee noted that patients who have a first language that is not English may have difficulty in understanding and discussing the potential adverse events of biopsy on recurrence and there may also be implications on obtaining consent for biopsy. For these patients, interpreters / family members should be available to assist. Patients with learning disabilities and cognitive impairments may require earlier screening and added guidance. The committee noted the challenges in obtaining consent for biopsy from those with conditions such as dementia. The committee noted that in some religions or cultures, cancer is not openly talked about which prevents family members from seeking further help. The committee noted that although the evidence related specifically to women, breast cancer can also affect men, yet this is much rarer in this group. The committee noted that there may be social implications relating to fertility, for example, treatment may prevent a young woman from pregnancy. Those with comorbidities such as poor cardiac function may not be eligible for treatment with trastuzumab and alternative management options may be considered.

2.71 Recommendations

2 **1. On recurrence, consider reassessing oestrogen receptor (ER) and human**
3 **epidermal growth factor 2 receptor (HER-2) status if a change in receptor status**
4 **will lead to a change in management. [2017]**

5 **Replaced recommendation:**

6 **1.1.6 Patients with tumours of known oestrogen receptor (ER) status whose disease**
7 **recurs should not have a further biopsy just to reassess ER status. [2009]**

8 **1.1.7 Patients with tumours of known human epidermal growth factor receptor 2 (HER-**
9 **2) status whose disease recurs should not have a further biopsy just to reassess HER-**
10 **2 status. [2009]**

11 **Deleted recommendations:**

12 **1.1.8 Assess ER and HER-2 status at the time of disease recurrence if receptor status**
13 **was not assessed at the time of initial diagnosis. In the absence of tumour tissue from**
14 **the primary tumour, and if feasible, obtain a biopsy of a metastasis to assess ER and**
15 **HER-2 status. [2009]**

2.86 Research recommendations

17 No research recommendations were prioritised by the committee.

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4

4 Glossary and abbreviations

Please refer to the NICE glossary.

Additional terms used in this document are listed below.

Advanced breast cancer: Disease that has spread from the breast to other body systems, travelling through the bloodstream or lymphatic system (locally advanced breast cancer is disease that has spread to large parts of the breast or nearby lymph nodes).

HER-2: A gene that encodes a growth-promoting protein which helps to control how cells divide and repair themselves.

Metastases: Deposits of cancer elsewhere in the body.

1 Appendices

2 Appendix A: Standing Committee 3 members and NICE teams

A.1 4 Core members

Name	Role
Tessa Lewis (Chair)	GP, Medical Advisor in Therapeutics
John Cape	Director of Psychological Therapies Programme
Alison Eastwood	Professor
Sarah Fishburn	Lay member
Gail Fortes-Mayer	Commissioner
Imran Jawaid	GP
Catriona McDaid	Senior Research Fellow
Nick Screaton	Radiologist
Vicky Hetherington	Senior Nurse Practitioner
Sophie Wilne (Vice Chair)	Paediatric Oncologist

A.2 5 Topic expert Committee members

Name	Role
Rosemary Buck	Advanced Nurse Practitioner
Maureen Daly	Lay member
John Graham	Consultant Oncologist
Miles Howe	Consultant Histopathologist
Karen McAdam	Consultant in Medical Oncology

A.3 6 NICE project team

Name	Role
Mark Baker	Clinical Adviser
Steven Barnes	Technical Lead
Christine Carson	Guideline Lead
Emma Chambers	PIP Lead
Anne-Louise Clayton	Editor
Laura Gibson	Quality Standards Lead
Sarah Glover	Information Scientist
Caroline Kier	Guideline Commissioning Manager
Ross Maconachie	Health Economics Adviser
Sandra Robinson	MIP Lead
Sarahjane Tierney	Guidelines Coordinator
David Tyldesley	Resource Impact Lead

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A.41 Guideline updates team

Name	Role
Omnia Abdulrazeg	Technical Analyst
Emma Banks	Co-ordinator
Chris Carmona	Guideline Lead
Martin Domanski	Project Manager
Susannah Gyton Moon	Programme Manager
Ben Johnson	Health Economist
Joshua Pink	Technical Adviser
Nitara Prasannan	Technical Analyst
Charlotte Purves	Administrator
Susan Spiers	Associate Director

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Appendix B: Declarations of interest

The standing committee and topic experts interests have been declared and collated and are available here.

1 Appendix C: Review protocol

	Details
Review question	In patients (women and men) with advanced breast cancer* and ER/PR/HER-2 status known in primary tumour, does receptor status change on disease recurrence at any site? *Advanced breast cancer defined as invasive adenocarcinoma of the breast of clinical stage 4 (i.e. with known metastatic disease).
Background/ objectives	In November 2015, the NICE surveillance team reviewed the NICE guideline on Advanced breast cancer to see if it needed to be updated. 2 new studies (1 which was a pooled analysis of individual patient data from 2 prospective studies and the other a prospective cohort study) were identified examining discordance between primary and recurrent breast cancer in terms of ER, HER-2 and progesterone receptor status. The 2 studies found there could be discordance in receptor status between the primary tumour and metastases, which led to altered management in 14.2–20% of cases. The topic experts agreed that it was important to review whether reassessment of receptor status on disease recurrence was necessary. They noted that the Breast Cancer Quality Standard already states that people with recurrent disease (if clinically appropriate) have the ER and HER-2 status of the tumour assessed. It appears that the QS statement is supported by the evidence from the current surveillance review. However it was recognised that the QS doesn't align with the current recommendations in the clinical guideline – which state that, if disease recurs, further biopsy just to reassess ER and HER-2 status should not be done. This area should therefore be reviewed to see if the clinical guideline needs to be updated in light of the new evidence. The existing quality standard will need to be reviewed in light of the guideline update.
Population	Patients (men and women) with advanced breast tumour and ER/PR /HER-2 status known at first diagnosis.
Intervention	Reassessment of ER/PR/HER-2 receptor status on biopsy from recurrence
Comparator	ER/PR/HER-2 receptor status at first diagnosis
Outcomes	Changes in receptor expression between the two samples Quality of life Change in management Change in tumour type eg: breast to lung Adverse events related to biopsy Note: Survival and progression to recurrence will be revisited as a post-hoc analysis if the data is available in the included studies. Deviation from review protocol: data relating to the change in direction of HER-2 status was extracted as a post-hoc analysis to feed into the health economic model for both the locoregional and distant subgroups. For breast cancer, it is known that ER/PR/HER-2 status may differ between primary and recurrent tumours. Of these markers, a change in HER-2 status has the largest impact on change in management, as HER-2-positive tumours are responsive to treatment with trastuzumab.
Type of review question	Epidemiological
Types of study to be included	Cohort studies/case series and any other study designs comparing paired biopsy samples from the first diagnosis versus the recurrent tumour

	Note: the comparison biopsy at recurrence versus no biopsy at recurrence is not of interest for this question as we are only interested in paired biopsy samples.
Language	English language only
Status	Published papers (full text only) – searches to be run from start of database to present. All studies included in the original guideline will also be considered.
Any other information or criteria for inclusion/exclusion	For inclusion Women and men with invasive adenocarcinoma of the breast of clinical stage 4 (i.e. with known metastatic disease). Settings: primary care (excluding population-based and opportunistic screening), secondary care, tertiary care by specialist breast cancer teams and palliative care services. Mixed study populations will be included if the data for the advanced breast group alone can be extracted or if this is not possible but the advanced breast cancer population is 90% or more. For exclusion Women and men with invasive adenocarcinoma of the breast of clinical stages 1, 2 and 3 (this will be covered by the NICE guideline on 'Early breast cancer: diagnosis and treatment) unless it is a stage 1/2/3 disease that has recurred and become stage 4. Women and men with metastases to the breast from other primary tumours. Women and men with rare breast tumours (for example, angiosarcoma, lymphoma). Women and men with benign breast tumours (for example, fibroadenoma, benign phyllodes tumours).
Analysis of subgroups or subsets	Receptor status change in primary disease recurrence Receptor status change in second metastases
Data extraction and quality assessment	Sifting Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the review question (measured against protocol). In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered being not relevant to the topic will be excluded. i) Selection based on titles and abstracts A full double-sifting of titles and abstracts will not be conducted due to the nature of the review question (narrow question with clearly defined straightforward inclusion and exclusion criteria. The original review included a reasonable evidence base (18 studies) and so the implications of missing one study are minimal). However in cases of uncertainty the following mechanisms will be in place: technical analyst will discuss with a support analyst comparison with included studies of other current (within 5 years) systematic reviews recourse to members of the committee ii) Selection based on full papers

A full double-selecting of full papers for inclusion/exclusion will not be conducted (narrow question with clearly defined straightforward inclusion and exclusion criteria. The original review included a reasonable evidence base (18 studies) and so the implications of missing one study are minimal). However in cases of uncertainty the same mechanisms stated in i) above will be followed.

The committee will also be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been wrongly sifted out.

Data extraction

Relevant information from included studies will be extracted into standardised evidence tables adapted to suit this particular question.

The following baseline characteristics will be extracted:
Age
Gender
Ethnicity
Treatment at baseline
Biopsy site
Biopsy type
Hormone status
Disease stage
Survival/time to recurrence or progression

Critical appraisal

The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual appropriate for the design of each included study.

Quality assessment

An adapted GRADE methodology will be used to assess the quality of evidence on an outcome basis:
Risk of bias will be assessed using the Joanna Briggs checklist for case series.
Inconsistency will not be assessed as it is not anticipated the data will be pooled due to the heterogeneous populations
Indirectness will be assessed after considering the population, intervention and outcomes of included studies, relative to the target population as specified in the review protocol;
Imprecision will not be assessed using whether the confidence intervals around point estimates cross the MIDs for each outcome. COMET and published literature will be checked for appropriate minimal important differences (MID) for each outcome and if none are available, Topic experts will be asked to provide MID's.
Quality Assurance
A full double-scoring quality assessment will not be conducted due to the nature of the review question (narrow question) and the type of studies included. Other quality assurance mechanisms will be in place as follows:

	Internal QA (10%) by CGUT technical adviser on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. The Committee will be sent the evidence synthesis prior to the committee meeting and will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	The original guideline did not perform a meta-analysis of the data. It is not anticipated a meta-analysis will be carried out in this update as it is expected the studies will be heterogeneous in terms of population (eg: varying regions from which second sample obtained). No comparative (controlled) data are anticipated. A narrative evidence summary outlining key issues such as volume, generalisability and quality of evidence and presenting the key findings from the evidence will be produced.
Searches	Sources to be searched Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA. Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques None identified Limits Studies reported in English Animal studies will be excluded from the search results Conference abstracts will be excluded from the search results No date limit will be set.
Key papers	Studies identified by surveillance process Simmons C, Miller N, Geddie W et al. (2009) Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Annals of Oncology 20:1499-1504. Amir E, Clemons M, Purdie CA et al. (2012) Tissue confirmation of disease recurrence in breast cancer patients: pooled analysis of multi-centre, multi-disciplinary prospective studies. Cancer Treat Rev 38:708-714.

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Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 13: Clinical search summary. The Medline search strategy is shown in Table 14: Clinical search terms (Medline). The same strategy was translated for the other databases listed.

Table 13: Clinical search summary

Databases	Date searched	No. retrieved
CDSR (Wiley)	26/08/2016	1
Database of Abstracts of Reviews of Effects – DARE (Wiley)	26/08/2016	0
HTA database (Wiley)	26/08/2016	0
CENTRAL (Wiley)	26/08/2016	343
MEDLINE (Ovid)	26/08/2016	3607
MEDLINE In-Process (Ovid)	26/08/2016	224
EMBASE (Ovid)	26/08/2016	4614
PubMed	26/08/2016	1293?

Table 14: Clinical search terms (Medline)

Database: Medline
Strategy used: Database: Ovid MEDLINE(R) <1946 to August Week 3 2016> Search Strategy: --- 1 exp Breast Neoplasms/ (248079) 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ (32836) 3 1 or 2 (258469) 4 exp Breast/ (40576) 5 breast$.tw. (324795) 6 4 or 5 (335785) 7 (breast adj milk).tw. (9569) 8 (breast adj tender$).tw. (475) 9 7 or 8 (10042) 10 6 not 9 (325743) 11 exp Neoplasms/ (2886766) 12 10 and 11 (247311) 13 (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)).tw. (240632) 14 (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)).tw. (29895) 15 Paget's Disease, Mammary/ (694) 16 (paget$ and (breast$ or mammary or nipple$ or areola*)).tw. (999) 17 or/12-16 (286303) 18 3 or 17 (331174) 19 Receptor, erbB-2/ (19459)

Database: Medline

20 Genes, erbB-2/ (2912)

21 (HER-2 or HER-2 or erbb-2 or erbb2 or c erbB2 or c-erbB2 or human epidermal growth factor receptor$ or cd340 antigen* or neu proto-oncogene protein or neu proto oncogene protein or neu receptor).tw. (27378)

22 exp Receptors, Estrogen/ (43693)

23 ((oestrogen$ or estrogen* or EgR or ER) adj3 (status or test$ or level$ or receptor$ or express* or hormone*)).tw. (67787)

24 ((ER adj2 positiv$) or (ER adj2 negativ$) or (EgR adj2 positiv$) or (EgR adj2 negativ$) or (oestrogen$ adj2 positiv$) or (oestrogen$ adj2 negativ$) or (estrogen adj2 negativ$) or (estrogen adj2 positiv$)).tw. (12913)

25 Receptors, Progesterone/ (17204)

26 ((progesteron$ or progestin or PgR or PR) adj3 (status or test$ or level$ or receptor$ or express* or hormone*)).tw. (33912)

27 ((PR adj2 positiv$) or (PR adj2 negativ$) or (PgR adj2 positiv$) or (PgR adj2 negativ$) or (progesteron$ adj2 positiv$) or (progesteron$ adj2 negativ$) or (progestin adj2 negativ$) or (progestin adj2 positiv$)).tw. (3959)

28 or/19-27 (120466)

29 18 and 28 (48871)

30 ((change or alter or acquire$ or alter$ or conserve$ or lost or unchange$ or revert$ or reassess*) adj2 (status or express$)).tw. (44448)

31 ((concordan$ or discordan$) adj5 (status or express$)).tw. (2267)

32 ((primary or primitive) adj (tumo?r or disease or breast cancer or invasive breast cancer or focus* or diagnos* or lesion$ or site* or tissue* or region*)).tw. (67142)

33 Disease Progression/ (124847)

34 (tumo?r progress$ or cancer progress$ or disease progress$ or breast cancer progress$ or exacerbation).tw. (118285)

35 Neoplasm metastasis/ or Neoplasm recurrence, local/ (179654)

36 (distant metast* or local* recur$ or minimal residual disease or locoregional).tw. (60024)

37 ((metast* or recur*) adj (focus* or site$ or lesion$ or breast cancer or tissue$ or disease$ or tumo?r or region* or invasive breast cancer or diagnos*)).tw. (66834)

38 or/30-37 (547211)

39 29 and 38 (13110)

40 exp Biopsy/ (247761)

41 biops*.tw. (303243)

42 (re-biops* or rebiops* or re-test* or retest*).tw. (25852)

43 (tissue adj4 confirm*).tw. (4163)

44 Immunohistochemistry/ (269228)

45 (immunohistochem* or immunocytochem* or immunohistocytochem* or immunogold* or immunolabel*).tw. (338262)

46 In Situ Hybridization, Fluorescence/ (38540)

47 fluorescen*.tw. (334487)

48 (FISH adj4 (technic* or technique*)).tw. (1903)

49 Cytodiagnosis/ (15105)

50 cytodiagnos*.tw. (2270)

51 or/40-50 (1208271)

52 39 and 51 (3997)

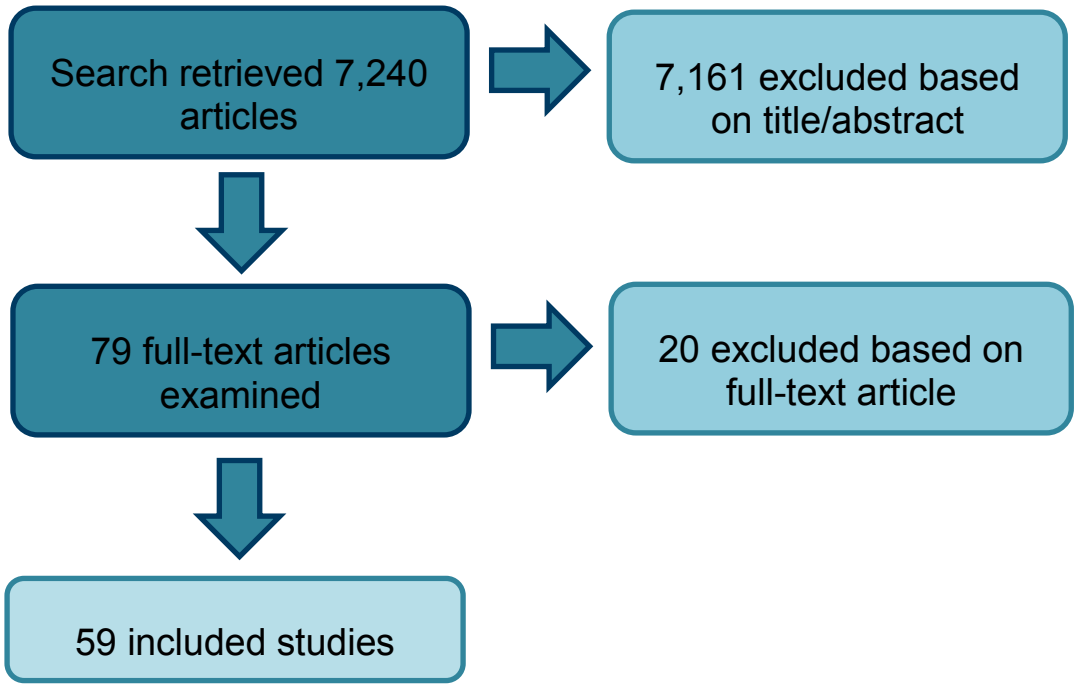
53 animals/ not humans/ (4268987)

54 52 not 53 (3920)

55 limit 54 to english language (3673)

1

Appendix E: Review flowchart



1 Appendix F:Excluded studies

Reference	Reason for exclusion
Aurilio G, Disalvatore D, Pruneri G et al. (2014). A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. European Journal of Cancer, 50(2), pp.277-289.	2011 meta-analysis: individual references checked for inclusion
Brankovic-Magic MV., Nikolic-Vukosavljevic DB., Neskovic-Konstantinovic ZB., Kanjer KS and Spuzic IV (1992) Variations in the content of steroid receptors in breast cancer. Comparison between primary tumors and metastatic lesions. Acta Oncol 31: 629-633.	No relevant outcomes
Edgerton S M, Moore Ii D, Merkel D, and Thor A D. (2003). erbB-2 (HER-2) and breast cancer progression. Applied Immunohistochemistry and Molecular Morphology, 11(3), pp.214-221.	No relevant outcomes reported
Fuchs I B, Loebbecke M, Buhler H et al. (2002). HER-2 in brain metastases: Issues of concordance, survival, and treatment [9]. Journal of Clinical Oncology, 20(19), pp.4130-4133.	Letter to editor
Iguchi Chikage, Nio Yoshinori, and Itakura Masayuki. (2003). Heterogeneic expression of estrogen receptor between the primary tumor and the corresponding involved lymph nodes in patients with node-positive breast cancer and its implications in patient outcome. Journal of surgical oncology, 83(2), pp.85-93.	Locoregional recurrence: does not report HER-2 change
Johnston S R, Saccani-Jotti G, Smith I E, Salter J, Newby J, Coppen M, Ebbs S R, and Dowsett M. (1995). Changes in estrogen receptor, progesterone receptor, and pS2 expression in tamoxifen-resistant human breast cancer. Cancer research, 55(15), pp.3331-8.	Not all had recurrence
Liedtke C, Broglio K, Moulder S et al. (2009). Prognostic impact of discordance between triple-receptor measurements in primary and recurrent breast cancer. Annals of Oncology, 20(12), pp.1953-1958.	Study does not report on ER, PR, HER-2 but on TNBC status
Matsumoto Akiko, Jinno Hiromitsu, Murata Takeshi, Seki Tomoko, Takahashi Maiko, Hayashida Tetsu, Kameyama Kaori, and Kitagawa Yuko. (2015). Prognostic implications of receptor discordance between primary and recurrent breast cancer. International journal of clinical oncology, 20(4), pp.701-8.	Stage 4 is an exclusion criterion
Mavrova R, Radosa J, Schmitt K et al. (2014). Estrogen, progesterone, and her-2/neu receptor expression discrepancy in primary tumors and in-breast relapse in patients with breast cancer. Breast Journal, 20(3), pp.322-324.	Letter to editor
Montagna E, Bagnardi V, Rotmensz N et al. (2012). Breast cancer subtypes and outcome after local and regional relapse. Annals of Oncology, 23(2), 324-331.	Locoregional recurrence: does not report HER-2 change
Nedergaard L, Haerslev T, and Jacobsen G K. (1995). Immunohistochemical study of estrogen receptors in primary breast carcinomas and their lymph node metastases including comparison of two monoclonal antibodies. APMIS : acta pathologica, microbiologica, and et immunologica Scandinavica, 103(1), pp.20-4.	Locoregional recurrence: does not report HER-2 change
Niikura N, Liu J, Hayashi N, Mittendorf E A, Gong Y, Palla S L, Tokuda Y, Gonzalez-Angulo A M, Hortobagyi G N, and Ueno N T. (2012). Loss of human epidermal growth factor receptor 2 (HER-2) expression in metastatic sites of HER-2-overexpressing primary breast tumors. Journal of Clinical Oncology, 30(6), pp.593-599.	Selected population of HER-2 positive breast cancers

Reference	Reason for exclusion
Rom J., Aulmann S., Schneeweiss A., Sohn C and Sinn HP (2006) Comparison of immunohistological parameters in primary breast cancers and corresponding locoregional recurrences. Pathol Res Pract 202: 125-130	Locoregional recurrence: does not report HER-2 change
Pectasides D, Gaglia A, Arapantoni-Dadioti P, Bobota A, Valavanis C, Kostopoulou V, Mylonakis N, Karabelis A, Pectasides M, and Economopoulos T. (2006). HER-2/neu status of primary breast cancer and corresponding metastatic sites in patients with advanced breast cancer treated with trastuzumab-based therapy. Anticancer research, 26(1B), pp.647-53.	Selected sample for HER-2 positivity
Simon R, Nocito A, Hubscher T, Bucher C, Torhorst J, Schraml P, Bubendorf L, Mihatsch M M, Moch H, Wilber K, Schotzau A, Kononen J, and Sauter G. (2001). Patterns of HER-2/neu amplification and over-expression in primary and metastatic breast cancer. Journal of the National Cancer Institute, 93(15), pp.1141-1146.	Locoregional recurrence: does not report HER-2 change
Tahmasebi S, Dalfardi B, Talei A, Safaei A, Monabati A, and Akrami M. (2013). Concordant expression of estrogen and progesterone receptors in primary and loco-regional recurrent breast cancer. Middle East Journal of Cancer, 4(3), pp.113-118.	Locoregional recurrence: does not report HER-2 change
van Agthoven , T , Timmermans M, Dorssers L C, and Henzen-Logmans S C. (1995). Expression of estrogen, progesterone and epidermal growth factor receptors in primary and metastatic breast cancer. International journal of cancer, 63(6), pp.790-3.	Locoregional recurrence: does not report HER-2 change
Wirk B and Geiger X (2006) Concordance of HER-2 and hormone receptor expression in primary and recurrent breast cancer. Breast Cancer Res Tr 94: S89	Conference abstract – insufficient information to assess quality
Zhu Y Y, Si W, Ji T F, Guo X Q, Hu Y, and Yang J L. (2016). The variation and clinical significance of hormone receptors and Her-2 status from primary to metastatic lesions in breast cancer patients. Tumor Biology, 37(6), pp.7675-7684.	Inclusion criteria: stage 1- 3 cancer only
Zheng W Q, Lu J, Zheng J M, Hu F X, and Ni C R. (2001). Variation of ER status between primary and metastatic breast cancer and relationship to p53 expression. Steroids, 66(12), 905-910.	Locoregional recurrence: does not report HER-2 change

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1 Appendix G: Evidence tables

G.12 Distant metastases

G.1.13 Amir 2008

Bibliographic reference	**Amir E, Ooi W S, Simmons C, Kahn H et al. Discordance between Receptor Status in Primary and Metastatic Breast Cancer: an Exploratory Study of Bone and Bone Marrow Biopsies. Clinical Oncology, 20(10), 763-768.**
Study type	Prospective cohort
Aim	To assess the incidence of discordant receptor status in primary and metastatic disease and evaluate the role of bone marrow biopsies for the reassessment of receptor status.
Patient characteristics	**Inclusion criteria** Patients with either stable bone metastases on bisphosphonate therapy or with progressive bone metastases despite bisphosphonate therapy **Exclusion criteria** Not reported **Baseline characteristics** Age median (range) : 57 (48-67) Gender : not reported Ethnicity : not reported Treatment at baseline : previous chemotherapy (n=4); hormonal therapy (n=9); previous radiotherapy (n=3) Biopsy site: bone Biopsy type : radiologically guided bone biopsy Hormone status : not reported Disease stage : not reported Survival/time to recurrence or progression, median (range) : 5 (1 to 13) years
Number of Patients	N=9
Intervention	Each patient underwent bone biopsy and bone marrow aspirate and trephine examination on a single day.

<table>
<tr><td>Bibliographic reference</td><td>Amir E, Ooi W S, Simmons C, Kahn H et al. Discordance between Receptor Status in Primary and Metastatic Breast Cancer: an Exploratory Study of Bone and Bone Marrow Biopsies. Clinical Oncology, 20(10), 763-768.</td></tr>
<tr><td></td><td>Samples were embedded in paraffin before histological and immunohistochemical analysis</td></tr>
<tr><td>Length of follow up</td><td>N/A</td></tr>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>5/9 (56%)
4/9 (44%)
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management
• ER
• PR
• HER-2</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>One patient developed a haematoma in the left iliac biopsy site. This resolved spontaneously after 2 weeks.</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the demographics of the participants in the study?</td><td>NO – demographics were poorly reported</td></tr>
<tr><td>Was there clear reporting of clinical information of the participants?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Amir E, Ooi W S, Simmons C, Kahn H et al. Discordance between Receptor Status in Primary and Metastatic Breast Cancer: an Exploratory Study of Bone and Bone Marrow Biopsies. Clinical Oncology, 20(10), 763-768.**

Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.1.21 Andersen 1988

Bibliographic reference	**Andersen et al 1988**
Study type	Case series
Aim	To compare the ER status of primary breast carcinomas with that of their regional and distant metastases using a histochemical technique in paraffin embedded tissue
Patient characteristics	**Inclusion criteria** • Randomly selected patients with ipsilateral lymph node metastases after the primary surgical treatment which involved mastectomy and lower axillary lymph node dissection • Randomly selected patients from whom paraffin embedded biopsies were accessible from the primary tumour and at least one simultaneous or sequential biopsy from distant metastases **Exclusion criteria** • Suitable histologic specimens not available **Baseline characteristics** Age – median (range) : regional lymph node metastases – 62 (33 to 84) years; distant metastases – 59 (26 to 74) years Gender : women (100%) Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : distant defined as sites outside the ipsilateral mammary region, ipsilateral axilla or ipsilateral periclavicular region. Biopsy type : Not reported Hormone status : Not reported

<table>
<tr><td>Bibliographic reference</td><td>Andersen et al 1988</td></tr>
<tr><td></td><td>Disease stage : Not reported
Survival/time to recurrence or progression median (range) : 0 to 92 months</td></tr>
<tr><td>Number of Patients</td><td>N= 51</td></tr>
<tr><td>Intervention</td><td>3 layer immunoperoxidase technique</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Denmark</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>5/51 (3%)
Not reported
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the demographics of the participants in the study?</td><td>NO – demographics were poorly reported</td></tr>
<tr><td>Was there clear reporting of clinical information of the participants?</td><td>YES</td></tr>
<tr><td>Were the outcomes or follow up results of cases clearly reported?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the presenting site(s)/clinic(s) demographic information?</td><td>YES</td></tr>
<tr><td>Was statistical analysis appropriate?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

G.1.31 Aurilio 2013

Bibliographic reference	**Aurilio G, Monfardini L, Rizzo S et al. (2013). Discordant hormone receptor and human epidermal growth factor receptor 2 status in bone metastases compared to primary breast cancer. Acta Oncologica, 52(8), 1649-56.**
Study type	Case series
Aim	To evaluate the discordance rate in hormone receptor and HER-2 status between primary tumour and paired bone metastases in a large consecutive series of breast cancer patients treated at the same institution, and its clinical impact on treatment planning.
Patient characteristics	**Inclusion criteria** Suspected bone metastases **Exclusion criteria** Not reported **Baseline characteristics** Age median (range) : 47.3 years (39.8 – 52.0) Gender : 122 (100%) female Ethnicity : not reported Treatment at baseline : unknown (3), no treatment (12)), only ET (20), only *CT (20), CT + ET (62), CT + ET + TT (1) Biopsy site: pelvic bones, sternum, vertebral bodies, ribs, skull, upper and lower limbs. Biopsy type : formalin-fixed, paraffin-embedded whole tumour sections Hormone status : not reported Disease stage : not reported but all had bone metastasis Survival/time to recurrence or progression : median 4.2 (0 – 18.9) years from primary breast surgery to bone biopsy *CT, chemotherapy; ET, endocrine treatment; TT, targeted therapy.
Number of Patients	122 samples available, 107 for ER and PR and 86 for HER-2.
Intervention	Samples of primary tumours were fixed in 10% buffered formalin, while all osteolythic and osteosclerotic metastatic lesions were fixed in 5% B5 for 90 minutes and decalcified in EDTA. All samples were embedded in paraffin. Immunoreactivity for ER, PgR and HER-2 was evaluated in all primary tumours and bone biopsies at the time of diagnosis. Three µ m-thick formalin-fixed, paraffin-embedded whole tumour sections were incubated following proper heat-induced antigen retrieval.

<table>
<tr><td>Bibliographic reference</td><td>Aurilio G, Monfardini L, Rizzo S et al. (2013). Discordant hormone receptor and human epidermal growth factor receptor 2 status in bone metastases compared to primary breast cancer. Acta Oncologica, 52(8), 1649-56.</td></tr>
<tr><td>Length of follow up</td><td>1997 – 2009</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
22 / 107 (20.5%)
47 / 107 (43.9%)
6 / 86 (6.9%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
74/86 (86%)
4/86 (5%)
2/86 (2%)
6/86 (7%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management
• ER
• PR
• HER-2</td><td>
13/22 (59.1%)
Not reported
4/6 (66.7%)</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*This additional data was extracted as a post-hoc analysis to feed into the health economic model.

Discordance in HER-2 receptor expression between primary and metastatic sites: 6.9% (95% CI: 2.6% – 14.6%)</td></tr>
<tr><td>Source of funding</td><td>None reported</td></tr>
<tr><td>Comments</td><td>Tumours with ≥ 1% of immunoreactivity were considered as positive. HER-2 immunoreactivity assessment was carried out according to the intensity and completeness of cell membrane staining. Fluorescence in-situ hybridization 2+ HER-2 score by IHC.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Aurilio G, Monfardini L, Rizzo S et al. (2013). Discordant hormone receptor and human epidermal growth factor receptor 2 status in bone metastases compared to primary breast cancer. Acta Oncologica, 52(8), 1649-56.**	
	Were valid methods used for identification of the condition for all participants included in the case series?	YES
	Did the case series have consecutive inclusion of participants?	YES
	Did the case series have complete inclusion of participants?	NO – Not all eligible patients had tissues samples for both primary tumour and locoregional recurrence / distant metastases
	Was there clear reporting of the demographics of the participants in the study?	NO – demographics were poorly reported
	Was there clear reporting of clinical information of the participants?	YES
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

G.1.41 Curigliano 2011

Bibliographic reference	**Curigliano G, Bagnardi V, Viale G, et al. (2011). Should liver metastases of breast cancer be biopsied to improve treatment choice?. Annals of Oncology, 22(10), 2227-33.**
Study type	Retrospective case series
Aim	To the occurrence of ER, PR, and HER-2 discordance in liver metastases
Patient characteristics	**Inclusion criteria** Diagnosis of primary, unilateral breast cancer with development of liver recurrent disease and recorded expression status of ER, PR, and HER-2 in both primary tumour and liver metastasis. **Exclusion criteria** bilateral breast cancer, male gender, ductal carcinoma in situ as initial diagnosis, synchronous metastases **Baseline characteristics**

<table>
<tr><td>Bibliographic reference</td><td>Curigliano G, Bagnardi V, Viale G, et al. (2011). Should liver metastases of breast cancer be biopsied to improve treatment choice?. Annals of Oncology, 22(10), 2227-33.</td></tr>
<tr><td></td><td>Age - median (range) : 45 (26 – 75)
Gender : 255 (100%) female
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : Liver (255)
Biopsy type : Ultrasound-guided biopsy
Hormone status : Not reported
Disease stage : T stage 1 (112), T stage 2 (102), T stage 3-4 (26), unknown (150: N stage 0 (99), N stage 1 (121), N stage 2-3 (26), unknown 9: M stage o (227), M stage 1 (22), unknown (6)
Survival/time to recurrence or progression – median (range) : 3.4 years (0 - 18).</td></tr>
<tr><td>Number of Patients</td><td>255</td></tr>
<tr><td>Intervention</td><td>Immunohistchemical analysis
Fluorescence in situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>37 / 255 (14.5%)
124 / 255 (48.6%)
24 / 172 (14.0%)*</td></tr>
<tr><td>Change in receptor expression direction for HER-2**
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>111/172 (68%)
7/172 (4%)
17/172 (10%)
37/172 (22%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>31 / 255**
(12.1%)</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Curigliano G, Bagnardi V, Viale G, et al. (2011). Should liver metastases of breast cancer be biopsied to improve treatment choice?. Annals of Oncology, 22(10), 2227-33.</td></tr>
<tr><td></td><td>*83 had missing values at primary or liver biopsy site.
**This additional data was extracted as a post-hoc analysis to feed into the health economic model.

**Change in management is across all 3 receptor types. N is total number of subjects as opposed to total discordant as total discordant over all 3 receptor types not reported.</td></tr>
<tr><td>Source of funding</td><td>None reported</td></tr>
<tr><td>Comments</td><td>16 patients with synchronous metastases

ER and PR was scored as follows: 0 (no staining or faint membrane staining), 1+ (faint membrane staining in >10% of tumour cells, incomplete membrane staining), 2+ (weak to moderate membrane staining in >10% of tumour cells), and 3+ (intense circumferential membrane staining in >10% of tumour cells).
For this analysis, HER-2 scores of 0 and 1+ were considered negative. HER-2 IHC 3+ and FISH-amplified tumours were considered positive. All IHC 2+ tumours and tumours for which IHC was not assessable were also tested for gene amplification by FISH

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>NO – Not all eligible patients had tissues samples for both primary tumour and locoregional recurrence / distant metastases</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the demographics of the participants in the study?</td><td>NO – demographics were poorly reported</td></tr>
<tr><td>Was there clear reporting of clinical information of the participants?</td><td>YES</td></tr>
<tr><td>Were the outcomes or follow up results of cases clearly reported?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the presenting site(s)/clinic(s) demographic information?</td><td>YES</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Curigliano G, Bagnardi V, Viale G, et al. (2011). Should liver metastases of breast cancer be biopsied to improve treatment choice?. Annals of Oncology, 22(10), 2227-33.	
	Was statistical analysis appropriate?	YES

G.1.51 Duchnowska 2012

Bibliographic reference	Duchnowska R, Dziadziuszko R, Trojanowski T, et al. (2012). Conversion of epidermal growth factor receptor 2 and hormone receptor expression in breast cancer metastases to the brain. Breast Cancer Research, 14(4)
Study type	Case series
Aim	To compare the status of ER, PR, and HER-2 in primary tumours and in paired excised brain metastases
Patient characteristics	**Inclusion criteria** Women with a diagnosis of unilateral breast cancer with synchronous or metachronous excised brain metastases. **Exclusion criteria** Not reported **Baseline characteristics** Age – mean (range) : 49 years (26 - 80) Gender : 120 (100%) female Ethnicity : Not reported Treatment at baseline : Most patients received chemotherapy, and more than 40% received endocrine therapy in the (neo)adjuvant or metastatic settings before brain surgery. Biopsy site : Brain Biopsy type : formalin-fixed paraffin-embedded tissue blocks Hormone status : ER+ (51) / ER- (69) : PR+ (40) / PR- (78) / unknown (1): HER-2 + (51) / HER-2- (62) / unknown (1) Disease stage : Not reported Survival/time to recurrence or progression mean (no SD): 3 years
Number of Patients	120
Intervention	Immunohistochemstry Fluorescence in situ hybridisation
Length of follow up	Median 97 months (range, 6 – 176)
Location	Poland

<table>
<tr><td>Bibliographic reference</td><td>Duchnowska R, Dziadziuszko R, Trojanowski T, et al. (2012). Conversion of epidermal growth factor receptor 2 and hormone receptor expression in breast cancer metastases to the brain. Breast Cancer Research, 14(4)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>35 / 120 (29.2%)
34 / 119 (28.6%)*
17 / 119 (14.3%)*</td></tr>
<tr><td>Change in receptor expression direction for HER-2**
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
51/119 (43%)
10/119 (8%)
7/119 (6%)
51/119 (43%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*PR and HER-2 status not determined in 1 patient.
**This additional data was extracted as a post-hoc analysis to feed into the health economic model.
</td></tr>
<tr><td>Source of funding</td><td>None reported</td></tr>
<tr><td>Comments</td><td>Expression of HRs was scored using the Allred system - proportion of positive cells (graded 0 to 5) and staining intensity (graded 0 to 3) - The proportion of positive cells and intensity were summed to produce total scores of 0 or 2 through 8. A score of 0 or 2 was regarded as negative, whereas a score of 3 to 8, as positive. A positive result of either ER or PR classified the case as HR-positive.
In additional analyses, the currently recommended more-stringent criteria for HR positivity (≥ 1% staining) were used
HER-2 positive was defined as > 30% of tumour cells (scored 3+). The samples showing intermediate expression (scored 2 +) were subjected to additional analysis of HER-2 gene copy number by using FISH

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Duchnowska R, Dziadziuszko R, Trojanowski T, et al. (2012). Conversion of epidermal growth factor receptor 2 and hormone receptor expression in breast cancer metastases to the brain. Breast Cancer Research, 14(4)**

Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	UNCLEAR
Did the case series have complete inclusion of participants?	NO
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.1.61 Fabi 2011

Bibliographic reference	**Fabi A, Di Benedetto , A , Metro G, et al. (2011). HER-2 protein and gene variation between primary and metastatic breast cancer: Significance and impact on patient care. Clinical Cancer Research, 17(7), 2055-64.**
Study type	Case series
Aim	To analyse HER-2 status in primary breast cancer (PBC) compared with correspondent metachronous metastases and to investigate whether BC phenotype may be predictive of change in HER-2 expression
Patient characteristics	**Inclusion criteria** Patients diagnosed with invasive BC between 1999 – 2007 and underwent biopsies to pathologically confirm presence of metastasis during follow-up. **Exclusion criteria** None reported **Baseline characteristics** Age - median (range) : 56 years (26 – 92) Gender : not reported Ethnicity : not reported Treatment at baseline : neoadjuvant/adjuvant therapy: anthracycline-base, taxane-based, anthracycline plus taxane-based, other, hormone, none.

<table>
<tr><td>Bibliographic reference</td><td>Fabi A, Di Benedetto , A , Metro G, et al. (2011). HER-2 protein and gene variation between primary and metastatic breast cancer: Significance and impact on patient care. Clinical Cancer Research, 17(7), 2055-64.</td></tr>
<tr><td></td><td>Biopsy site : visceral disease 19%, nonvisceral disease 81%
Biopsy type : formalin fixed paraffin embedded blocks
Hormone status : unclear
Disease stage : unclear
Survival/time to recurrence or progression – mean (range): 45.4 months (1 – 94)</td></tr>
<tr><td>Number of Patients</td><td>137</td></tr>
<tr><td>Intervention</td><td>Tissue microarray (TMA) was constructed from original formalin fixed paraffin embedded (FFPE) blocks. HER-2 was investigated by immunohistochemistry, silver in situ hybridization (SISH), and FISH. Each primary breast cancer and metastatic breast cancer were analysed on the same slide.</td></tr>
<tr><td>Length of follow up</td><td>1999 – 2007</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
14/137 (10%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
100/137 (73%)
12/137 (8.8%)
2/137 (1.5%)
23/137 (16.8%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*This additional data was extracted as a post-hoc analysis to feed into the health economic model.
</td></tr>
<tr><td>Source of funding</td><td>Italian Association for Cancer Research, Italian Ministry of Health</td></tr>
<tr><td>Comments</td><td>19% only with visceral distant metastasis.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Fabi A, Di Benedetto , A , Metro G, et al. (2011). HER-2 protein and gene variation between primary and metastatic breast cancer: Significance and impact on patient care. Clinical Cancer Research, 17(7), 2055-64.	
	Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
	Were valid methods used for identification of the condition for all participants included in the case series?	YES
	Did the case series have consecutive inclusion of participants?	YES
	Did the case series have complete inclusion of participants?	YES
	Was there clear reporting of the demographics of the participants in the study?	NO – demographic are reported poorly
	Was there clear reporting of clinical information of the participants?	YES
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

G.1.71 Gancberg 2002

Bibliographic reference	Gancberg D, Jarvinen T, di Leo, A et al. (2002). Evaluation of HER-2/NEU protein expression in breast cancer by immunohistochemistry: an interlaboratory study assessing the reproducibility of HER-2/NEU testing. Breast cancer research and treatment, 74(2), 113-20.
Study type	Case series
Aim	To compare HER-2 over-expression and amplification in primary tumours and their distant metastases
Patient characteristics	**Inclusion criteria** Patients with samples from primary tumour and distant metastases **Exclusion criteria** Locoregonal metastases **Baseline characteristics** Age : Not reported Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported

<table>
<tr><td>Bibliographic reference</td><td>Gancberg D, Jarvinen T, di Leo, A et al. (2002). Evaluation of HER-2/NEU protein expression in breast cancer by immunohistochemistry: an interlaboratory study assessing the reproducibility of HER-2/NEU testing. Breast cancer research and treatment, 74(2), 113-20.</td></tr>
<tr><td></td><td>Biopsy site : Bone (38), soft tissue (32), liver (26), lung or bronchus or pleura (13), stomach or duodenum or biliary tract or peritoneum (9), ovary (6), brain (2) and other (not reported)
Biopsy type : paraffin-embedded tissue
Hormone status : Not reported
Disease stage : Not reported
Survival/time to recurrence or progression – range : 1 months – 18 years</td></tr>
<tr><td>Number of Patients</td><td>107 by IHC, of which 7 unavailable due to detachment of the tissue during pre-treatment.
68 available using FISH.</td></tr>
<tr><td>Intervention</td><td>Fluorescence in situ hybridisation
Immunohistochemical</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Belgium</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
6 / 100 (6%) by IHC; 5/68 (7%) by FISH</td></tr>
<tr><td>Change in receptor expression direction for HER-2***
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
49/68 (72.1%)
3/68 (4.4%)
2/68 (2.9%)
14/68 (20.6%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*IHC: immunohistochemistry
**FISH: fluorescence in situ hybridisation
***This additional data was extracted as a post-hoc analysis to feed into the health economic model. Data using FISH only extracted.</td></tr>
</table>

Bibliographic reference	**Gancberg D, Jarvinen T, di Leo, A et al. (2002). Evaluation of HER-2/NEU protein expression in breast cancer by immunohistochemistry: an interlaboratory study assessing the reproducibility of HER-2/NEU testing. Breast cancer research and treatment, 74(2), 113-20.**
Source of funding	Les Amis de l'Institut Bordet Hoffmann-La Roche
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO
Did the case series have complete inclusion of participants?	NO
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.1.81 Hilton 2011

Bibliographic reference	**Hilton J F, Amir E, Hopkins S, et al. (2011). Acquisition of metastatic tissue from patients with bone metastases from breast cancer. Breast cancer research and treatment, 129(3), 761-5.**
Study type	Cohort
Aim	To compare the hormone receptor status of the metastasis to that of the primary tumour.
Patient characteristics	**Inclusion criteria** histologically confirmed breast cancer and radiological evidence of at least one bone metastasis that was amenable to CT-guided biopsy. **Exclusion criteria**

<table>
<tr><td>Bibliographic reference</td><td>Hilton J F, Amir E, Hopkins S, et al. (2011). Acquisition of metastatic tissue from patients with bone metastases from breast cancer. Breast cancer research and treatment, 129(3), 761-5.</td></tr>
<tr><td></td><td>Patients with a hematologic condition
Patients with a significant risk of bleeding

Baseline characteristics
Age – mean (range) : 55.3 (34 – 76)
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : Bone (40)
Biopsy type : CT-guided biopsy / Bone marrow trephine/aspirate
Hormone status : ER+ PR+ (26), ER+ PR- (9), ER- PR+ (0), ER- PR- (1), ER unknown (1), PR unknown (3)
Disease stage : Not reported
Survival/time to recurrence or progression</td></tr>
<tr><td>Number of Patients</td><td>40, of which 26 had sufficient bone metastases sample.</td></tr>
<tr><td>Intervention</td><td>Not reported</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
11 / 26 (42.3%)
12 / 26 (46.2%)
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td></td></tr>
<tr><td>Comments</td><td>Only 26 of the metastatic samples contained sufficient tumour for hormone receptor analysis

Positive result was defined as 10% or more of tumour cell nuclei staining positively with any intensity.</td></tr>
</table>

Bibliographic reference	**Hilton J F, Amir E, Hopkins S, et al. (2011). Acquisition of metastatic tissue from patients with bone metastases from breast cancer. Breast cancer research and treatment, 129(3), 761-5.**

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO – not all patients had paired samples
Did the case series have complete inclusion of participants?	NO – some patients withdrew consent
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.1.91 Hoefnagel 2010, Hoefnagel 2012

Bibliographic reference	**Hoefnagel LD, van de Vijver, MJ, van Slooten, H et al. (2010). Receptor conversion in distant breast cancer metastases. Breast Cancer Research, 12(5),** **Hoefnagel LD, Moelans CB, Meijer SL, et al. (2012). Prognostic value of estrogen receptor alpha and progesterone receptor conversion in distant breast cancer metastases. Cancer, 118(20), 4929-35.**
Study type	Case series
Aim	To evaluate the prognostic value of receptor conversion for ER and PR in distant non-bone breast cancer metastases
Patient characteristics	**Inclusion criteria** female breast cancer patients previously studied for receptor conversion of ER and PR in their metachronous non-bone distant metastases,

<table>
<tr><td>Bibliographic reference</td><td>Hoefnagel LD, van de Vijver, MJ, van Slooten, H et al. (2010). Receptor conversion in distant breast cancer metastases. Breast Cancer Research, 12(5),

Hoefnagel LD, Moelans CB, Meijer SL, et al. (2012). Prognostic value of estrogen receptor alpha and progesterone receptor conversion in distant breast cancer metastases. Cancer, 118(20), 4929-35.</td></tr>
<tr><td></td><td>Exclusion criteria
None reported

Baseline characteristics
Age – mean (range) : 53.7 years (25 – 88)
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : Brain (44), lung (43), liver (63), skin (76), gastro-intestinal (7)
Biopsy type : paraffin blocks
Hormone status : ER+ (147) / ER- (86) : PR+ (129) / PR- (104) : HER-2 + (47) / HER-2- (186)
Disease stage : Not reported
Survival/time to recurrence or progression : Not reported</td></tr>
<tr><td>Number of Patients</td><td>233</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical analysis</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>The Netherlands</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
24/ 233 (18.1%)
70 / 233 (41.7%)
12 / 233 (5.2%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Roche, Astra Zenica, and the American Women’s Club of The Hague/Pink Ribbon.</td></tr>
<tr><td>Comments</td><td></td></tr>
</table>

Bibliographic reference	**Hoefnagel LD, van de Vijver, MJ, van Slooten, H et al. (2010). Receptor conversion in distant breast cancer metastases. Breast Cancer Research, 12(5),** **Hoefnagel LD, Moelans CB, Meijer SL, et al. (2012). Prognostic value of estrogen receptor alpha and progesterone receptor conversion in distant breast cancer metastases. Cancer, 118(20), 4929-35.**
	Data on 10% threshold for conversion used for ER and PR Conversion data also available by individual site **JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.1.101 Idirisinghe 2010

Bibliographic reference	**Idirisinghe PK. A, Thike AA, Cheok PY, et al. (2010). Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. American journal of clinical pathology, 133(3), 416-29.**
Study type	Case series
Aim	To compare ER, PR, and c-ERBB2 status in series of primary breast carcinomas with their locoregional recurrences and distant metastases.
Patient characteristics	**Inclusion criteria**

<table>
<tr><td>Bibliographic reference</td><td>Idirisinghe PK. A, Thike AA, Cheok PY, et al. (2010). Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. American journal of clinical pathology, 133(3), 416-29.</td></tr>
<tr><td></td><td>Patients with primary breast carcinoma with subsequent histologically proven local recurrences and distant metastases

Exclusion criteria
None reported

Baseline characteristics
Age – mean (range) : 52.2 years (29 – 85)
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : distant metastases bone (35), skin (10), brain (6), lung (5), pleura (5), omentum (3), pericardium (3), ovary (2), intestine (1), adrenal gland (1), and liver (1).
Biopsy type : paraffin sections of the formalin-fixed tissue
Hormone status : ER+ (72) / ER- (45) : PR+ (59)/PR- (58) : HER-2 + (22)/HER-2- (95)
Disease stage : Not reported
Survival/time to recurrence or progression – mean (range) : 46.1 months (0.7 – 175.4)</td></tr>
<tr><td>Number of Patients</td><td>117 (72 distant, 45 local)</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical analysis</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Singapore</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
13 / 72 (18.1%)
30 / 72 (41.7%)
5 / 72 (6.9%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative</td><td>
57/72 (79.2%)
1/72 (1.4%)
4/72 (5.6%)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Idirisinghe PK. A, Thike AA, Cheok PY, et al. (2010). Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. American journal of clinical pathology, 133(3), 416-29.**
	• Positive to positive: 10/72 (13.9%) Quality of life: Not reported Change in management: Not reported Change in tumour type eg: breast to lung: Not reported Adverse events related to biopsy: Not reported ***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**
Source of funding	Singapore Cancer Syndicate
Comments	**Only data on patients (n = 72) with distant metastases used** **JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.1.111 Jensen 2012

Bibliographic reference	**Jensen J., Knoop A., Ewertz M., et al. (2012). ER, HER2, and TOP2A expression in primary tumor, synchronous axillary nodes, and asynchronous metastases in breast cancer. Breast cancer research and treatment, 132(2), pp.511-21.**
Study type	Case series

Bibliographic reference	**Jensen J., Knoop A., Ewertz M., et al. (2012). ER, HER2, and TOP2A expression in primary tumor, synchronous axillary nodes, and asynchronous metastases in breast cancer. Breast cancer research and treatment, 132(2), pp.511-21.**
Aim	To analyse paired samples of primary tumours, and later asynchronous metastases allowing a direct within patient comparison of changes in ER, HER-2, and TOP2A.
Patient characteristics	**Inclusion criteria** Patients with biopsies from distant metastases Patients with paired samples **Exclusion criteria** Patients with primary systemic metastases and with bilateral breast cancer were excluded. **Baseline characteristics** Age : Not reported Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : CNS (7), Bones (20), Liver (23), Skin (outside breast area) (4), Lungs (3), Pleural effusion (10), Abdomen (other than liver) (5), Lymph nodes chest (2), Lymph nodes contralateral: Axillary, supra/infraclavicular,collum (3), Other (7) Biopsy type : formalin-fixed paraffin-embedded tumor blocks Hormone status : ER+ (95) / ER- (23) : PR (Not reported) : HER-2+ (10) / HER-2- (104) Disease stage : Not reported Survival/time to recurrence or progression : median time from primary surgery to biopsy: 59 months (range: 8 – 323 months)
Number of Patients	118
Intervention	Immunohistochemical analysis Fluorescence In situ hybridisation Chromogenic In situ hybridisation
Length of follow up	NA
Location	Denmark
Outcomes measures and effect size	Data on distant metastases only reported

Bibliographic reference	**Jensen J., Knoop A., Ewertz M., et al. (2012). ER, HER2, and TOP2A expression in primary tumor, synchronous axillary nodes, and asynchronous metastases in breast cancer. Breast cancer research and treatment, 132(2), pp.511-21.**

Changes in receptor expression between the two samples • ER • PR • HER-2	 14/118 Not reported 10/114
Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

Source of funding: Not reported

Comments

ER positive defined as weak immunostaining in 1% of tumour nuclei (H-score C 1)

HER-2 was considered positive if IHC was scored as 3+, or IHC 2+ and had a HER-2 gene to chromosome 17 ratio for CISH of ≥2.2. CISH analysis was performed for all HER-2 IHC equivocal cases.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO – some tissue sample taken from a previous study
Did the case series have complete inclusion of participants?	NO – not all cases accounted for
Was there clear reporting of the demographics of the participants in the study?	NO – demographics were poorly reported
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES

Bibliographic reference	**Jensen J., Knoop A., Ewertz M., et al. (2012). ER, HER2, and TOP2A expression in primary tumor, synchronous axillary nodes, and asynchronous metastases in breast cancer. Breast cancer research and treatment, 132(2), pp.511-21.**	
	Was statistical analysis appropriate?	YES

1

G.1.122 Karagoz Ozen 2014

Bibliographic reference	**Karagoz Ozen DS, Ozturk Mehmet A, et al. (2014). Receptor expression discrepancy between primary and metastatic breast cancer lesions. Oncology research and treatment, 37(11), 622-6.**
Study type	Case series
Aim	To compare the receptor status of the primary breast cancer tumour to that of distant metastases.
Patient characteristics	**Inclusion criteria** Patients with histological evidence of breast cancer **Exclusion criteria** Non-metastatic breast cancer No biopsy from relapse / metastatic site(s) Inadequate data for assessing eligibility **Baseline characteristics** Age – median (range) : 48.5 years (30–77) Gender : 56 (96.6%) female Ethnicity : Not reported Treatment at baseline : neoadjuvant antracycline + taxane-based chemotherapy regimens, (3 stage I-III), antracycline- ± taxane-based chemotherapy regimens (34 stage I-III), hormonal treatments (8 stage I-III), systemic chemotherapy - antracycline or taxane or capecitabine - regimens (10 stage IV), hormonal therapy (stage IV). Biopsy site : Not reported Biopsy type : Not reported Hormone status : ER+ (39)/ ER- (17) : PR+ (35)/ PR- (20) : HER-2+ (9) / HER-2 – (36) Disease stage : 47 had stage I-III Survival/time to recurrence or progression : Not reported

<table>
<tr><td>Bibliographic reference</td><td>Karagoz Ozen DS, Ozturk Mehmet A, et al. (2014). Receptor expression discrepancy between primary and metastatic breast cancer lesions. Oncology research and treatment, 37(11), 622-6.</td></tr>
<tr><td>Number of Patients</td><td>58 – of which 56 available for ER, 55 available for PR and 45 available for HER-2.</td></tr>
<tr><td>Intervention</td><td>Immunohistochemistry</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Turkey</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
10 / 56 (17.9%)
25 / 55 (45.5%)
6 / 45 (13.3%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
31/45 (69%)
5/45 (11%)
4/45 (9%)
5/45 (11%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>11 / 27 (40.7%)**</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*This additional data was extracted as a post-hoc analysis to feed into the health economic model.

**A total of 27/58 (46.5%) patients had ER and/or PR changes in the primary and metastatic samples – the 11 of 27 reported for change in management relates to these 27 patients with ER and/or PR changes. Change in management was not reported separately for the individual receptors.</td></tr>
<tr><td>Source of funding</td><td>None</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Karagoz Ozen DS, Ozturk Mehmet A, et al. (2014). Receptor expression discrepancy between primary and metastatic breast cancer lesions. Oncology research and treatment, 37(11), 622-6.	
	Did the case series have consecutive inclusion of participants?	YES
	Did the case series have complete inclusion of participants?	NO – data on receptor status not available for all patients
	Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
	Was there clear reporting of clinical information of the participants?	NO – no report of site of distant metastases
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

G.1.131 Lorincz 2006

Bibliographic reference	Lorincz 2006
Study type	Case series
Aim	To analyse the HER-2/neu status of bone metastasis compared to the primary tumour in a larger cohort of breast cancer cases.
Patient characteristics	**Inclusion criteria** - Bone metastatic samples of breast cancer **Exclusion criteria** - Overdecalcination or insufficient amount of tumour tissue in the section Age – median (range) : 59 (not reported) Gender: 98% female Ethnicity: not reported Treatment at baseline: not reported Biopsy site: Bone Biopsy type: open biopsies of bone metastases obtained during transfocal stabilisation of impending, complete pathological fractures, or resection of bone metastases. Hormone status: not reported

<table>
<tr><th>Bibliographic reference</th><td>Lorincz 2006</td></tr>
<tr><td></td><td>Disease stage: not reported
Survival/time to recurrence or progression: not reported</td></tr>
<tr><th>Number of Patients</th><td>N=48; 23 with paired samples from primary tumour and recurrence</td></tr>
<tr><th>Intervention</th><td>Immunohistochemistry performed using the HercepTest

Fluorescence in situ hybridisation was performed in cases where the breast cancer had 2+ or 3+ HER-2/neu IHC status in the bone metastases and/or in the primary tumours or if discordance was found in HER-2/neu status detected by IHC between primary tumours and their corresponding bone metastases.</td></tr>
<tr><th>Length of follow up</th><td>NA</td></tr>
<tr><th>Location</th><td>Hungary</td></tr>
<tr><th>Outcomes measures and effect size</th><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
2/23 (9%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
19/23 (83%)
0/23 (0%)
2/23 (9%)
2/23 (9%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*This additional data was extracted as a post-hoc analysis to feed into the health economic model.
</td></tr>
<tr><th>Source of funding</th><td>Not reported</td></tr>
<tr><th>Comments</th><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Lorincz 2006	
	Were valid methods used for identification of the condition for all participants included in the case series?	YES
	Did the case series have consecutive inclusion of participants?	YES
	Did the case series have complete inclusion of participants?	NO; paired samples available for 23/48 subjects
	Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
	Was there clear reporting of clinical information of the participants?	YES
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

G.1.141 Lower 2005
2

Bibliographic reference	**Lower EE, Glass EL, Bradley DA, et al. (2005). Impact of metastatic estrogen receptor and progesterone receptor status on survival. Breast Cancer Research and Treatment, 90(1), 65-70.**
Study type	Retrospective case series
Aim	To investigate the concordance of primary and metastatic ER content between primary and metastatic invasive breast cancer
Patient characteristics	**Inclusion criteria** Patients with metastatic breast cancer **Exclusion criteria** Lack of biopsy-proven metastatic disease with hormone receptor status Metastatic data only available from axillary lymph node tissue **Baseline characteristics** Age range : 27 – 84 years Gender : Not reported

<table>
<tr><td>Bibliographic reference</td><td>Lower EE, Glass EL, Bradley DA, et al. (2005). Impact of metastatic estrogen receptor and progesterone receptor status on survival. Breast Cancer Research and Treatment, 90(1), 65-70.</td></tr>
<tr><td></td><td>Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : local (63), lymph node (5); bone (48), lung (37), brain (13), liver (22), orbit (1), ovary (3) skin (5), colon (1), pancreas (2)
Biopsy type : Not reported
Hormone status : ER+ (115) / ER- (85) : PR+(116) / PR- (88) / unknown (6)
Disease stage : Stage 1 (58); Stage 2 (100); Stage 3 (27); Stage 4 (12); unknown (3)
Survival/time to recurrence or progression :</td></tr>
<tr><td>Number of Patients</td><td>200, of which 137 distant for ER and 114 distant for PR</td></tr>
<tr><td>Intervention</td><td>Unclear</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>United States</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples – distant metastases only
• ER
• PR
• HER-2</td><td>36/137 (26%)
46/114 (40%)
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td></td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Lower EE, Glass EL, Bradley DA, et al. (2005). Impact of metastatic estrogen receptor and progesterone receptor status on survival. Breast Cancer Research and Treatment, 90(1), 65-70.**

Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO – population was selected
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.1.151 Okita 2013

Bibliographic reference	**Okita Y, Narita Y, Suzuki T et al. (2013). Extended trastuzumab therapy improves the survival of HER-2-positive breast cancer patients following surgery and radiotherapy for brain metastases. Molecular and Clinical Oncology, 1(6), 995-1001.**
Study type	Case series
Aim	To compare the expression of ER, PR and HER-2 in pathology samples from primary tumours and brain metastases in order to evaluate whether the previous therapy was able to modify this status and to determine whether biomarker alterations affect prognosis after brain metastases. To also investigated the effect of trastuzumab therapy after brain metastases.
Patient characteristics	**Inclusion criteria** Patients initially diagnosed with breast cancer and underwent surgical removal of brain metastases between 200 - 2012 **Exclusion criteria** None reported **Baseline characteristics** Age : median 45.5 yrs (range 31 – 76)

<table>
<tr><td>Bibliographic reference</td><td>Okita Y, Narita Y, Suzuki T et al. (2013). Extended trastuzumab therapy improves the survival of HER-2-positive breast cancer patients following surgery and radiotherapy for brain metastases. Molecular and Clinical Oncology, 1(6), 995-1001.</td></tr>
<tr><td></td><td>Gender : 95.2% female, 4.8% male
Ethnicity : not reported
Treatment at baseline : Prior to developing brain metastases, all with ER or PR alterations received hormone therapy and 2 with HER-2 alteration received trastuzumab. Brain metastases - 34 patients received whole-brain radiotherapy (WBRT), 3 received WBRT and local brain radiotherapy (LBRT) and 13 received WBRT and stereotactic radiosurgery (SRS). 9 patients received LBRT and 1 received LBRT plus SRS.
Biopsy site : breast and brain
Biopsy type : unclear, leptomeningeal metastasis (LMM) evaluated by lumbar puncture
Hormone status : unclear
Disease stage : unclear
Survival/time to recurrence or progression : median overall survival – 6.5 yrs, median survival time after brain metastases – 1.1 years</td></tr>
<tr><td>Number of Patients</td><td>62</td></tr>
<tr><td>Intervention</td><td>The ER, PR and HER-2 status was determined in the samples from the primary and metastatic lesions. The first brain metastatic free survival time was defined as the time from the first surgery for the primary tumour to the first detection of brain metastasis on magnetic resonance imaging (MRI). Surgical specimens were fixed in 10% formalin and embedded in paraffin. Hematoxylin and eosin‑stained specimens were examined in order to determine the histological tumour type.</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow up</td><td>Patients underwent surgical removal of brain metastases between 2000 and 2012. These patients received treatment for primary breast cancer between 182 and 2011.</td></tr>
<tr><td>Location</td><td>Japan</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
13/60 (22%)
6/58 (10%)
7/58 (12%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative</td><td>
30/58 (52%)
4/58 (7%)
3/58 (5%)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Okita Y, Narita Y, Suzuki T et al. (2013). Extended trastuzumab therapy improves the survival of HER-2-positive breast cancer patients following surgery and radiotherapy for brain metastases. Molecular and Clinical Oncology, 1(6), 995-1001.**

• Positive to positive	21/58 (36%)
Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	4/15 with HER-2 who did not receive trastuzumab positive presented with LMM 6/35 in HER-2 negative presented with LMM
Adverse events related to biopsy	Not reported

***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**

Source of funding	Ministry of Education, Science and Culture of Japan
Comments	The HER-2/neu status, as assessed using the HercepTest assay was scored by the pathologists at each centre on a scale of 0 to 3+, according to the Dako scoring system. HER-2/neu positivity was defined as HER-2/neu 3+ or HER-2/neu 2+ and fluorescence in situ hybridization positivity

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

Bibliographic reference	Okita Y, Narita Y, Suzuki T et al. (2013). Extended trastuzumab therapy improves the survival of HER-2-positive breast cancer patients following surgery and radiotherapy for brain metastases. Molecular and Clinical Oncology, 1(6), 995-1001.

1

G.1.162 Omoto 2010

Bibliographic reference	Omoto Y, Kurosumi M, Hozumi Y, et al. (2010). Immunohistochemical assessment of primary breast tumors and metachronous brain metastases, with particular regard to differences in the expression of biological markers and prognosis. Experimental and Therapeutic Medicine, 1(4), 561-7.
Study type	Case series
Aim	To compare receptor status between primary breast tumours and metachronous brain metastases.
Patient characteristics	**Inclusion criteria** Patients diagnosed as having breast cancer and who underwent breast surgery Developed metachronous brain metastasis **Exclusion criteria** None reported **Baseline characteristics** Age – median (range) : 47 years (33 – 69) Gender : 21 (100%) female Ethnicity : Not reported Treatment at baseline : Biopsy site : Brain (21) Biopsy type : tumour resection Hormone status : ER+ (9) / ER- (12) : PR+ (6) / PR- (15) : HER-2+ (7) / HER-2- (14) Disease stage : Not reported Survival/time to recurrence or progression – mean : 44.5 months
Number of Patients	21
Intervention	Resected tissues were fixed in 10% formalin solution, embedded in paraffin and stained with H&E for routine histopathologic examination.

<table>
<tr><td>Bibliographic reference</td><td>Omoto Y, Kurosumi M, Hozumi Y, et al. (2010). Immunohistochemical assessment of primary breast tumors and metachronous brain metastases, with particular regard to differences in the expression of biological markers and prognosis. Experimental and Therapeutic Medicine, 1(4), 561-7.</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Japan</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
4 / 21 (19.0%)
4 / 21 (19.0%)
4 / 21 (19.0%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
11/21 (52%)
3/21 (14%)
1/21 (5%)
6/21 (29%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*This additional data was extracted as a post-hoc analysis to feed into the health economic model.
</td></tr>
<tr><td>Source of funding</td><td>Japanese Breast Cancer Society.</td></tr>
<tr><td>Comments</td><td>The results for ER and PR p53 were considered positive when >10% of the nuclei of the carcinoma cells showed positive staining for the respective markers.
Scores of 0 and 1+ represented a negative result for HER-2/neu overexpression, whereas scores of 2+ and 3+ were considered a positive result.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Omoto Y, Kurosumi M, Hozumi Y, et al. (2010). Immunohistochemical assessment of primary breast tumors and metachronous brain metastases, with particular regard to differences in the expression of biological markers and prognosis. Experimental and Therapeutic Medicine, 1(4), 561-7.**

Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.1.172 Regitnig 2004

Bibliographic reference	**Regitnig P, Schippinger W, Lindbauer M et al. (2004). Change of HER-2/neu status in a subset of distant metastases from breast carcinomas. The Journal of pathology, 203(4), 918-26.**
Study type	Case series
Aim	To compare HER-2 status from primary tumour and their distant metastases
Patient characteristics	**Inclusion criteria** Samples from primary tumour and distant metastases **Exclusion criteria** None reported **Baseline characteristics** Age – median (range): 53.7 years (33 – 78) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Bone/bone marrow (8), skin other than ipsilateral breast (6), brain (5), lung or pleura (4), liver (3) pancreas (10) stomach (1), kidney (1) peritoneum (1) and cervical lymph node (1) Biopsy type : Stored serum

<table>
<tr><td>Bibliographic reference</td><td>Regitnig P, Schippinger W, Lindbauer M et al. (2004). Change of HER-2/neu status in a subset of distant metastases from breast carcinomas. The Journal of pathology, 203(4), 918-26.</td></tr>
<tr><td></td><td>Hormone status : Not reported
Disease stage : Not reported
Survival/time to recurrence or progression mean (range): 45.5 months (2 – 103)</td></tr>
<tr><td>Number of Patients</td><td>31</td></tr>
<tr><td>Intervention</td><td>Fluorescence in situ hybridisation
ELISA</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Austria</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
8 / 31 (25.8%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Austria Cancer Aid/Styria</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>NO</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Regitnig P, Schippinger W, Lindbauer M et al. (2004). Change of HER-2/neu status in a subset of distant metastases from breast carcinomas. The Journal of pathology, 203(4), 918-26.

Did the case series have complete inclusion of participants?	NO
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

[1] *<Insert Note here>*

G.1.183 Santinelli 2008

Bibliographic reference	Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.
Study type	Case series
Aim	To determine HER-2 status in primary breast invasive carcinomas and in the paired lymph node metastases, locoregional recurrence and distant metastases,
Patient characteristics	**Inclusion criteria** Patients with metachronous breast cancer metastases (local and distant) **Exclusion criteria** Not reported **Baseline characteristics** Age – mean (range) : 50.4 years (31 – 76) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Bone (4), cervical (1), CNS (5), colon (2), liver (4), lung (3), ovary (1), peritoneum (1), pleura (9), retroperitoneum (1), skin (3), stomach (1)

<table>
<tr><td>Bibliographic reference</td><td>Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.</td></tr>
<tr><td></td><td>Biopsy type : paraffin-embedded blocks
Hormone status : ER+ (9) / ER- (16) / unknown (10) : PR+ (11) / PR- (14) / unknown (0) : HER-2 + (12) / HER-2- (42).
Disease stage : Not reported
Survival/time to recurrence or progression : Not reported</td></tr>
<tr><td>Number of Patients</td><td>35</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical analysis
Fluorescence in situ hybridization</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
7 / 35 (20.0%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
20/35 (57%)
6/35 (17%)
4/35 (11%)
5/35 (14%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*This additional data was extracted as a post-hoc analysis to feed into the health economic model.
**FISH results not reported - 2+ score considered HER-2+
***FISH results not reported - 2+ score considered HER-2+
**** Assumed that FISH is the definitive test
</td></tr>
</table>

Bibliographic reference	**Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.**
Source of funding	None reported
Comments	Data on 35 cases with distant metastases only used in analyses HER-2 positivity defined as 2+ or 3+ in IHC analysis **JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

[2] *<Insert Note here>*

1

G.1.192 Shen 2015

Bibliographic reference	**Shen Q, Sahin AA, Hess KR, et al. (2015). Breast cancer with brainmetastases: Clinicopathologic features, survival, and paired biomarker analysis. Oncologist, 20(5), 466-73.**
Study type	Case series
Aim	To compare ER, PR, and HER-2 expression in the paired primary and brain tumours.
Patient characteristics	**Inclusion criteria** Patients undergoing craniotomy for breast cancer brain metastasis **Exclusion criteria** Not reported **Baseline characteristics** Age – median (range) : 46 years (24 – 73). Gender : Not reported Ethnicity : White (99), Black and other (40) Treatment at baseline : Not reported Biopsy site : Brain Biopsy type : Not reported Hormone status : ER+ (58) / ER- (76) : PR+ (51) / PR- (82) : HER-2+ (56) / HER-2- (72) Disease stage : Stage I (25) , stage II (37), stage III (54), stage IV (21) Survival/time to recurrence or progression – median (range) : 46 months (0 – 266).
Number of Patients	140 of which known primary and metastases for ER = 34, for PR = 34 and for HER-2 = 36.
Intervention	Immunohistochemical staining Fluorescence in situ staining
Length of follow up	NA
Location	United States
Outcomes measures and effect size	Changes in receptor expression between the two samples • ERPR: 10 / 35 (29%)

Bibliographic reference	**Shen Q, Sahin AA, Hess KR, et al. (2015). Breast cancer with brainmetastases: Clinicopathologic features, survival, and paired biomarker analysis. Oncologist, 20(5), 466-73.**

• HER-2	7 / 34 (21%) 1 / 36 (3%)
Change in receptor expression direction for HER-2* • Negative to negative • Negative to positive • Positive to negative • Positive to positive	 19/36 (53%) 1/36 (3%) 0/36 (0%) 16/36 (44%)
Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**

Source of funding	Sheila Wynne Research Fund.
Comments	Tumours with HER-2 immunohistochemical staining intensity of 3+ were considered positive, whereas those with 2+ staining intensity were further evaluated by fluorescent in situ hybridization (FISH).

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	NO – not all participants had paired samples
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES

Bibliographic reference	**Shen Q, Sahin AA, Hess KR, et al. (2015). Breast cancer with brainmetastases: Clinicopathologic features, survival, and paired biomarker analysis. Oncologist, 20(5), 466-73.**
	Was statistical analysis appropriate? — YES

1

G.1.202 Shiino 2016

Bibliographic reference	**Shiino Sho, Kinoshita Takayuki, Yoshida Masayuki, et al. (2016). Prognostic Impact of Discordance in Hormone Receptor Status Between Primary and Recurrent Sites in Patients With Recurrent Breast Cancer. Clinical breast cancer, 16(4), .e133-40.**
Study type	Retrospective case series
Aim	To assess the prognostic impact of discordance in hormone receptor status between primary and recurrent sites in patients with recurrent breast cancer
Patient characteristics	**Inclusion criteria** Patients who underwent surgery for primary breast cancer between 1985 and 2013 in the database of the Department of Breast Surgery in the National Cancer Centre Hospital. **Exclusion criteria** Not reported **Baseline characteristics** Age – median (range): 54 years (30 – 81). Gender : Not reported Ethnicity : Not reported Treatment at baseline: Neoadjuvant therapy – 23%; adjuvant chemotherapy – 78%; adjuvant hormone therapy – 73%; Trastuzumab – 12% Biopsy site : Breast, chest wall, regional lymph node, lung, bone, liver, brain, distant lymph node, other metastatic sites Biopsy type : Either core needle biopsy or surgical excision for recurrent breast cancer Hormone status, n : ER+ (110) / ER- (43) : PR+ (82) / PR- (71) : HER-2+ (32) / HER-2- (121) Disease stage: not reported Survival/time to recurrence or progression – not reported

<table>
<tr><td>Bibliographic reference</td><td>Shiino Sho, Kinoshita Takayuki, Yoshida Masayuki, et al. (2016). Prognostic Impact of Discordance in Hormone Receptor Status Between Primary and Recurrent Sites in Patients With Recurrent Breast Cancer. Clinical breast cancer, 16(4), .e133-40.</td></tr>
<tr><td>Number of Patients</td><td>N=153, of which 49 distant.</td></tr>
<tr><td>Intervention</td><td>Formalin-fixed paraffin-embedded tumour tissues specimens of the primary and recurrent sites were cut into 3um thick sections and subjected to immunohistochemical staining for ER, PR and HER-2.</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Japan</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>12/49 (8%)
15/49 (10%)
6/49 (4)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Supported in part by a grant I aid for Scientific Research from Japan Society for Promotion of Science and the National Centre Research and Development Fund</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the demographics of the participants in the study?</td><td>NO – demographic data was reported poorly</td></tr>
<tr><td>Was there clear reporting of clinical information of the participants?</td><td>YES</td></tr>
<tr><td>Were the outcomes or follow up results of cases clearly reported?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the presenting site(s)/clinic(s) demographic information?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Shiino Sho, Kinoshita Takayuki, Yoshida Masayuki, et al. (2016). Prognostic Impact of Discordance in Hormone Receptor Status Between Primary and Recurrent Sites in Patients With Recurrent Breast Cancer. Clinical breast cancer, 16(4), .e133-40.	
	Was statistical analysis appropriate?	YES

1

G.1.212 Shimizu 2000

Bibliographic reference	Shimizu C, Fukutomi T, Tsuda H, et al. (2000). c-erbB-2 protein overexpression and p53 immunoreaction in primary and recurrent breast cancer tissues. Journal of surgical oncology, 73(1), 17-20.
Study type	Case series
Aim	T determine whether expression levels of c-rebB-2 and p53 proteins in breast cancer tissues differ in primary tumours and their respective metastatic lesions.
Patient characteristics	**Inclusion criteria** Patients who had undergone radical surgery for primary tumours and surgical resection of asynchronous metastatic lesions **Exclusion criteria** Not reported **Baseline characteristics** Age – mean (range) : 50 years (35 – 75) Gender : 21/21 (100%) women Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Liver (1), Lung (3),Supraclavicular lymph nodes (3), skin (14) Biopsy type : Not reported Hormone status : Not reported Disease stage : Not reported Survival/time to recurrence or progression – mean (range) 19 months (5 – 104)
Number of Patients	21
Intervention	Immunohistochemical staining and sandwich enzyme immunoassay
Length of follow up	Average time between biopsy was 19 months (range 5 to 104)
Location	Japan

Bibliographic reference	**Shimizu C, Fukutomi T, Tsuda H, et al. (2000). c-erbB-2 protein overexpression and p53 immunoreaction in primary and recurrent breast cancer tissues. Journal of surgical oncology, 73(1), 17-20.**
Outcomes measures and effect size	

Changes in receptor expression between the two samples • ER • PR • HER-2	 5 / 20 (25.0%) 6 / 20 (30.0%) 0 / 21 (0%)
Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

.

Source of funding	None reported
Comments	One patient did not have tissue tested at for ER/PR on metastatic site

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	NO – not all participants had paired samples
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

Bibliographic reference	Shimizu C, Fukutomi T, Tsuda H, et al. (2000). c-erbB-2 protein overexpression and p53 immunoreaction in primary and recurrent breast cancer tissues. Journal of surgical oncology, 73(1), 17-20.

[3] *<Insert Note here>*

G.1.224 Simmons 2009

Bibliographic reference	Simmons C, Miller N, Geddie W, et al. (2009). Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases?. Annals of Oncology, 20(9), 1499-504.
Study type	Prospective cohort
Aim	To evaluate possible changes that occur in ER, PR, and HER-2 status between primary tumour and distant metastases
Patient characteristics	**Inclusion criteria** Suspected clinical or radiological recurrence **Exclusion criteria** Patients with operable breast or axillary recurrence with no evidence of metastatic disease or if they had already started on therapy for metastatic disease. If the location of the lesion was not amenable to biopsy by the following criteria: rib lesion, brain metastases, lesion <1 cm in size, or lesion in a location that could not be reached by core biopsy techniques available with interventional radiology. international normalized ratio or partial thromboplastin time above the upper limit of normal for the institution. **Baseline characteristics** Age – Not reported Gender : Not reported Ethnicity : Not reported Treatment at baseline : adjuvant chemotherapy (21), endocrine therapy (19), trastuzumab (1) Biopsy site : Bone (11), Soft tissue (not surgically curable) (10), Pleural effusion (3), Liver (3), Lung (1), CSF (1) Biopsy type : core biopsy by an interventional radiologist, fine needle aspirate by a diagnostic pathologist, or drainage of pleural fluid by ultrasound guidance Hormone status : ER+ (23) / ER- (12) : PR+ (13) / PR- (22): HER-2 + (13) / HER-2- (22)

<table>
<tr><td>Bibliographic reference</td><td>Simmons C, Miller N, Geddie W, et al. (2009). Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases?. Annals of Oncology, 20(9), 1499-504.</td></tr>
<tr><td></td><td>Disease stage : Stage 1 (6), stage 2a (6), stage 2b (8), stage 3a (9), stage 3b (3), stage 3c (4)
Survival/time to recurrence or progression – median (IQR range) : 2.4 years (1.2 – 6.5).</td></tr>
<tr><td>Number of Patients</td><td>35, of which 29 included in analysis. 3 samples were diagnosed as benign disease and 1 as low grade follicular lymphoma.</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical analysis
Fluorescence in situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
3 / 25 (12.0%)
7 / 25 (28.0%)
2 / 25 (8.0%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>6 / 29 (20.7%)</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Canadian Breast Cancer Foundation, Ontario Chapter</td></tr>
<tr><td>Comments</td><td>three diagnosed as benign disease (two bone biopsies and one cerebrospinal fluid) and one sample diagnosed as low-grade follicular lymphoma.

The threshold values for reporting positivity were 10% for ER and PR

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>NO</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Simmons C, Miller N, Geddie W, et al. (2009). Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases?. Annals of Oncology, 20(9), 1499-504.

Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.1.232 Tapia 2007

Bibliographic reference	Tapia C, Savic S, Wagner U, et al. (2007). HER-2 gene status in primary breast cancers and matched distant metastases. Breast Cancer Research, 9(3)
Study type	Case series
Aim	To compare HER-2 status in a series of primary breast cancers and matched distant metastases
Patient characteristics	**Inclusion criteria** Availability of matched samples from primary tumour and distant metastases **Exclusion criteria** Not reported **Baseline characteristics** Age – mean (range) : 57.5 years (26 – 85) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Ascites (3), liver (4), lung (9), distant lymph nodes (3), pericardium (1), pleura (74), skin/soft tissue (3) and central nervous system (8) Biopsy type : Not reported

<table>
<tr><td>Bibliographic reference</td><td>Tapia C, Savic S, Wagner U, et al. (2007). HER-2 gene status in primary breast cancers and matched distant metastases. Breast Cancer Research, 9(3)</td></tr>
<tr><td></td><td>Hormone status : Not reported
Disease stage : Not reported
Survival/time to recurrence or progression – median (range) : 66 months (0 – 254)</td></tr>
<tr><td>Number of Patients</td><td>105</td></tr>
<tr><td>Intervention</td><td>Fluorescence in situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>66 months (0 – 254)</td></tr>
<tr><td>Location</td><td>Switzerland</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
8 / 105 (7.6%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
80/105 (76%)
3/105 (3%)
5/105 (5%)
17/105 (16%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*This additional data was extracted as a post-hoc analysis to feed into the health economic model.
</td></tr>
<tr><td>Source of funding</td><td>Produits Roche</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Tapia C, Savic S, Wagner U, et al. (2007). HER-2 gene status in primary breast cancers and matched distant metastases. Breast Cancer Research, 9(3)	
	Were valid methods used for identification of the condition for all participants included in the case series?	YES
	Did the case series have consecutive inclusion of participants?	YES
	Did the case series have complete inclusion of participants?	YES
	Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
	Was there clear reporting of clinical information of the participants?	YES
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

[4] *<Insert Note here>*

G.1.244 Vincent Salomon 2002

Bibliographic reference	**Vincent-Salomon A, Jouve M, Genin P, et al. (2002). HER-2 status in patients with breast carcinoma is not modified selectively by preoperative chemotherapy and is stable during the metastatic process. Cancer, 94(8), 2169-73.**
Study type	Cohort study
Aim	To verify that the HER-2 status of patients with metastatic breast carcinoma was identical in primary tumours and metastatic tumours.
Patient characteristics	**Inclusion criteria** Availability of matched samples from primary tumour and distant metastases **Exclusion criteria** Not reported **Baseline characteristics**

<table>
<tr><td>Bibliographic reference</td><td>Vincent-Salomon A, Jouve M, Genin P, et al. (2002). HER-2 status in patients with breast carcinoma is not modified selectively by preoperative chemotherapy and is stable during the metastatic process. Cancer, 94(8), 2169-73.</td></tr>
<tr><td></td><td>Age – mean (range) : 49 years (31 – 74)
Gender : 44 (100%) female
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : liver (17), lung (27)
Biopsy type : surgical hepatic or bronchopulmonary biopsy specimens.
Hormone status : ER + (29) / ER- (15), PR + (22) / PR- (22); HER-2 + (11) / HER-2- (33)
Disease stage : Not reported
Survival/time to recurrence or progression – mean (range) : 6.5 years (1 – 19).</td></tr>
<tr><td>Number of Patients</td><td>44</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical analysis
Fluorescence in situ hybridization (FISH).</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>United States</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
2 / 44 (4.5%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
33/44 (75%)
0/44 (0%)
2/44 (5%)
9/44 (20%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Vincent-Salomon A, Jouve M, Genin P, et al. (2002). HER-2 status in patients with breast carcinoma is not modified selectively by preoperative chemotherapy and is stable during the metastatic process. Cancer, 94(8), 2169-73.**
	***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**
Source of funding	
Comments	HER-2 was considered positive when > 60% of the cells were stained. **JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YEs
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.1.252 Wu 2008

Bibliographic reference	**Wu J M, Fackler M J, Halushka M K, et al. (2008). Heterogeneity of breast cancer metastases: Comparison of therapeutic target expression and promoter methylation between primary tumors and their multifocal metastases. Clinical Cancer Research, 14(7), 1938-46.**
Study type	Case series

<table>
<tr><td>Bibliographic reference</td><td>Wu J M, Fackler M J, Halushka M K, et al. (2008). Heterogeneity of breast cancer metastases: Comparison of therapeutic target expression and promoter methylation between primary tumors and their multifocal metastases. Clinical Cancer Research, 14(7), 1938-46.</td></tr>
<tr><td>Aim</td><td>To analyse cancer metastases using tissues derived from “rapid autopsies” done within 4 hours of the deaths of 10 patients with metastatic breast cancer.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
Patients with metastatic breast cancer

Exclusion criteria
None reported

Baseline characteristics
Age median (range) : 49.4 years (29 – 82)
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : Bone (8), liver (7)
Biopsy type : Paraffin-tissue blocks
Hormone status : ER + (6) / ER- (4), PR + (5) / PR- (5); HER-2 + (1) / HER-2- (9)
Disease stage : Not reported
Survival/time to recurrence or progression –: Not reported</td></tr>
<tr><td>Number of Patients</td><td>10</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical staining
Fluorescence in situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>United States</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
0 / 10 (0%)
1 / 10 (10.0%)
0 / 10 (0%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Wu J M, Fackler M J, Halushka M K, et al. (2008). Heterogeneity of breast cancer metastases: Comparison of therapeutic target expression and promoter methylation between primary tumors and their multifocal metastases. Clinical Cancer Research, 14(7), 1938-46.**

• Negative to negative • Negative to positive • Positive to negative • Positive to positive	9/10 (90%) 1/10 (10%) 0/10 (0%) 0/10 (0%)
Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**

Source of funding	Department of Defense Center of Excellence, Belfer Foundation, and Avon Foundation.
Comments	HER-2 positivity was defined as uniform intense membrane staining of >30% of tumour cells.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1 [5]
2

G.1.261 Yang 2014

Bibliographic reference	**Yang YF, Liao YY, Yang M, et al. (2014). Discordances in ER, PR and HER-2 receptors between primary and recurrent/metastatic lesions and their impact on survival in breast cancer patients. Medical Oncology, 31(10), 1-10.**
Study type	Case series
Aim	To evaluate the frequency of discordance regarding the ER, PR and HER-2 status between primary tumours and recurrent/ metastatic lesions
Patient characteristics	**Inclusion criteria** Patients who underwent biopsy or surgical resection of suspected recurrent breast cancer **Exclusion criteria** Not reported **Baseline characteristics** Age – mean (range) : 48 years (26 – 77) Gender : 133 (100%) female Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Locoregional (28), distant soft tissue (28), lung (26), bone (23), liver (15), ovary (3), serous membranes (3), cutaneous lesions (3), gastrointestinal (2), renal (2) Biopsy type : surgical hepatic or bronchopulmonary biopsy specimens. Hormone status : ER + (88) / ER- (45), PR + (91) / PR- (42); HER-2 + (25) / HER-2- (108) Disease stage : Not reported Survival/time to recurrence or progression : Not reported
Number of Patients	133, of which 105 with distant metastases
Intervention	Immunohistochemical analysis Fluorescence in situ hybridisation
Length of follow up	NA
Location	China
Outcomes measures and effect size	Changes in receptor expression between the two samples – distant metastases only • ER: 21 / 105 (20.0%)

Bibliographic reference	**Yang YF, Liao YY, Yang M, et al. (2014). Discordances in ER, PR and HER-2 receptors between primary and recurrent/metastatic lesions and their impact on survival in breast cancer patients. Medical Oncology, 31(10), 1-10.**

• PR • HER-2	40 / 105 (38.1%) 7 / 105 (6.7%)
Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**

Source of funding	National Natural Science Foundation of China.
Comments	In four (2.6 %) cases, the biopsy of the suspected metastatic lesion showed benign disease. Data on distant metastases only reported Positive ER/PR requires at least 1 % of tumour cells showing positive nuclear staining of any intensity. HER- 2 positive was defined as f IHC 3+ score and/or FISH amplified, and negative in the case of IHC 0/1+ and/or non-FISH amplified.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YEs
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

Bibliographic reference	Yang YF, Liao YY, Yang M, et al. (2014). Discordances in ER, PR and HER-2 receptors between primary and recurrent/metastatic lesions and their impact on survival in breast cancer patients. Medical Oncology, 31(10), 1-10.

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G.1.272 Yonemori 2008

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Bibliographic reference	Yonemori Kan, Tsuta Koji, Shimizu Chikako et al (2008). Immunohistochemical profiles of brain metastases from breast cancer. Journal of neuro-oncology, 90(2), 223-8.
Study type	Case series
Aim	To explore immunohistochemical profiles of brain metastases from breast cancer
Patient characteristics	**Inclusion criteria** Patients with breast cancer treated with trastuzumab based chemotherapy between January 1999 and January 2006 **Exclusion criteria** None reported **Baseline characteristics** Age median (range) : 53 (39 to 78) years Gender : Not reported Ethnicity : Not reported Treatment at baseline* : systematic chemotherapy (n=14), supportive care alone (n=6) Biopsy site : brain Biopsy type : Hormone status : not reported Disease stage : not reported Survival/time to recurrence or progression – median : 14.7 months *Reported as after the completion of the locoregional treatment for metastatic brain tumour
Number of Patients	N=29, tumour specimens from primary breast cancers available for 24 of 29 patients

<table>
<tr><td>Bibliographic reference</td><td>Yonemori Kan, Tsuta Koji, Shimizu Chikako et al (2008). Immunohistochemical profiles of brain metastases from breast cancer. Journal of neuro-oncology, 90(2), 223-8.</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Intervention</td><td>Immunohistochemical analysis</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Japan</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
3/24 (12.5%)
1/24 (4.2%)
3/24 (12.5%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
14/24 (58%)
1/24 (4%)
2/24 (8%)
7/24 (29%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>6/24 (25%)</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*This additional data was extracted as a post-hoc analysis to feed into the health economic model.
</td></tr>
<tr><td>Source of funding</td><td>Supported by grants from the Ministry of Health, Labour and Welfare.</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Yonemori Kan, Tsuta Koji, Shimizu Chikako et al (2008). Immunohistochemical profiles of brain metastases from breast cancer. Journal of neuro-oncology, 90(2), 223-8.	
	Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
	Was there clear reporting of clinical information of the participants?	YES
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

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G.1.282 Zidan 2005

Bibliographic reference	Zidan J, Dashkovsky I, Stayerman C, et al. (2005). Comparison of HER-2 overexpression in primary breast cancer and metastatic sites and its effect on biological targeting therapy of metastatic disease. British journal of cancer, 93(5), 552-6.
Study type	Case series
Aim	To determine the expression of HER-2 in the primary breast cancer and its metastases
Patient characteristics	**Inclusion criteria** Patients with metastatic breast cancer with paired tumour samples available and suitable for immunohistochemistry analysis **Exclusion criteria** None reported **Baseline characteristics** Age median (range) : 56 years (29 – 82) Gender : 57 (98%) female Ethnicity : Not reported Treatment at baseline : lumpectomy (35), mastectomy (23) Biopsy site : Bone (39), skin/soft tissue (20), liver (21), lung (19), pleura (11) Biopsy type : Not reported Hormone status : ER + (35) / ER- (23), PR + (31) / PR- (27); HER-2 + (14) / HER-2- (44) Disease stage : Not reported

<table>
<tr><td>Bibliographic reference</td><td>Zidan J, Dashkovsky I, Stayerman C, et al. (2005). Comparison of HER-2 overexpression in primary breast cancer and metastatic sites and its effect on biological targeting therapy of metastatic disease. British journal of cancer, 93(5), 552-6.</td></tr>
<tr><td></td><td>Survival/time to recurrence or progression – median (range) : 3.5 years (1 – 12)</td></tr>
<tr><td>Number of Patients</td><td>58</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical staining
Fluorescence in-situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Israel</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Discordance in HER-2 expression between primary and metastatic sites: 8/58 (14%).

<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
8 / 58 (13.8%)</td></tr>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
37/58 (64%)
7/58 (12%)
1/58 (2%)
13/58 (22%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management **</td><td>4 / 8 (50%)</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
**This additional data was extracted as a post-hoc analysis to feed into the health economic model.
**Reported as “treated with trastuzumab due to HER-2 evaluation in the metastases”</td></tr>
<tr><td>Source of funding</td><td>Israel Cancer Association</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)</td></tr>
</table>

Bibliographic reference	Zidan J, Dashkovsky I, Stayerman C, et al. (2005). Comparison of HER-2 overexpression in primary breast cancer and metastatic sites and its effect on biological targeting therapy of metastatic disease. British journal of cancer, 93(5), 552-6.	
	Were there clear criteria for inclusion in the case series?	YES
	Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
	Were valid methods used for identification of the condition for all participants included in the case series?	YES
	Did the case series have consecutive inclusion of participants?	YES
	Did the case series have complete inclusion of participants?	YES
	Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
	Was there clear reporting of clinical information of the participants?	YES
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

[6] *<Insert Note here>*

G.2 Mixed locoregional and distant metastases

G.2.1 Amir 2012

Bibliographic reference	Amir E, Miller N, Geddie W, Freedman O, et al. (2012). Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. Journal of Clinical Oncology, 30(6), 587-92.
Study type	Prospective cohort
Aim	To address the success rates of biopsy of metastatic lesions in women with distant metastatic disease when a change in treatment is contemplated.
Patient characteristics	**Inclusion criteria** Women with recurrent or progressive metastatic breast cancer were eligible. Availability of archival primary tumour was mandatory.

<table>
<tr><td>Bibliographic reference</td><td>Amir E, Miller N, Geddie W, Freedman O, et al. (2012). Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. Journal of Clinical Oncology, 30(6), 587-92.</td></tr>
<tr><td></td><td>Exclusion criteria
operable locoregional recurrence with no evidence of metastatic disease,
clotting disorder precluding biopsy, rapidly progressive disease,
history of non-breast second malignancies.

Baseline characteristics
Age – median (range) : 59 years (29 – 83)
Gender : 121 (100%) female
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : Lymph node (25), cutaneous (24), bone (20), liver (19), soft tissue (10), bone marrow (9), paracentesis (7), lung (5), central nervous system (2)
Biopsy type : fine-needle aspiration : bone
Hormone status : Not reported
Disease stage : Not reported
Survival/time to recurrence or progression median (range) : 35 months (0 – 274)</td></tr>
<tr><td>Number of Patients</td><td>121</td></tr>
<tr><td>Intervention</td><td>Fluorescence in situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>121 of which 94 were sufficient for analysis and 83 for HER-2 FISH.</td></tr>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
15 / 94 (16.0%)
38 / 84 (45.2%)
8 / 83 (9.6%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>17* / 83 (20.5%)</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>1** / 83 (1.2%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Amir E, Miller N, Geddie W, Freedman O, et al. (2012). Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. Journal of Clinical Oncology, 30(6), 587-92.</td></tr>
<tr><td></td><td>* Changes in management included the addition of trastuzumab in women with gain of HER-2 overexpression (n=6), the use of chemotherapy in place of endocrine therapy in those with loss of ER (n=5), no change to previous treatment in those with benign disease or second primary (n=4), and provision of endocrine therapy in place of chemotherapy for those gaining ER (n=2).
**bleeding from a punch biopsy of the skin leading to admission</td></tr>
<tr><td>Source of funding</td><td>Canadian Breast Cancer Foundation–Ontario Chapter.</td></tr>
<tr><td>Comments</td><td>117 of the 121 biopsies confirmed recurrent breast cancer. In 3 women, biopsies showed benign disease, and 1 participant, a second malignancy (basal cell carcinoma) was discovered.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>NO – Not all eligible patients had tissues samples for both primary tumour and locoregional recurrence / distant metastases</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the demographics of the participants in the study?</td><td>NO – demographics were poorly reported</td></tr>
<tr><td>Was there clear reporting of clinical information of the participants?</td><td>NO – not all samples produced results</td></tr>
<tr><td>Were the outcomes or follow up results of cases clearly reported?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the presenting site(s)/clinic(s) demographic information?</td><td>YES</td></tr>
<tr><td>Was statistical analysis appropriate?</td><td>YES</td></tr>
</table></td></tr>
</table>

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G.2.21 Amir 2012b

Bibliographic reference	**Amir E, Clemons M, Purdie CA et al. (2012b). Tissue confirmation of disease recurrence in breast cancer patients: pooled analysis of multi-centre, multi-disciplinary prospective studies. Cancer treatment reviews, 38(6), 708-14.**
Study type	Pooled analysis of individual patient data from 2 prospective studies (the Brits and Destiny studies)
Aim	To provide improved accuracy and precision for the estimate of the clinical impact of undertaking biopsy of recurrent breast cancer
Patient characteristics	**Inclusion criteria** - Written informed consent - Availability of archival primary tumour for the purposes of re-analysis **Exclusion criteria** - Patients with bleeding diatheses precluding biopsy - Those with rapidly progressing disease and or a life expectancy less than 3 months **Baseline characteristics** Age – median (range) : 61 (28 to 87) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Locoregional – 48.1%; Distant (skin, soft tissue, bone, bone marrow, liver, lung, distant lymph node, other/unspecified – 51.9% Biopsy type : Not reported Hormone status : Not reported Disease stage : Not reported Survival/time to recurrence or progression median (range) : 86 months (0 to 332)
Number of Patients	N=342 of which 289 underwent biopsy of recurrent lesion and 231 of these were sufficient for analysis.
Intervention	Immunohistochemistry for ER and PR, immunohistochemistry and/or fluorescent in situ hybridisation for HER-2.
Length of follow up	NA
Location	UK and Canada
Outcomes measures and effect size	Changes in receptor expression between the two samples |

Bibliographic reference	**Amir E, Clemons M, Purdie CA et al. (2012b). Tissue confirmation of disease recurrence in breast cancer patients: pooled analysis of multi-centre, multi-disciplinary prospective studies. Cancer treatment reviews, 38(6), 708-14.**

• ER • PR • HER-2	29/231 (12.6%) 72/231 (31.2%) 12/220 (5.5%)
Quality of life	Not reported
Change in management	41/220 (18.8%)
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

Source of funding	Not reported

Comments

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO – Not all eligible patients had tissues samples for both primary tumour and local recurrence / distant metastases
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographics were poorly reported
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

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G.2.32 Andersen 1988

Bibliographic reference	Andersen et al 1988
Study type	Case series
Aim	To compare the ER status of primary breast carcinomas with that of their regional and distant metastases using a histochemical technique in paraffin embedded tissue
Patient characteristics	**Inclusion criteria** • Randomly selected patients with ipsilateral lymph node metastases after the primary surgical treatment which involved mastectomy and lower axillary lymph node dissection • Randomly selected patients from whom paraffin embedded biopsies were accessible from the primary tumour and at least one simultaneous or sequential biopsy from distant metastases **Exclusion criteria** • Suitable histologic specimens not available **Baseline characteristics** Age – median (range) : regional lymph node metastases – 62 (33 to 84) years; distant metastases – 59 (26 to 74) years Gender : women (100%) Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : ipsilateral lymph node and sites outside the ipsilateral mammary region, ipsilateral axilla or ipsilateral periclavicular region. Biopsy type : Not reported Hormone status : Not reported Disease stage : Not reported Survival/time to recurrence or progression median (range) : 0 to 92 months
Number of Patients	N= 143 (92 with regional lymph node metastases and 51 distant metastases)
Intervention	3 layer immunoperoxidase techniquw
Length of follow up	NA

Bibliographic reference	**Andersen et al 1988**	
Location	Denmark	
Outcomes measures and effect size	Changes in receptor expression between the two samples • ER • PR • HER-2	 10/143 (7%) Not reported Not reported
	Quality of life	Not reported
	Change in management	Not reported
	Change in tumour type eg: breast to lung	Not reported
	Adverse events related to biopsy	Not reported
Source of funding	Not reported	
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)	
	Were there clear criteria for inclusion in the case series?	YES
	Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
	Were valid methods used for identification of the condition for all participants included in the case series?	YES
	Did the case series have consecutive inclusion of participants?	YES
	Did the case series have complete inclusion of participants?	YES
	Was there clear reporting of the demographics of the participants in the study?	NO – demographics were poorly reported
	Was there clear reporting of clinical information of the participants?	YES
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

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G.2.42 Arapantoni-Dadioti 2012

Bibliographic reference	**Arapantoni-Dadioti et al 2012**
Study type	Case series

Bibliographic reference	Arapantoni-Dadioti et al 2012
Aim	To compare the expression of the ER, PR and HER-2 proteins, analysed by IHC, in primary breast cancer with that in its metachronous recurrences or metastases in order to estimate discordant cases
Patient characteristics	**Inclusion criteria** • Consecutive metachronous breast cancer metastases and local recurrences along with their primary tumours **Exclusion criteria** • Not reported **Baseline characteristics** Age – mean (range) : 55.4 (30 to 94) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : lymph nodes (17.3%), other local recurrence (1.8%). Skin (20.9%), stomach (5.4%), small bowel (7.3%), large bowel (1.8%), liver (15.4%), thyroid gland (1.8%), soft tissues (1.8%), bone marrow (6.4%), omentum (1.8%), bones (6.4%), lung (8.2%), ovary (3.6%) Biopsy type : Not reported Hormone status : Not reported Disease stage : Not reported Survival/time to recurrence or progression median (range) : Not reported
Number of Patients	N=110
Intervention	Immunohistochemistry
Length of follow up	NA
Location	Greece
Outcomes measures and effect size	Changes in receptor expression between the two samples • ER: 30/110 (27%) • PR: 28/110 (25%) • HER-2: 20/110 (18%)

Bibliographic reference	**Arapantoni-Dadioti et al 2012**
	Quality of life: Not reported Change in management: Not reported Change in tumour type eg: breast to lung: Not reported Adverse events related to biopsy: Not reported
Source of funding	Funded by Roche Hellas
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html) Were there clear criteria for inclusion in the case series? YES Was the condition measured in a standard, reliable way for all participants included in the case series? YES Were valid methods used for identification of the condition for all participants included in the case series? YES Did the case series have consecutive inclusion of participants? YES Did the case series have complete inclusion of participants? YES Was there clear reporting of the demographics of the participants in the study? NO – demographics were poorly reported Was there clear reporting of clinical information of the participants? YES Were the outcomes or follow up results of cases clearly reported? YES Was there clear reporting of the presenting site(s)/clinic(s) demographic information? YES Was statistical analysis appropriate? YES

1

G.2.52 Bogina 2011

Bibliographic reference	**Bogina G, Bortesi L, Marconi M, et al. (2011). Comparison of hormonal receptor and HER-2 status between breast primary tumours and relapsing tumours: clinical implications of progesterone receptor loss. Virchows Archiv : an international journal of pathology, 459(1), 1-10.**
Study type	Case series
Aim	To compare the expression of ER, PR and HER-2 status between primary tumour and corresponding loacal recurrence or distant metastasis can modify this status and whether biomarkers change can can affect prognosis
Patient characteristics	**Inclusion criteria**

<table>
<tr><td>Bibliographic reference</td><td>Bogina G, Bortesi L, Marconi M, et al. (2011). Comparison of hormonal receptor and HER-2 status between breast primary tumours and relapsing tumours: clinical implications of progesterone receptor loss. Virchows Archiv : an international journal of pathology, 459(1), 1-10.</td></tr>
<tr><td></td><td>Breast cancer with histological samples of locoregional recurrence/distant metastases and primary tumour samples on file

Exclusion criteria
Not reported

Baseline characteristics
Age – mean (range) : 61.7 years (34 – 93)
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : Local recurrence - Breast (21), axilla (23), homolateral clavicular nodes (2), Metasynchronous distant metastases - liver (5), lung (9) pleura (2), bone (10) skin (3), ovary (3), peritoneum (1), stomach (5), duodenum (3), thyroid (1),, cervix (1) and node (3), Synchronous distant metastases - colon (1) bone (1), node (1) brain (1)
Biopsy type : Local recurrence – surgical , Distant metastases – surgical (23) and bioptic (23)
Hormone status : Not reported
Disease stage : Not reported
Survival/time to recurrence or progression - mean (range) : 73.6 months (6 – 216 months)</td></tr>
<tr><td>Number of Patients</td><td>140</td></tr>
<tr><td>Intervention</td><td>Immunochemistry

Silver in-situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>73.6 months (6 – 216 months)</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
9/140 (6.4%)
30/140 (21.4%)
1/136 (0.7%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Bogina G, Bortesi L, Marconi M, et al. (2011). Comparison of hormonal receptor and HER-2 status between breast primary tumours and relapsing tumours: clinical implications of progesterone receptor loss. Virchows Archiv : an international journal of pathology, 459(1), 1-10.**
	Change in tumour type eg: breast to lung — Not reported Adverse events related to biopsy — Not reported
Source of funding	None reported
Comments	4 metastases were synchronous **JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO – Not all eligible patients had tissues samples for both primary tumour and locoregional recurrence / distant metastases
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographics were poorly reported
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.61 Chan 2012

Bibliographic reference	**Chan-Arlene et al 2012** **Chan A, Morey A, Brown B, et al. (2012). A retrospective study investigating the rate of HER-2 discordance between primary breast carcinoma and locoregional or metastatic disease. BMC cancer, 12, 555.**
Study type	Case series
Aim	To assess for the incidence of HER-2 status of both primary and metastatic recurrence in patients from a single institution assessed in a high volume reference laboratory using uniform methodology, namely in-situ hybridization.
Patient characteristics	**Inclusion criteria** • Patients who had adequate tissue available from paired primary and recurrent tumour samples for assessment of HER-2 amplification. • Patients who presented with primary breast cancer and synchronous metastatic disease who underwent biopsy of the metastatic lesion were also included. **Exclusion criteria** • Insufficient tissue being available for central analysis **Baseline characteristics** Age, median (range): 50 (31 to 85) Gender : all women Ethnicity : not reported Treatment at baseline : Endocrine only 6 (5.9); Non-anthracycline chemotherapy 11 (10.8); Anthracycline-base chemotherapy 38 (37.3); Anthracycline and taxane 29 (28.4); Taxane only 4 (3.9); Adjuvant trastuzumab 10 (8.6) Biopsy site : Breast 24 (20); Lymph nodes 20 (17); Chest wall / Skin 18 (16); Bone 14 (12); Liver 9 (8) ; Brain 9 (8); Lung 7 (6); Others 15 (13) Biopsy type : fine needle aspiration 34 (29); core/excisional biopsy 82 (71) Hormone status : not reported Disease stage : not reported Survival/time to recurrence or progression: not reported
Number of Patients	N=116
Intervention	Silver in situ hybridisation and fluorescent in situ hybridisation
Length of follow up	NA
Location	Australia
Outcomes measures and effect size	Changes in receptor expression between the two samples • ER — Not reported

Bibliographic reference	**Chan-Arlene et al 2012** **Chan A, Morey A, Brown B, et al. (2012). A retrospective study investigating the rate of HER-2 discordance between primary breast carcinoma and locoregional or metastatic disease. BMC cancer, 12, 555.**
	• PR • HER-2 — Not reported 21/116 (18.1%) Quality of life — Not reported Change in management — Not reported Change in tumour type eg: breast to lung — Not reported Adverse events related to biopsy — Not reported
Source of funding	Supported by Roche Products Pty Limited
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.72 Chang 2011

Bibliographic reference	**Chang HJ, Han SW, Oh DY et al. (2011). Discordant human epidermal growth factor receptor 2 and hormone receptor status in primary and metastatic breast cancer and response to trastuzumab. Japanese journal of clinical oncology, 41(5), 593-9.**
Study type	Case series

Bibliographic reference	**Chang HJ, Han SW, Oh DY et al. (2011). Discordant human epidermal growth factor receptor 2 and hormone receptor status in primary and metastatic breast cancer and response to trastuzumab. Japanese journal of clinical oncology, 41(5), 593-9.**
Aim	to compare tumour HR and HER-2 status between primary and distant metastatic sites and to evaluate the impact of HER-2 conversion in metastatic lesions on prognosis and response to trastuzumab treatment.
Patient characteristics	**Inclusion criteria** - Patients with HR and HER-2 results available from primary and metastatic tumours **Exclusion criteria** - None reported **Baseline characteristics** Age : median 48 yrs (range 32 – 73 yrs) Gender : not reported Ethnicity : not reported Treatment at baseline : unclear, patients who converted from HER-2 negative to HER-2 positive received trastuzumab after diagnosis of HER-2 positive. Biopsy site : Liver, lung, lymph node, bone, others. Biopsy type : Unclear of method, assessed using immunohistochemistry (IHC). Hormone status : Menopause status unclear. ER+/PR+ = 30.4%, ER+/PR - = 16.1%, ER-/PR+ = 7.1% Disease stage : Unclear Survival/time to recurrence or progression :
Number of Patients	56
Intervention	Patients with HR and HER-2 results available from primary and metastatic tumours were included in the present analysis. Clinicopathologic data and follow-up information, including results from treatment with adjuvant hormone therapy, trastuzumab and lapatinib, were retrieved from medical records. Patients were classified by change (or lack of change) in HER-2 status from the primary to metastatic sites as follows: Group 1 (negative to negative), Group 2 (positive to positive), Group 3 (negative to positive) and Group 4 (positive to negative).
Comparison	N/A
Length of follow up	2003 – 2009
Location	South Korea
Outcomes measures and effect size	Changes in receptor expression between the two samples |

Bibliographic reference	**Chang HJ, Han SW, Oh DY et al. (2011). Discordant human epidermal growth factor receptor 2 and hormone receptor status in primary and metastatic breast cancer and response to trastuzumab. Japanese journal of clinical oncology, 41(5), 593-9.**
	• ER: 17/56 (30%) • PR: 14/56 (25%) • HER-2: 7/56 (12.5%)
	Quality of life: Not reported
	Change in management: Not reported
	Change in tumour type eg: breast to lung: Not reported
	Adverse events related to biopsy: Not reported
Source of funding	Korean Healthcare Technology R&D project, Ministry for Health.
Comments	All but 3 metastases were asynchronous JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html) 1. Were there clear criteria for inclusion in the case series? Yes 2. Was the condition measured in a standard, reliable way for all participants included in the case series? Yes 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have consecutive inclusion of participants? Yes 5. Did the case series have complete inclusion of participants? Yes 6. Was there clear reporting of the demographics of the participants in the study? Unclear 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? Yes 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Yes 10. Was statistical analysis appropriate? Yes

1

G.2.82 Dieci 2013

Bibliographic reference	**Dieci MV, Barbieri E, Piacentini F et al. (2013). Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO, 24(1), 101-8**
Study type	Case series

Bibliographic reference	**Dieci MV, Barbieri E, Piacentini F et al. (2013). Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO, 24(1), 101-8**
Aim	To assess the discordance rate in HR and HER-2 expression from primary breast tumour to matched recurrent disease, and to evaluate the prognostic impact of the change in tumour phenotype in a single-Institution series.
Patient characteristics	**Inclusion criteria** - Patients who underwent biopsy or surgical resection of suspected recurrent breast cancer. **Exclusion criteria** - None reported **Baseline characteristics** Age : median 51 yrs (range 26 – 87 yrs) Gender : not reported Ethnicity : not reported Treatment at baseline : neo-/adjuvant chemotherapy, neo-/adjuvant hormone therapy, neo-/adjuvant trastzumab Biopsy site : distant metastases 63%, locoregional soft tissues or lymph nodes 37% Biopsy type : not reported, fine needle aspirate only excluded Hormone status : not reported Disease stage : 19.3% stage 1, 34.5% stage 2A/2B, 18.5% stage 3A/B, 25.2% stage 3C/4 Survival/time to recurrence or progression : mean time 68 months (range 0.5 – 238 months)
Number of Patients	119 with confirmed recurrent breast cancer
Intervention	Patients underwent histological sampling of suspected breast cancer recurrence. All the pathology assessments (ER, PgR and human epidermal growth factor receptor 2 (HER-2)) on both primaries and confirmed recurrences were performed at the same laboratory.
Comparison	N/A
Length of follow up	1997 – 2007
Location	Italy
Outcomes measures and effect size	Changes in receptor expression between the two samples • ER • PR • HER-2 Quality of life
	 16/119 (13.4%) 46/118 (39%) 14/119 (11.8%) Not reported

Bibliographic reference	**Dieci MV, Barbieri E, Piacentini F et al. (2013). Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO, 24(1), 101-8**
	Change in management: Not reported Change in tumour type eg: breast to lung: Not reported Adverse events related to biopsy: Not reported
Source of funding	
Comments	25% stage 3C/4 breast cancer JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html) 1. Were there clear criteria for inclusion in the case series? YES 2. Was the condition measured in a standard, reliable way for all participants included in the case series? Unclear 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have consecutive inclusion of participants? Yes 5. Did the case series have complete inclusion of participants? No, some excluded based on fine needle aspirate only and no metastasis 6. Was there clear reporting of the demographics of the participants in the study? No 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? Yes 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? No 10. Was statistical analysis appropriate? Yes

1

G.2.92 Dieci 2014

Bibliographic reference	**Dieci 2014**
Study type	Case series
Aim	To evaluate the prognostic impact of quantitative estrogen receptor expression at relapse for ER-positive breast cancer with ER positive recurrence
Patient characteristics	**Inclusion criteria**

<table>
<tr><th>Bibliographic reference</th><th>Dieci 2014</th></tr>
<tr><td></td><td>
Consecutive cases of patients who underwent biopsy or surgical resection of suspected recurrent breast cancer between January 1994 and December 2011
Exclusion criteria
Not reported
Baseline characteristics
Age, median (range) : 52 years (26 to 87)
Gender : not reported
Ethnicity : not reported
Treatment at baseline : 86% received hormone treatment before relapse biopsy either as adjuvant therapy or as treatment for advanced disease or both
Biopsy site : Distant (75%), Locoregional (25%)
Biopsy type : Not reported
Hormone status : All ER+
Disease stage : 1 (20%); 2 (37%); 3 (36%); 4 (7%)
Survival/time to recurrence or progression : Not reported
</td></tr>
<tr><td>Number of Patients</td><td>81</td></tr>
<tr><td>Intervention</td><td>Immunohistochemistry</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
ER
PR
HER-2</td><td>19/81 (23%)
Not reported
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Dieci 2014**
Source of funding	Supported by the Monica Boscolo Research Grant 2012 and a Ministry of Health Research Grant
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.102 Falck 2010

Bibliographic reference	**Falck AK, Ferno M, Bendahl PO et al. (2010). Does analysis of biomarkers in tumor cells in lymph node metastases give additional prognostic information in primary breast cancer?. World journal of surgery, 34(7), 1434-41.**
Study type	Case series
Aim	To determine the molecular characteristics of the primary tumour and corresponding lymph node metastases using a cohort of patients treated with adjuvant tamoxifen for 2 years.
Patient characteristics	**Inclusion criteria** - Not reported **Exclusion criteria** - Not reported

<table>
<tr><td>Bibliographic reference</td><td>Falck AK, Ferno M, Bendahl PO et al. (2010). Does analysis of biomarkers in tumor cells in lymph node metastases give additional prognostic information in primary breast cancer?. World journal of surgery, 34(7), 1434-41.</td></tr>
<tr><td></td><td>Baseline characteristics
Age : median = 63 years, (range = 26-81)
Gender : not reported
Ethnicity : not reported
Treatment at baseline : adjuvant tamoxifen for 2 years, irrespective of ER status.
Biopsy site : primary tumour (breast), one from corresponding lymph node
Biopsy type : unclear – embedded in paraffin blocks.
Hormone status : unclear
Disease stage : at baseline, all stage 2. Disease free survival within 5 years until distant metastases calculated
Survival/time to recurrence or progression :</td></tr>
<tr><td>Number of Patients</td><td>425, of which 262 available for ER, 257 for PR and 104 for HER-2.</td></tr>
<tr><td>Intervention</td><td>All patients underwent surgery in the form of a modified radical mastectomy or breast-conserving surgery with axillary lymph node dissection (levels I and II). After breast-conserving surgery, radiotherapy was given to the breast, and patients with axillary lymph node metastases received locoregional radiotherapy. The patients were followed for 5 years with annual mammogram and physical investigations. None of the patients received any systemic adjuvant therapy other than tamoxifen.
Tissue microarrays from the primary tumours and corresponding lymph node metastases were constructed. Two 0.6-mm-diameter tissue core biopsies from tumour blocks of the primary tumour were punched out, and one biopsy specimen was taken from the corresponding lymph node metastases. Biopsies from corresponding lymph node metastases were obtained from patients with lymph node-positive disease.</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow up</td><td>5 years</td></tr>
<tr><td>Location</td><td>Sweden</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
19/262 (7%)
42/257 (16%)
3/104 (3%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Falck AK, Ferno M, Bendahl PO et al. (2010). Does analysis of biomarkers in tumor cells in lymph node metastases give additional prognostic information in primary breast cancer?. World journal of surgery, 34(7), 1434-41.**
	Change in tumour type eg: breast to lung — Not reported Adverse events related to biopsy — Not reported
Source of funding	Medical faculty and University Hospital Lund (ALF), The University Hospital of Lund Research Foundation, Swedish Pink Ribbon Campaign and Skåne County Council's research and development Foundation.
Comments	JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html) 1. Were there clear criteria for inclusion in the case series? No 2. Was the condition measured in a standard, reliable way for all participants included in the case series? Unclear 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have consecutive inclusion of participants? Unclear 5. Did the case series have complete inclusion of participants? Unclear 6. Was there clear reporting of the demographics of the participants in the study? No 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? Yes 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Yes 10. Was statistical analysis appropriate? Yes

1 [7]

G.2.112 Gomez-Fernandez 2008

Bibliographic reference	**Gomez-Fernandez et al 2008**
Study type	Case series
Aim	To evaluate estrogen receptor phenotype of recurrent and/or metastatic breast cancers and compared it with the ER status of the primary tumour.
Patient characteristics	**Inclusion criteria** • Presence of local recurrence and/or distant metastases **Exclusion criteria** • Not reported **Baseline characteristics**

<table>
<tr><th>Bibliographic reference</th><th>Gomez-Fernandez et al 2008</th></tr>
<tr><td></td><td>Age – mean (range) : Not reported
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : Chest wall, skin, ipsilateral breast, bone, brain, female genital tract, gastrointestinal tract, kidney, liver, lung, gallbladder, serosal surfaces
Biopsy type : Not reported
Hormone status : ER+: 159, ER-: 119
Disease stage : Not reported
Survival/time to recurrence or progression: Distant metastases occurred up to 21 years after the primary diagnosis. Locoregional recurrence occurred from 2 months to 7 years later.</td></tr>
<tr><td>Number of Patients</td><td>N=278</td></tr>
<tr><td>Intervention</td><td>Immunohistochemistry</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Miami</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>9/278 (3%)
Not reported
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Gomez-Fernandez et al 2008	
	Were valid methods used for identification of the condition for all participants included in the case series?	YES
	Did the case series have consecutive inclusion of participants?	YES
	Did the case series have complete inclusion of participants?	YES
	Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
	Was there clear reporting of clinical information of the participants?	YES
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

G.2.121 Gong 2005

Bibliographic reference	**Gong et al 2005** **Gong Y, Booser DJ, and Sneige N. (2005). Comparison of HER-2 status determined by fluorescence in situ hybridization in primary and metastatic breast carcinoma. Cancer, 103(9), 1763-9.**
Study type	Retrospective case series
Aim	To compare HER-2 status n primary tumour before chemotherapy with metastases sampled after chemotherapy
Patient characteristics	**Inclusion criteria** Known HER-2 status from primary tumours and paired metastatic tumours **Exclusion criteria** Not reported **Baseline characteristics** Age – mean (range) : 52 (26 – 79) Gender : 60 (100%) female Ethnicity : Not reported Treatment at baseline : Not reported for all patents Biopsy site : Locoregional - axillary lymph node (30), soft tissue chest (5), supraclavicular lymph node (8), Distant – Lung (9), liver (4), pleura (1), bone (3) Biopsy type : paraffin-embedded tissue / fine-needle aspiration

<table>
<tr><td>Bibliographic reference</td><td>Gong et al 2005
Gong Y, Booser DJ, and Sneige N. (2005). Comparison of HER-2 status determined by fluorescence in situ hybridization in primary and metastatic breast carcinoma. Cancer, 103(9), 1763-9.</td></tr>
<tr><td></td><td>Hormone status : ER+ (22) / ER- (29) / not determined (9); PR + (28) / PR- (22) / not determined (10) : HER-2+ (20) / HER-2- (40)
Disease stage : Not reported
Survival/time to recurrence or progression : Not reported</td></tr>
<tr><td>Number of Patients</td><td>60</td></tr>
<tr><td>Intervention</td><td>Flourescence in situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>United States</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
2 / 60 (3.3%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*Unclear whether this 60 includes 22 patients with synchronous metastases
</td></tr>
<tr><td>Source of funding</td><td>None reported</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Gong et al 2005 Gong Y, Booser DJ, and Sneige N. (2005). Comparison of HER-2 status determined by fluorescence in situ hybridization in primary and metastatic breast carcinoma. Cancer, 103(9), 1763-9.

Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

[8] *<Insert Note here>*

G.2.133 Gong 2011

Bibliographic reference	Gong Y, Han E Y, Guo M et al. (2011). Stability of estrogen receptor status in breast carcinoma. Cancer, 117(4), 705-13.
Study type	Case series
Aim	To use immunohistochemistry (IHC) to evaluate stability of ER status in paired primary and metastatic tumour samples from 227 patients, and to determine the effect of previous disease course and intervening systemic therapy on ER status of metastatic tumours.
Patient characteristics	**Inclusion criteria** - Identified metastatic breast carcinomas between 2003 and 2008. **Exclusion criteria** - None reported. **Baseline characteristics** Age : 57% ≤ 50 years, 43% ≥ 50 Gender : all women Ethnicity : 63% Caucasian, 37% other Treatment at baseline : 56.4% received endocrine therapy, 43.6% no endocrine therapy Biopsy site: locoregional: axillary lymph node, supraclavicular lymph node, infraclavicular lymph node, Ipsilateral anterior chest wall. Distant metastases: lung, liver, effusion fluid, bone, distant lymph node, distant soft tissue, other visceral organs. Biopsy type: 4 via core needle or excision and 223 via fine-needle aspiration

<table>
<tr><td>Bibliographic reference</td><td>Gong Y, Han E Y, Guo M et al. (2011). Stability of estrogen receptor status in breast carcinoma. Cancer, 117(4), 705-13.</td></tr>
<tr><td></td><td>Hormone status : not reported
Disease stage : not reported
Survival/time to recurrence or progression : median 61 months (range 1.5 – 275 months)</td></tr>
<tr><td>Number of Patients</td><td>227</td></tr>
<tr><td>Intervention</td><td>Identified metastatic breast carcinomas and recorded ER status of the paired primary breast carcinoma. Retrospectively reviewed and recorded each patient’s demographic information, the systemic treatment received and characteristics. ER status was tested on formalin-fixed, paraffin-embedded tissue sections by IHC staining.</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow up</td><td>1984 – 2006</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>17/227 (7.5%)
Not reported
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
1. Were there clear criteria for inclusion in the case series? Yes
2. Was the condition measured in a standard, reliable way for all participants included in the case series? Unclear
3. Were valid methods used for identification of the condition for all participants included in the case series? Yes
4. Did the case series have consecutive inclusion of participants? Unclear
5. Did the case series have complete inclusion of participants? Unclear
6. Was there clear reporting of the demographics of the participants in the study? No
7. Was there clear reporting of clinical information of the participants? Yes</td></tr>
</table>

Bibliographic reference	Gong Y, Han E Y, Guo M et al. (2011). Stability of estrogen receptor status in breast carcinoma. Cancer, 117(4), 705-13.
	8. Were the outcomes or follow up results of cases clearly reported? Yes 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Yes 10. Was statistical analysis appropriate? Yes

1

G.2.142 Guarneri 2008

Bibliographic reference	Guarneri V, Giovannelli S, Ficarra G, et al. (2008). Comparison of HER-2 and hormone receptor expression in primary breast cancers and asynchronous paired metastases: impact on patient management. The oncologist, 13(8), 838-44.
Study type	Case series
Aim	to compare the HER-2 status of primary tumours and paired asynchronous metastases in breast cancer patients.
Patient characteristics	**Inclusion criteria** Diagnosis of breast cancer with available samples from primary tumour and metastatic site Patients with stage IV disease at diagnosis were included only in cases when sampling of metastases was performed on metachronous lesions. **Exclusion criteria** None reported **Baseline characteristics** Age – median (range): 53 (27 – 67) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Unclear Biopsy site : locoregional soft tissues (30), liver (20), central nervous system (5), bone (5), pleura (4), distant soft tissues (3), stomach/colon/peritoneum) (3), bronchus (3), and bone marrow (2). Biopsy type : Not reported Hormone status : ER+(55) / ER-(20): PR status nt reported : HER-2+ (14) / HER-2- (61) Disease stage (reported at diagnosis) : Stage I (19), Stage IIA/IIB (26), Stage IIIA/IIIB (13), Stage IIIC/IV (17) Survival/time to recurrence or progression median (range) : Locoregional 42.8 months (7.2 – 197.4) : Distant 54.2 months (7.4 – 308.2)
Number of Patients	75

<table>
<tr><td>Bibliographic reference</td><td>Guarneri V, Giovannelli S, Ficarra G, et al. (2008). Comparison of HER-2 and hormone receptor expression in primary breast cancers and asynchronous paired metastases: impact on patient management. The oncologist, 13(8), 838-44.</td></tr>
<tr><td>Intervention</td><td>Immunohistochemistry
Fluorescence in situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Italy</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
17 / 75 (22.7%)
27 / 75 (36.0%)
12 / 75 (16.0%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported*</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*only reported for some patients as follows “Among the 10 patients who changed from HER-2 negative to HER-2 positive, seven subsequently received trastuzumab (two of these patients received trastuzumab followed by lapatinib)” “Three of the seven patients who converted from a negative to positive HR status subsequently received hormonal therapy.
</td></tr>
<tr><td>Source of funding</td><td>None reported</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>NO – not all patients had paired samples</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>NO</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Guarneri V, Giovannelli S, Ficarra G, et al. (2008). Comparison of HER-2 and hormone receptor expression in primary breast cancers and asynchronous paired metastases: impact on patient management. The oncologist, 13(8), 838-44.

Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

2

G.2.153 Holdaway 1983

Bibliographic reference	Holdaway I M, and Bowditch J V. (1983). Variation in receptor status between primary and metastatic breast cancer. Cancer, 52(3), 479-85.
Study type	Case series
Aim	To carry out a retrospective analysis of serial receptor measurements over a five year period.
Patient characteristics	**Inclusion criteria** - Not reported **Exclusion criteria** - Not reported **Baseline characteristics** Age : mean age not reported Gender : not reported Ethnicity : not reported Treatment at baseline : 1 patient received tamoxifen Biopsy site : ipsilateral axillary lymph nodes, ipsilateral supraclavicular lymph nodes, contralateral lymph nodes, local chest wall, skin metastases beyond chest, opposite breast and visceral sites

<table>
<tr><td>Bibliographic reference</td><td>Holdaway I M, and Bowditch J V. (1983). Variation in receptor status between primary and metastatic breast cancer. Cancer, 52(3), 479-85.</td></tr>
<tr><td></td><td>Biopsy type : unclear, dextran-charcoal assay used
Hormone status: ‘5 patients received endocrine therapy or underwent natural menopause between biopsies’.
Disease stage : unclear
Survival/time to recurrence or progression : not reported</td></tr>
<tr><td>Number of Patients</td><td>28</td></tr>
<tr><td>Intervention</td><td>Oestrogen receptors (ER) and progesterone receptors (PR) were measured by a dextran-charcoal assay.
The response of patients to hormone manipulation was assessed using the criteria of Hayward et al (1977), except that complete and partial remissions were required to last at least three months to be considered valid.</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow up</td><td>5 years</td></tr>
<tr><td>Location</td><td>Not reported, study author’s location New Zealand</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>15/28 (54%)
7/20 (35%)
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>Unclear how many patients stage 4

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
1. Were there clear criteria for inclusion in the case series? No
2. Was the condition measured in a standard, reliable way for all participants included in the case series? Unclear (biopsy method not clearly stated)
3. Were valid methods used for identification of the condition for all participants included in the case series? Unclear
4. Did the case series have consecutive inclusion of participants? Yes
5. Did the case series have complete inclusion of participants? Unclear</td></tr>
</table>

Bibliographic reference	Holdaway I M, and Bowditch J V. (1983). Variation in receptor status between primary and metastatic breast cancer. Cancer, 52(3), 479-85.
	6. Was there clear reporting of the demographics of the participants in the study? No 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? Yes 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Yes 10. Was statistical analysis appropriate? Yes

1

2

G.2.163 Kamby 1989

Bibliographic reference	Kamby C, Rasmussen B B, and Kristensen B. (1989). Oestrogen receptor status of primary breast carcinomas and their metastases. Relation to pattern of spread and survival after recurrence. British journal of cancer, 60(2), pp.252-7.
Study type	Observational cohort
Aim	To describe and to compare the immunohistochemical ER content in primary breast cancer, involved regional lymph nodes and subsequent distant metastases.
Patient characteristics	**Inclusion criteria** Patients with primary locally advanced breast cancer or with distant metastases at the time of initial diagnosis were also included. **Exclusion criteria** Patients older than 75 years of age patients with previous or concomitant other primary cancers. **Baseline characteristics** Age at recurrence mean (range) : 53 (30 – 74) Gender : Not reported Ethnicity : Not reported Treatment at baseline : systemic adjuvant therapy (70%); adjuvant endocrine therapy with or without chemotherapy (24%) Biopsy site: bone (43), Liver .(20)] regional lymph nodes (29) Biopsy type : formalin-fixed, paraffin-embedded whole tumour sections

<table>
<tr><td>Bibliographic reference</td><td>Kamby C, Rasmussen B B, and Kristensen B. (1989). Oestrogen receptor status of primary breast carcinomas and their metastases. Relation to pattern of spread and survival after recurrence. British journal of cancer, 60(2), pp.252-7.</td></tr>
<tr><td></td><td>Hormone status : ER + (25) / ER- (37)
Disease stage : not reported
Survival/time to recurrence or progression : median 27 months (25-75%: 11-50 months)</td></tr>
<tr><td>Number of Patients</td><td>62</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical analysis</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Denmark</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER – Bone*
• ER – Liver*
• PR
• HER-2</td><td>
5/20 (75%)
18/43 (42%)
Not reported
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management
• ER
• PR
• HER-2</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
*One person had both bone and liver metastases.
</td></tr>
<tr><td>Source of funding</td><td>Danish Medical Research Council,
the Hafnia Haand-i-Haand Foundation
Mrs A. Thaysen's Foundation.</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Kamby C, Rasmussen B B, and Kristensen B. (1989). Oestrogen receptor status of primary breast carcinomas and their metastases. Relation to pattern of spread and survival after recurrence. British journal of cancer, 60(2), pp.252-7.**

Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO – selected based on site of metastases
Did the case series have complete inclusion of participants?	NO – Not all eligible patients had tissues samples for both primary tumour and local recurrence / distant metastases
Was there clear reporting of the demographics of the participants in the study?	NO – demographics were poorly reported
Was there clear reporting of clinical information of the participants?	NO
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.172 Kuukasjarvi 1996

Bibliographic reference	**Kuukasjarvi T, Kononen J, Helin H, Holli K, and Isola J. (1996). Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy. Journal of Clinical Oncology, 14(9), pp.2584-2589.**
Study type	Case series
Aim	To evaluate ER and PR status changed in asynchronous recurrent tumours of breast cancer and to correlate these changes with therapy response in a retrospective study design.
Patient characteristics	**Inclusion criteria** - Primary breast carcinomas and matched asynchronous recurrent tumours

<table>
<tr><td>Bibliographic reference</td><td>Kuukasjarvi T, Kononen J, Helin H, Holli K, and Isola J. (1996). Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy. Journal of Clinical Oncology, 14(9), pp.2584-2589.</td></tr>
<tr><td></td><td>Exclusion criteria
- Bilateral breast carcinomas
- Other malignancies
- Systematic adjuvant therapy

Baseline characteristics
Age, mean (range): 53 (24 to 77) years
Gender: not reported
Ethnicity: not reported
Treatment at baseline: not reported
Biopsy site: supraclavicular (6); pelvis (4); bone marrow (3); lung (3); distant soft tissues (2); abdominal cavity (1)
Biopsy type: not reported
Hormone status: not reported
Survival/time to recurrence or progression, median (range): 25 (3 to 228)</td></tr>
<tr><td>Number of Patients</td><td>N=50</td></tr>
<tr><td>Intervention</td><td>Immunohistochemistry</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Finland</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
12/50 (24%)
12/50 (24%)
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Supported by the Pirkanmaa Cancer Society, Finnish Cancer Society, Academy of Finland, Pirkanmaa Cultural Foundation and Sigrid Juselius Foundation</td></tr>
</table>

Bibliographic reference	**Kuukasjarvi T, Kononen J, Helin H, Holli K, and Isola J. (1996). Loss of estrogen receptor in recurrent breast cancer is associated with poor response to endocrine therapy. Journal of Clinical Oncology, 14(9), pp.2584-2589.**
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO – population was selected
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.2.181 Lindstrom 2012

Bibliographic reference	**Li Lindstrom L S, Karlsson E, Wilking U M, Johansson U, Hartman J, Lidbrink E K, Hatschek T, Skoog L, and Bergh J. (2012). Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. Journal of Clinical Oncology, 30(21), pp.2601-2608.**
Study type	Case series
Aim	To investigate whether hormonal receptors and human epidermal growth factor receptor 2 (HER-2) change throughout tumour progression, because this may alter patient management.
Patient characteristics	**Inclusion criteria** • Diagnosis of local or systemic breast cancer relapse from January 1997 to December 2007

<table>
<tr><td>Bibliographic reference</td><td>Li Lindstrom L S, Karlsson E, Wilking U M, Johansson U, Hartman J, Lidbrink E K, Hatschek T, Skoog L, and Bergh J. (2012). Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. Journal of Clinical Oncology, 30(21), pp.2601-2608.</td></tr>
<tr><td></td><td>Exclusion criteria
Advanced disease at the time of primary breast cancer diagnosis
Synchronous bilateral breast cancer
Baseline characteristics
Age range : Not reported
Gender : females (100%)
Ethnicity : Not reported
Treatment at baseline :
Biopsy site : Local and systemic relapse (specific sites not reported)
Biopsy type : Not reported
Hormone status : Not reported
Disease stage : Not reported
Survival/time to recurrence or progression : Not reported</td></tr>
<tr><td>Number of Patients</td><td>1010 of which 459 available for ER, 430 for PR and 104 HER-2.</td></tr>
<tr><td>Intervention</td><td>Either biochemical or immunohistochemical/immunocytochemical methods were used to determine receptor status which was then confirmed by fluorescent in situ hybridisation for IHC/ICC 2+ and 3+ status.</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Sweden</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
ER
PR
HER-2</td><td>149/459 (32.5%)
175/430 (40.7%)
15/104 (14.5%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Li Lindstrom L S, Karlsson E, Wilking U M, Johansson U, Hartman J, Lidbrink E K, Hatschek T, Skoog L, and Bergh J. (2012). Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. Journal of Clinical Oncology, 30(21), pp.2601-2608.**
	Adverse events related to biopsy: Not reported
Source of funding	Jonas Bergh
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.192 Lower 2005

Bibliographic reference	**Lower EE, Glass EL, Bradley DA, et al. (2005). Impact of metastatic estrogen receptor and progesterone receptor status on survival. Breast Cancer Research and Treatment, 90(1), 65-70.**
Study type	Retrospective case series
Aim	To investigate the concordance of primary and metastatic ER content between primary and metastatic invasive breast cancer
Patient characteristics	**Inclusion criteria** Patients with metastatic breast cancer

<table>
<tr><th>Bibliographic reference</th><th>Lower EE, Glass EL, Bradley DA, et al. (2005). Impact of metastatic estrogen receptor and progesterone receptor status on survival. Breast Cancer Research and Treatment, 90(1), 65-70.</th></tr>
<tr><td></td><td>Exclusion criteria
Lack of biopsy-proven metastatic disease with hormone receptor status
Metastatic data only available from axillary lymph node tissue

Baseline characteristics
Age range : 27 – 84 years
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : local (63), lymph node (5); bone (48), lung (37), brain (13), liver (22), orbit (1), ovary (3) skin (5), colon (1), pancreas (2)
Biopsy type : Not reported
Hormone status : ER+ (115) / ER- (85) : PR+(116) / PR- (88) / unknown (6)
Disease stage : Stage 1 (58); Stage 2 (100); Stage 3 (27); Stage 4 (12); unknown (3)
Survival/time to recurrence or progression :</td></tr>
<tr><td>Number of Patients</td><td>200 locoregional and distant</td></tr>
<tr><td>Intervention</td><td>Unclear</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>United States</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
60/200 (30%)
68/173 (39%)
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Lower EE, Glass EL, Bradley DA, et al. (2005). Impact of metastatic estrogen receptor and progesterone receptor status on survival. Breast Cancer Research and Treatment, 90(1), 65-70.**
Source of funding	
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO – population was selected
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.2.201 Macfarlane 2012

Bibliographic reference	**Macfarlane R, Seal M, Speers C, et al. (2012). Molecular alterations between the primary breast cancer and the subsequent locoregional/metastatic tumor. The oncologist, 17(2), 172-8.**
Study type	Case series
Aim	To compare the hormone receptor and HER-2 status of relapsed or metastatic breast cancer with those of the original tumour with identical contemporaneous methodology for detection and scoring for both the primary and relapsed lesions.
Patient characteristics	**Inclusion criteria** Diagnosis of breast cancer and a biopsy-proven locoregional, regional, or distant relapse.

<table>
<tr><td>Bibliographic reference</td><td>Macfarlane R, Seal M, Speers C, et al. (2012). Molecular alterations between the primary breast cancer and the subsequent locoregional/metastatic tumor. The oncologist, 17(2), 172-8.</td></tr>
<tr><td></td><td>Exclusion criteria
women diagnosed with an interval contralateral new reast primary and women with a prior nonbreast cancer malignancy or a synchronous presentation of bilateral breast cancer.

Baseline characteristics
Age – median (range) : 60 years (23–89)
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline : No systemic treatment (71), Hormones (44), Chemotherapy (33), Chemotherapy and hormones (12)
Biopsy site : Local (34), regional (99), distant (27)
Biopsy type :
Hormone status : ER+ (97) / ER- (56) / Unknown (4) : PR+ (69) / PR- (71) / Unknown (20) // HER-2 + (29) / HER-2- (125) / Unknown (6)
Disease stage : Stage I (51), stage II (90), stage III (15), unknown (4)
Survival/time to recurrence or progression – median (range) : 35 months (4–149).</td></tr>
<tr><td>Number of Patients</td><td>160</td></tr>
<tr><td>Intervention</td><td>Unclear</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>35 / 160 (21.9%)

8 / 160 (5.0%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Macfarlane R, Seal M, Speers C, et al. (2012). Molecular alterations between the primary breast cancer and the subsequent locoregional/metastatic tumor. The oncologist, 17(2), 172-8.**
Source of funding	Not reported
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	NO – not all patients accounted for
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	No – discrepancy between text and graphs
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.212 Masood 2000

Bibliographic reference	**Masood S, and Bui M M. (2000). Assessment of Her-2/neu overexpression in primary breast cancers and their metastatic lesions: an immunohistochemical study. Annals of clinical and laboratory science, 30(3), pp.259-65.**
Study type	Case series
Aim	To assess whether the pattern of HER-2/neu overexpression of metastatic breast cancer is also present in the primary lesion

<table>
<tr><td>Bibliographic reference</td><td>Masood S, and Bui M M. (2000). Assessment of Her-2/neu overexpression in primary breast cancers and their metastatic lesions: an immunohistochemical study. Annals of clinical and laboratory science, 30(3), pp.259-65.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
Metastatic breast cancer
Exclusion criteria
Not reported
Baseline characteristics
Age – mean (range): 50.5 (30 to 72)
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline : Not reported
Biopsy site : Lymph node, skin, liver, spleen, lung, bone
Biopsy type : Not reported
Hormone status : Not reported
Disease stage : Not reported
Survival/time to recurrence or progression : Not reported</td></tr>
<tr><td>Number of Patients</td><td>56</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical staining</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Florida</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
ER
PR
HER-2</td><td>Not reported
Not reported
1/56 (2%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Masood S, and Bui M M. (2000). Assessment of Her-2/neu overexpression in primary breast cancers and their metastatic lesions: an immunohistochemical study. Annals of clinical and laboratory science, 30(3), pp.259-65.**
	Adverse events related to biopsy: Not reported
Source of funding	Not reported
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographics were poorly reported
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.222 Mobbs 1987

Bibliographic reference	**Mobbs B G, Fish E B, Pritchard K I, Oldfield G, and Hanna W H. (1987). Estrogen and progesterone receptor content of primary and secondary breast carcinoma: influence of time and treatment. European journal of cancer & clinical oncology, 23(6), pp.819-26.**
Study type	Case series
Aim	To examine in both quantitative and qualitative terms the relationships between receptor concentrations in primary and secondary breast carcinoma specimens from patients undergoing breast surgery at Women's College hospital, Toronto.
Patient characteristics	**Inclusion criteria** Group 1 • Both specimens obtained on the same occasion and assayed at the same time

Bibliographic reference	**Mobbs B G, Fish E B, Pritchard K I, Oldfield G, and Hanna W H. (1987). Estrogen and progesterone receptor content of primary and secondary breast carcinoma: influence of time and treatment. European journal of cancer & clinical oncology, 23(6), pp.819-26.**
	• Postmenopausal, pre and peri-menopausal women <u>Group 2</u> • Primary and secondary specimens obtained on different occasions 1 to 75 months apart • Postmenopausal, pre or peri-menopausal. One subject changed from peri- to postmenopausal during the time interval between biopsies <u>Group 3</u> • Primary and secondary specimens obtained on different occasions 4 to 87 months apart • Postmenopausal and pre/perimenopausal **Exclusion criteria** • Not reported **Baseline characteristics** Age median (range) : not reported Gender : all women Ethnicity : not reported Treatment at baseline : not reported Biopsy site: lymph nodes, chest wall, breast tissue, mastectomy scar, muscle of the back, abdominal wall, lung, neck muscle, peritoneum Biopsy type : Not reported Hormone status : Not reported Disease stage : Not reported Survival/time to recurrence or progression : not reported
Number of Patients	N=129
Intervention	Receptor assays using cytosol preparation
Length of follow up	NA
Location	Canada

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Mobbs B G, Fish E B, Pritchard K I, Oldfield G, and Hanna W H. (1987). Estrogen and progesterone receptor content of primary and secondary breast carcinoma: influence of time and treatment. European journal of cancer & clinical oncology, 23(6), pp.819-26.</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="2"><table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
18/129 (14%)
29/129 (22%)
Not reported</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td colspan="2">Not reported</td></tr>
<tr><td>Comments</td><td colspan="2">JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the demographics of the participants in the study?</td><td>NO – demographics were poorly reported</td></tr>
<tr><td>Was there clear reporting of clinical information of the participants?</td><td>YES</td></tr>
<tr><td>Were the outcomes or follow up results of cases clearly reported?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the presenting site(s)/clinic(s) demographic information?</td><td>YES</td></tr>
<tr><td>Was statistical analysis appropriate?</td><td>YES</td></tr>
</table></td></tr>
</table>

G.2.231 Niehans 1993

Bibliographic reference	**Niehans GA, Singleton TP, Dykoski D, et al. (1993). Stability of HER-2/neu expression over time and at multiple metastatic sites. Journal of the National Cancer Institute, 85(15), 1230-5.**
Study type	Case series
Aim	To determine the frequency of overexpression HER-2/neu protein during progression from primary lesions at the time of diagnosis and metastatic sites at the end of the disease course.
Patient characteristics	**Inclusion criteria** • Tumour tissue obtained at autopsy from two to five metastatic organ sites in patients who died with metastatic breast carcinoma. **Exclusion criteria** Not reported **Baseline characteristics** Age : Not reported Gender : 14 (100%) were female Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Breast, lung, liver, lymph node, skin, ovary, central nervous system, adrenal, stomach, bowel, contralateral breast, kidney, spleen, omentum and heart Biopsy type : formalin-fixed, paraffin-embedded tissue Hormone status : Not reported Disease stage : Unclear Survival/time to recurrence or progression : Not reported
Number of Patients	14
Intervention	Formalin-fixed, paraffin-embedded tissue from original biopsy or surgical resection of primary site were used. Tumour tissue from between 2 and 5 metastatic sites was collected from each patient.
Length of follow up	Average time between primary biopsy and death was 4 years (range 2 to 9) and length of time between autopsy and study was between 1 and 12.5 years

<table>
<tr><td>Bibliographic reference</td><td>Niehans GA, Singleton TP, Dykoski D, et al. (1993). Stability of HER-2/neu expression over time and at multiple metastatic sites. Journal of the National Cancer Institute, 85(15), 1230-5.</td></tr>
<tr><td>Location</td><td>United States</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Discordance in HER-2 receptor expression between primary and metastatic sites: 0/14 (0%)

<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
Not reported
Not reported
2 / 14 (14.3%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Supported by the University of Minnesota, Department of Laboratory Medicine and Pathology and by Public Health service Grant from the National Cancer Institute</td></tr>
<tr><td>Comments</td><td>Study based on autopsy samples
Results presented are for the 14 out of 30 for whom tissue sample from biopsy of primary tumour were available

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
1. Were there clear criteria for inclusion in the case series? NO
2. Was the condition measured in a standard, reliable way for all participants included in the case series? NO – not all case has biopsy from primary tumour available
3. Were valid methods used for identification of the condition for all participants included in the case series? YES
4. Did the case series have consecutive inclusion of participants? YES
5. Did the case series have complete inclusion of participants? UNCLEAR
6. Was there clear reporting of the demographics of the participants in the study? NO
7. Was there clear reporting of clinical information of the participants? YES
8. Were the outcomes or follow up results of cases clearly reported? NOT APPLICABLE
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? NO
10. Was statistical analysis appropriate? YES</td></tr>
</table>

1

G.2.242 Nishimura 2011

Bibliographic reference	**Nishimura Reiki, Osako Tomofumi, Okumura Yasuhiro, Tashima Rumiko, Toyozumi Yasuo, and Arima Nobuyuki. (2011). Changes in the ER, PgR, HER-2, p53 and Ki-67 biological markers between primary and recurrent breast cancer: discordance rates and prognosis. World journal of surgical oncology, 9, pp.131.**
Study type	Case series
Aim	To compare biological markers in recurrent breast cancer in comparison with the primary tumour status
Patient characteristics	**Inclusion criteria** Patients from whom the lesion was resected either by surgery or biopsy and evaluated by immunostaining. **Exclusion criteria** None reported **Baseline characteristics** Age median (range) : 53 years (31 – 83) Gender : 97 (100%) female Ethnicity : Not reported Treatment at baseline : Surgery Biopsy site: Chest wall (39), In-breast (34), Regional lymph node (11), Lung (3), Bone (1), Brain (3), Ovary (3), Distant skin (3) Biopsy type : Not reported Hormone status : ER + (62) / ER- (35) : PR + (55) / PR = (42) : HER-2 + (22) / HER-2 – (75) Disease stage : Not reported Survival/time to recurrence or progression : Not reported
Number of Patients	97
Intervention	Immunostaining
Length of follow up	NA
Location	Japan
Outcomes measures and effect size	Changes in receptor expression between the two samples • ER • PR 10 / 97 (10.3%) 25 / 97 (25.8%)

Bibliographic reference	**Nishimura Reiki, Osako Tomofumi, Okumura Yasuhiro, Tashima Rumiko, Toyozumi Yasuo, and Arima Nobuyuki. (2011). Changes in the ER, PgR, HER-2, p53 and Ki-67 biological markers between primary and recurrent breast cancer: discordance rates and prognosis. World journal of surgical oncology, 9, pp.131.**
	• HER-2: 14 / 97 (14.4%) Quality of life: Not reported Change in management: Not reported Change in tumour type eg: breast to lung: Not reported Adverse events related to biopsy: Not reported
Source of funding	None reported
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographics were poorly reported
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.2.251 Santinelli 2008

Bibliographic reference	**Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.**
Study type	Case series

Bibliographic reference	**Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.**
Aim	To determine HER-2 status in primary breast invasive carcinomas and in the paired lymph node metastases, locoregional recurrence and distant metastases,
Patient characteristics	**Inclusion criteria** Patients with metachronous breast cancer metastases (local and distant) **Exclusion criteria** Not reported **Baseline characteristics** Age – mean (range) : 52.4 years (26 – 76) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Local - axillary lymph node (53), supraclavicular lymph node (1), breast (5), thorax skin and chest wall (25): Distant - liver (4), lung (3), pleura (9), bone (4), CNS (5), skin (3), colon (2), ovary 1), peritoneum (1), stomach (1), retroperitoneum (1), cervical node 1) Biopsy type : paraffin-embedded blocks Hormone status : ER+ (28) / ER- (66) / unknown (25) : PR+ (43) / PR- (51) / unknown (25) : HER-2 + (12) / HER-2- (42). Disease stage : Not reported Survival/time to recurrence or progression :
Number of Patients	N=65
Intervention	Immunohistochemical analysis Fluorescence in situ hybridization
Length of follow up	NA
Location	Italy
Outcomes measures and effect size	Changes in receptor expression between the two samples • ER • PR • HER-2 Not reported Not reported 14/65 (%)

Bibliographic reference	**Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.**
	Quality of life: Not reported Change in management: Not reported Change in tumour type eg: breast to lung: Not reported Adverse events related to biopsy: Not reported
Source of funding	Not reported
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html) Were there clear criteria for inclusion in the case series? YES Was the condition measured in a standard, reliable way for all participants included in the case series? YES Were valid methods used for identification of the condition for all participants included in the case series? YES Did the case series have consecutive inclusion of participants? YES Did the case series have complete inclusion of participants? YES Was there clear reporting of the demographics of the participants in the study? NO – demographic data was reported poorly Was there clear reporting of clinical information of the participants? YES Were the outcomes or follow up results of cases clearly reported? YES Was there clear reporting of the presenting site(s)/clinic(s) demographic information? YES Was statistical analysis appropriate? YES Only data for the mixed group (local recurrence and distant) has been extracted.

G.2.261 Sari 2011

Bibliographic reference	**Sari E, Guler G, Hayran M, ET AL. (2011). Comparative study of the immunohistochemical detection of hormone receptor status and HER-2 expression in primary and paired recurrent/metastatic lesions of patients with breast cancer. Medical Oncology, 28(1), 57-63.**
Study type	Case series
Aim	To compare the immunohistochemical expression of ER, PR, HER-2 between the primary tumour and matched RML in patients with metastatic breast cancer (MBC) and find out the degree of discordance.

<table>
<tr><td>Bibliographic reference</td><td>Sari E, Guler G, Hayran M, ET AL. (2011). Comparative study of the immunohistochemical detection of hormone receptor status and HER-2 expression in primary and paired recurrent/metastatic lesions of patients with breast cancer. Medical Oncology, 28(1), 57-63.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
Female patients having biopsy-proven recurrent breast carcinoma

Exclusion criteria
Patients in whom biopsy of the recurrent carcinoma was not possible

Baseline characteristics
Age – mean (range) : 44.5 years (21–76)
Gender : 78 (100%) female
Ethnicity : Not reported
Treatment at baseline : chemotherapy and endocrine therapy
Biopsy site : Locoregional disease (23), Distant soft tissue (18), Liver (10), Serous membranes (3), Lung (7), Bone (5), Ovary (4), Brain (3), Other (5)
Biopsy type : core or trucut biopsy or surgical resection.
Hormone status : ER+ (49) / ER- (27) / unknown (2) : PR+ (49) / PR- (24) / unknown (5): HER-2 + (20) / HER-2- (46) / unknown (12).
Disease stage : Stage I (6), Stage IIA (12), Stage IIB (10), Stage IIIA (13), Stage IIIB (2), Stage IIIC (17) Stage IV (6), Unknown (12)
Survival/time to recurrence or progression: Not reported</td></tr>
<tr><td>Number of Patients</td><td>78 of which 75 known for ER, 72 known for PR and 61 known for HER-2.</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical analysis
Fluorescence in situ hybridisation</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Turkey</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
27 / 75 (36%)
39 / 72 (54.2%)
9 / 61 (14.7%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Sari E, Guler G, Hayran M, ET AL. (2011). Comparative study of the immunohistochemical detection of hormone receptor status and HER-2 expression in primary and paired recurrent/metastatic lesions of patients with breast cancer. Medical Oncology, 28(1), 57-63.</td></tr>
<tr><td></td><td>
<table>
<tr><td>Change in management</td><td>Not reported</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
<tr><td>Adverse events related to biopsy</td><td>Not reported</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>For ER and PR, nuclear staining of >1% was accepted as positive.
HER-2 evaluation was made using a standard 0 to 3+ scoring system according to membrane staining. Intensity pattern with scores 0 and 1+ considered negative, 3+ considered positive and for 2+ cases a FISH analysis was made.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>NO – outcome data for all patients not reported</td></tr>
<tr><td>Was there clear reporting of the demographics of the participants in the study?</td><td>NO – demographic data was reported poorly</td></tr>
<tr><td>Was there clear reporting of clinical information of the participants?</td><td>YES</td></tr>
<tr><td>Were the outcomes or follow up results of cases clearly reported?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the presenting site(s)/clinic(s) demographic information?</td><td>YES</td></tr>
<tr><td>Was statistical analysis appropriate?</td><td>YES</td></tr>
</table>
</td></tr>
</table>

G.2.271 Saedi 2012

Bibliographic reference	**Saedi, H.S., Nasiri, M.R.G., ShahidSales, S et al. (2012). Comparison of hormone receptor status in primary and recurrent breast cancer. Iranian journal of cancer prevention, 5(2), pp.69-73.**
Study type	Case series
Aim	To compare the status of ER and PR in primary tumors and recurrent sites of breast cancer
Patient characteristics	**Inclusion criteria** • Patients with primary tumours and recurrent sites of breast cancer **Exclusion criteria** • Not reported **Baseline characteristics** Age mean (SD) : 51 years (12.06) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Locoregional (26), bone (4), lung (2), brain (2), liver (1). Biopsy type : Not reported Hormone status : ER + (9) / ER- (26) : PR + (9) / PR = (26) : HER-2 + (not reported) / HER-2 – (not reported) Disease stage : not reported Survival/time to recurrence or progression : mean (SD) : 23.54 months (19.17)
Number of Patients	35
Intervention	Immunohistochemical analysis
Length of follow up	NA
Location	Iran
Outcomes measures and effect size	

Changes in receptor expression between the two samples • ER or PR	11 / 35 (31.4%)
Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

Bibliographic reference	**Saedi, H.S., Nasiri, M.R.G., ShahidSales, S et al. (2012). Comparison of hormone receptor status in primary and recurrent breast cancer. Iranian journal of cancer prevention, 5(2), pp.69-73.**
Source of funding	None reported
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	NO – Not all eligible patients had tissues samples for both primary tumour and local recurrence / distant metastases
Was there clear reporting of the demographics of the participants in the study?	NO – demographics were poorly reported
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

Samples with cellular staining rate less than 10 % were classed negative, and those above that considered positive.

G.2.281 Sekido 2003

Bibliographic reference	**Sekido, Y., Umemura, S., Takekoshi, S. et al (2003). Heterogeneous gene alterations in primary breast cancer contribute to discordance between primary and asynchronous metastatic/recurrent sites: HER-2 gene amplification and p53 mutation. International journal of oncology, 22(6), pp.1225-32.**
Study type	Case series
Aim	To clarify differences in genetic events between primary breast cancers and asynchronous metastatic/recurrent lesions, by examining HER-2 gene amplification and p53 mutation.

<table>
<tr><td>Bibliographic reference</td><td>Sekido, Y., Umemura, S., Takekoshi, S. et al (2003). Heterogeneous gene alterations in primary breast cancer contribute to discordance between primary and asynchronous metastatic/recurrent sites: HER-2 gene amplification and p53 mutation. International journal of oncology, 22(6), pp.1225-32.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
Asynchronous metastatic/recurrent breast cancer tumours
Exclusion criteria
Cases with bilateral breast cancers
Cases with multiple cancers at other sites (because of the possibility of metastasis from another site)
Cases with bone metastasis insufficiently processed due to decalcification
Baseline characteristics
Age – mean (range) : 50.7 (28 to 74 years)
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline: Not reported
Biopsy site : Chest wall, Skin, Lung, Lymph node
Biopsy type : Not reported
Hormone status : Not reported
Disease stage : Not reported
Survival/time to recurrence or progression: Not reported</td></tr>
<tr><td>Number of Patients</td><td>N=44</td></tr>
<tr><td>Intervention</td><td>Immunohistochemistry
Fluorescent in situ hybridisation for cases with discordant results for HER-2 overexpression</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Japan</td></tr>
<tr><td>Outcomes measures and effect size</td><td><table><tr><td>Changes in receptor expression between the two samples
ER
PR
HER-2</td><td>
7/44 (16%)
10/44 (23%)
2/44 (5%)</td></tr></table></td></tr>
</table>

Bibliographic reference	**Sekido, Y., Umemura, S., Takekoshi, S. et al (2003). Heterogeneous gene alterations in primary breast cancer contribute to discordance between primary and asynchronous metastatic/recurrent sites: HER-2 gene amplification and p53 mutation. International journal of oncology, 22(6), pp.1225-32.**
	Quality of life: Not reported Change in management: Not reported Change in tumour type eg: breast to lung: Not reported Adverse events related to biopsy: Not reported
Source of funding	Not reported
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html) Were there clear criteria for inclusion in the case series? YES Was the condition measured in a standard, reliable way for all participants included in the case series? YES Were valid methods used for identification of the condition for all participants included in the case series? YES Did the case series have consecutive inclusion of participants? YES Did the case series have complete inclusion of participants? YES Was there clear reporting of the demographics of the participants in the study? NO – demographic data was reported poorly Was there clear reporting of clinical information of the participants? YES Were the outcomes or follow up results of cases clearly reported? YES Was there clear reporting of the presenting site(s)/clinic(s) demographic information? YES Was statistical analysis appropriate? YES

G.2.291 Shiino 2016

Bibliographic reference	**Shiino Sho, Kinoshita Takayuki, Yoshida Masayuki, et al. (2016). Prognostic Impact of Discordance in Hormone Receptor Status Between Primary and Recurrent Sites in Patients With Recurrent Breast Cancer. Clinical breast cancer, 16(4), .e133-40.**
Study type	Retrospective case series
Aim	To assess the prognostic impact of discordance in hormone receptor status between primary and recurrent sites in patients with recurrent breast cancer
Patient characteristics	**Inclusion criteria**

<table>
<tr><td>Bibliographic reference</td><td>Shiino Sho, Kinoshita Takayuki, Yoshida Masayuki, et al. (2016). Prognostic Impact of Discordance in Hormone Receptor Status Between Primary and Recurrent Sites in Patients With Recurrent Breast Cancer. Clinical breast cancer, 16(4), .e133-40.</td></tr>
<tr><td></td><td>Patients who underwent surgery for primary breast cancer between 1985 and 2013 in the database of the Department of Breast Surgery in the National Cancer Centre Hospital.

Exclusion criteria
Not reported

Baseline characteristics
Age – median (range): 54 years (30 – 81).
Gender : Not reported
Ethnicity : Not reported
Treatment at baseline: Neoadjuvant therapy – 23%; adjuvant chemotherapy – 78%; adjuvant hormone therapy – 73%; Trastuzumab – 12%
Biopsy site : Breast, chest wall, regional lymph node, lung, bone, liver, brain, distant lymph node, other metastatic sites
Biopsy type : Either core needle biopsy or surgical excision for recurrent breast cancer
Hormone status, n : ER+ (110) / ER- (43) : PR+ (82) / PR- (71) : HER-2+ (32) / HER-2- (121)
Disease stage: not reported
Survival/time to recurrence or progression – not reported</td></tr>
<tr><td>Number of Patients</td><td>N=153 distant and local</td></tr>
<tr><td>Intervention</td><td>Formalin-fixed paraffin-embedded tumour tissues specimens of the primary and recurrent sites were cut into 3um thick sections and subjected to immunohistochemical staining for ER, PR and HER-2.</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>Japan</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
28/153 (18%)
40/153 (26%)
10/153 (7%)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Shiino Sho, Kinoshita Takayuki, Yoshida Masayuki, et al. (2016). Prognostic Impact of Discordance in Hormone Receptor Status Between Primary and Recurrent Sites in Patients With Recurrent Breast Cancer. Clinical breast cancer, 16(4), .e133-40.**
	Change in tumour type eg: breast to lung — Not reported Adverse events related to biopsy — Not reported
Source of funding	Supported in part by a grant I aid for Scientific Research from Japan Society for Promotion of Science and the National Centre Research and Development Fund
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.301 Soomro 2014

Bibliographic reference	**Soomro R, Beg M, Sheeraz ur Rahman S. (2014). Discordance of biomarker status in recurrent breast cancer. JPMA. The Journal of the Pakistan Medical Association, 64(2), 163-5**
Study type	Cohort
Aim	To quantify the percentage of tumour that changes receptor status for ER, PR and HER-2/neu between original and recurrent disease.
Patient characteristics	**Inclusion criteria** Female patients having biopsy-proven recurrent breast carcinoma **Exclusion criteria** Patients in whom biopsy of the recurrent carcinoma was not possible **Baseline characteristics** Age – mean (range) : 46 years (28 – 64) Gender : 58 (100%) female Ethnicity : Not reported Treatment at baseline : Biopsy site : I Biopsy type : Not reported Hormone status : ER+ (26) / ER- (32) : PR+ (27) / PR- (31) : HER-2 + (28) / HER-2- (30). Disease stage : Not reported Survival/time to recurrence or progression – mean (SD) : 2.3 years (1.9)
Number of Patients	58
Intervention	Immunohistochemistry Fluorescence In Situ Hybridization
Length of follow up	NA
Location	Pakistan
Outcomes measures and effect size	Changes in receptor expression between the two samples • ER: 15 / 58 (25.9%) • PR: 21 / 58 (36.2%) • HER-2: 13 / 58 (22.4%)

Bibliographic reference	**Soomro R, Beg M, Sheeraz ur Rahman S. (2014). Discordance of biomarker status in recurrent breast cancer. JPMA. The Journal of the Pakistan Medical Association, 64(2), 163-5**

Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

Source of funding: None reported

Comments

Criteria for ER/PR positivity was ascertained using H-scoring: 1.< 50 receptor count was taken as negative; 2. >50 receptor count was considered as positive.

Criteria for positivity was ascertained by: 2. Score of 0 and +1 was taken as negative; 2+ were further tested for Fluorescence In Situ Hybridization (FISH); and 3. 3+ were taken as positive for HER-2/neu receptor.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.311 Spataro 1992

Bibliographic reference	**Spataro V, Price K, Goldhirsch A et al. (1992). Sequential estrogen receptor determinations from primary breast cancer and at relapse: Prognostic and therapeutic relevance. Annals of Oncology, 3(9), 733-40.**
Study type	Cohort
Aim	To determine the prognostic importance of discordant or concordant from the primary to the subsequent receptor status
Patient characteristics	**Inclusion criteria** Breast cancer patients with availability of ER assay from both primary tumour and from a biopsy-accessible relapse site **Exclusion criteria** None reported **Baseline characteristics** Age – median (range) : 53 years (19 – 81) Gender : 401 (100%) female Ethnicity : Not reported Treatment at baseline : Chemotherapy (210), chemotherapy + endocr. Therapy (64), endocr. Therapy (30), no treatment (67) Biopsy site : Breast (223), regional and breast (68), distant soft tissue (13), contra-lateral breast (44) bone (23), visceral (30) Biopsy type : Not reported Hormone status : ER - = 140; ER + = 261 Disease stage : Not reported Survival/time to recurrence or progression reported as time between ER assays: 22 months (2 – 122)
Number of Patients	401
Intervention	Unclear
Length of follow up	NA
Location	Switzerland, Italy, International
Outcomes measures and effect size	Discordance in estrogen receptor status between primary and recurrent metastasis: 122/401 (30%) Changes in receptor expression between the two samples • ER — 122 / 401 (30.4%)

Bibliographic reference	**Spataro V, Price K, Goldhirsch A et al. (1992). Sequential estrogen receptor determinations from primary breast cancer and at relapse: Prognostic and therapeutic relevance. Annals of Oncology, 3(9), 733-40.**

• PR • HER-2	Not reported Not reported
Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

Source of funding

Comments

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO – population recruited from 5 separate studies
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

[9]

G.2.321 Tanner 2001

Bibliographic reference	**Tanner M, Jarvinen P, and Isola J. (2001). Amplification of HER-2/neu and topoisomerase IIalpha in primary and metastatic breast cancer. Cancer research, 61(14), 5345-8.**
Study type	Case series
Aim	To report results from a systematic study of HER-2 and topo IIa amplification in primary breast cancers and their metastatic tumors that developed later during follow up.
Patient characteristics	Age: not reported Gender : not reported Ethnicity : not reported Treatment at baseline: not reported Biopsy site: locoregional or regional in 33 cases, and 12 were haematogeneously-spread distant metastases (no data are available for three metastases). Biopsy type : not reported Hormone status : not reported Disease stage : not reported Survival/time to recurrence or progression: 1 month to 19 years.
Number of Patients	N=46
Intervention	In situ hybridisation
Length of follow up	NA
Location	Finland
Outcomes measures and effect size	

Changes in receptor expression between the two samples • ER • PR • HER-2	 Not reported Not reported 0/46 (0%)
Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

Source of funding	Supported by the Scientific Foundation of Tampere University Hospital, the Academy of Finland, and the Finnish Cancer Society.

Bibliographic reference	**Tanner M, Jarvinen P, and Isola J. (2001). Amplification of HER-2/neu and topoisomerase IIalpha in primary and metastatic breast cancer. Cancer research, 61(14), 5345-8.**
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.2.332 Thompson 2010

Bibliographic reference	**Thompson AM, Jordan LB, Quinlan P et al. (2010). Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the Breast Recurrence In Tissues Study (BRITS). Breast cancer research: BCR, 12(6), R92.**
Study type	Case series
Aim	To quantify the percentage of tumours that changed receptor status (positive to negative or negative to positive) for ER, PR, and HER-2 expression between the original and recurrent tumour in women with breast cancer and to determine the proportion of patients in which a switch in ER, PR, or HER-2 led to a change in the subsequent treatment plan.
Patient characteristics	**Inclusion criteria** - Available a formalin fixed paraffin-embedded (FFPE) tumour from both the primary cancer and the recurrence

<table>
<tr><td>Bibliographic reference</td><td>Thompson AM, Jordan LB, Quinlan P et al. (2010). Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the Breast Recurrence In Tissues Study (BRITS). Breast cancer research: BCR, 12(6), R92.</td></tr>
<tr><td></td><td>Exclusion criteria
- None reported

Baseline characteristics
Age : 62.6, sd = 12.3 (mean age at disease recurrence)
Gender : 137/137 women
Ethnicity : 135/137 Caucasian
Treatment at baseline: endocrine therapy 100/136 (73%) (one patient not known), previous chemotherapy 62/135 (45.3%) (two patients not known), previous radiotherapy 108/136 (78.8%) (one patient not known).
Biopsy site: Unclear, states: locoregional 64.2%, distant soft tissues 11.7%, other distant metastasis 24.1%.
Biopsy type : fixed paraffin-embedded (FFPE)
Hormone status : 83/137 postmenopausal
Disease stage : Not reported
Survival/time to recurrence or progression: 8 years (93.2 months) – mean time to first recurrence following completion of primary therapy.</td></tr>
<tr><td>Number of Patients</td><td>205 consented, 137 included with paired primary and recurrent tissue samples.</td></tr>
<tr><td>Intervention</td><td>FFPE tissue at the time of recurrent breast cancer was biopsied (as a core biopsy or resected tissue) and diagnostic review was conducted by the local pathologist to confirm the presence of invasive breast cancer. FFPE from primary cancer was subsequently retrieved, paired with prospectively collected recurrent breast cancer FFPE block and sent for pathology review.</td></tr>
<tr><td>Comparison</td><td>N/A</td></tr>
<tr><td>Length of follow up</td><td>Length of follow up unclear. Study dates 2007 - 2008</td></tr>
<tr><td>Location</td><td>UK</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Changes in receptor expression between the two samples
• ER
• PR
• HER-2</td><td>
14/137 (10.2)
34/137 (24.8)
4/137 (2.9)</td></tr>
<tr><td>Quality of life</td><td>Not reported</td></tr>
<tr><td>Change in management</td><td>24/137 (17.5)</td></tr>
<tr><td>Change in tumour type eg: breast to lung</td><td>Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Thompson AM, Jordan LB, Quinlan P et al. (2010). Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the Breast Recurrence In Tissues Study (BRITS). Breast cancer research: BCR, 12(6), R92.**
	Adverse events related to biopsy: Not reported Discordance in HER-2 receptor expression between primary and metastatic sites: unclear, most patients (>80%) were HER-2 negative on both occasions
Source of funding	AstraZeneca
Comments	Unclear if stage 4 only – has both locally and distant recurrent metastasis. JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html) 1. Were there clear criteria for inclusion in the case series? Yes 2. Was the condition measured in a standard, reliable way for all participants included in the case series? Yes 3. Were valid methods used for identification of the condition for all participants included in the case series? Yes 4. Did the case series have consecutive inclusion of participants? Unclear 5. Did the case series have complete inclusion of participants? Unclear 6. Was there clear reporting of the demographics of the participants in the study? Yes 7. Was there clear reporting of clinical information of the participants? Yes 8. Were the outcomes or follow up results of cases clearly reported? Yes 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Unclear 10. Was statistical analysis appropriate? Yes

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G.2.341 Wilking 2011

Bibliographic reference	**Wilking, U., Karlsson, E., Skoog, L. et al (2011). HER-2 status in a population-derived breast cancer cohort: discordances during tumor progression. Breast cancer research and treatment, 125(2), pp.553-61.**
Study type	Case series
Aim	To investigate the intra-individual correlation of HER-2 status between primary breast cancer tumours and corresponding recurrences.
Patient characteristics	**Inclusion criteria** • Breast cancer patients with relapse **Exclusion criteria** • Not reported **Baseline characteristics** Age – mean (range) : Not reported Gender : Not reported Ethnicity : Not reported Treatment at baseline :Not reported Biopsy site : Bone/bone marrow (30%); liver (16%); local recurrence (18%); lung or pleura (10%); axillary lymph nodes (9%); skin (7%); supra clavicular lymph nodes (5%) and other sites (7%) Biopsy type : Not reported Hormone status : Not reported Disease stage : Not reported Survival/time to recurrence or progression – Not reported
Number of Patients	N=151
Intervention	Immunohistochemistry, immunocytochemistry and fluorescent in situ hybridisation
Length of follow up	NA
Location	Sweden
Outcomes measures and effect size	Changes in receptor expression between the two samples • ER — Not reported • PR — Not reported • HER-2 — 15/151 (10%)

Bibliographic reference	**Wilking, U., Karlsson, E., Skoog, L. et al (2011). HER-2 status in a population-derived breast cancer cohort: discordances during tumor progression. Breast cancer research and treatment, 125(2), pp.553-61.**

Quality of life	Not reported
Change in management	Not reported
Change in tumour type eg: breast to lung	Not reported
Adverse events related to biopsy	Not reported

Source of funding

Comments

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

G.31 Locoregional metastases

G.3.12 Aitken 2010

Bibliographic reference	**Aitken SJ, Thomas JS, Langdon SP, et al. (2010). Quantitative analysis of changes in ER, PR and HER-2 expression in primary breast cancer and paired nodal metastases. Annals of Oncology, 21(6), 1254-61.**
Study type	Case series
Aim	To compare quantitative changes in ER, PR and HER-2 expression between primary and nodal disease
Patient characteristics	**Inclusion criteria** Patients with primary breast carcinomas and paired lymph nodes **Exclusion criteria** Not reported **Baseline characteristics** Age: not reported Gender : not reported Ethnicity : not reported Treatment at baseline : not reported Biopsy site : lymph node Biopsy type : not reported Hormone status : not reported Disease stage : not reported Survival/time to recurrence or progression: not reported
Number of Patients	N=385, of which 190 available for HER-2.
Intervention	Immunofluorescence/immunohistochemistry
Length of follow up	NA
Location	UK
Outcomes measures and effect size	Change in receptor expression direction for HER-2* • Negative to negative • Negative to positive 148/190 (77.9%) 14/190 (7.4%)

<table>
<tr><td>Bibliographic reference</td><td>Aitken SJ, Thomas JS, Langdon SP, et al. (2010). Quantitative analysis of changes in ER, PR and HER-2 expression in primary breast cancer and paired nodal metastases. Annals of Oncology, 21(6), 1254-61.</td></tr>
<tr><td></td><td>
<table>
<tr><td>• Positive to negative
• Positive to positive</td><td>3/190 (1.6%)
25/190 (13.2%)</td></tr>
</table>
*This additional data was extracted as a post-hoc analysis to feed into the health economic model.
</td></tr>
<tr><td>Source of funding</td><td>Breakthrough Breast Cancer; Scottish Funding Council (Strategic Research Development Grant) (HR07005); molecular pathology on tissue was supported by the Edinburgh CRUK Experimental Cancer Medicine Centre.</td></tr>
<tr><td>Comments</td><td>JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>NO – exclusion criteria not reported</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>NO – outcome data for all patients not reported</td></tr>
<tr><td>Was there clear reporting of the demographics of the participants in the study?</td><td>NO – demographic data was reported poorly</td></tr>
<tr><td>Was there clear reporting of clinical information of the participants?</td><td>YES</td></tr>
<tr><td>Were the outcomes or follow up results of cases clearly reported?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the presenting site(s)/clinic(s) demographic information?</td><td>YES</td></tr>
<tr><td>Was statistical analysis appropriate?</td><td>YES</td></tr>
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2

G.3.21 Carlsson 2004

Bibliographic reference	**Carlsson J, Nordgren H, Sjostrom J et al. (2004). HER-2 expression in breast cancer primary tumours and corresponding metastases. Original data and literature review. British journal of cancer, 90(12), 2344-8.**
Study type	Case series
Aim	To investigate the expression of HER-2 between primary and metastatic tumour cells
Patient characteristics	**Inclusion criteria** Patients with samples from both the primary tumour and from a lymph node metastasis **Exclusion criteria** Samples with less good histological quality were excluded if corresponding FISH analysis was also verified as being of bad quality **Baseline characteristics** Age - median: 52.2 years Gender : 47 (100%) female Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Lymph node (47) Biopsy type : paraffin-embedded tissue Hormone status : ER+ (23) / ER- (23) / unknown (1) Disease stage : Not reported Survival/time to recurrence or progression : Not reported
Number of Patients	47
Intervention	Flourescence in situ hybridisation Chromogenic in situ hybridisation
Length of follow up	NA
Location	Finland , Sweden
Outcomes measures and effect size	

Change in receptor expression direction for HER-2* • Negative to negative • Negative to positive • Positive to negative	 21/47 (44.7%) 0/47 (0%) 0/47 (0%) 26/47(55.3%)

Bibliographic reference	**Carlsson J, Nordgren H, Sjostrom J et al. (2004). HER-2 expression in breast cancer primary tumours and corresponding metastases. Original data and literature review. British journal of cancer, 90(12), 2344-8.**
	• Positive to positive ***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**
Source of funding	Helsinki University Hospital Swedish Cancer Research Society Aventis
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	NO
Did the case series have complete inclusion of participants?	NO
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.3.32 Xiang 2011

Bibliographic reference	**Xiang J, Pan X, Xu J, Fu X, Wu D, Zhang Y, Shen L, and Wei Q. (2011). Human epidermal growth factor receptor 2 protein expression between primary breast cancer and paired asynchronous local-regional recurrences. Experimental and Therapeutic Medicine, 2(6), pp.1187-1191.**
Study type	Case series

Bibliographic reference	**Xiang J, Pan X, Xu J, Fu X, Wu D, Zhang Y, Shen L, and Wei Q. (2011). Human epidermal growth factor receptor 2 protein expression between primary breast cancer and paired asynchronous local-regional recurrences. Experimental and Therapeutic Medicine, 2(6), pp.1187-1191.**
Aim	To investigate the expression of HER-2 immunohistochemically in a series of primary breast cancer samples and corresponding local-regional recurrent lesions.
Patient characteristics	**Inclusion criteria** • Breast cancer patients with formalin-fixed, paraffin-embedded tumour samples available from untreated primary tumours and later clinically manifested local or regional recurrent tumour deposits **Exclusion criteria** • No primary tumour blocks were found in the specimen database • No tumour cells in the sections supposed to be recurrent breast cancer **Baseline characteristics** Age: 31 to 74 years (median 51) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Lymph nodes Biopsy type : Not reported Hormone status : Not reported Disease stage : Not reported Survival/time to recurrence or progression : 5 to 61 months (median 20)
Number of Patients	35
Intervention	Immunohistochemistry
Length of follow up	NA
Location	China
Outcomes measures and effect size	Change in receptor expression direction for HER-2* • Negative to negative — 16/35 (45.7%) • Negative to positive — 2/35 (5.7%)

Bibliographic reference	**Xiang J, Pan X, Xu J, Fu X, Wu D, Zhang Y, Shen L, and Wei Q. (2011). Human epidermal growth factor receptor 2 protein expression between primary breast cancer and paired asynchronous local-regional recurrences. Experimental and Therapeutic Medicine, 2(6), pp.1187-1191.**
	• Positive to negative: 3/35 (8.6%) • Positive to positive: 14/35 (40%) ***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**
Source of funding	Science and Technology Project of Zhejiang, the Outstanding Young Investigator fund from the Health Bureau of Zhejiang China, and the National Natural Science Foundation of China to Q. Wei.
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.3.42 Zhao 2015

Bibliographic reference	**Zhao S, Xu L, Liu W, et al. (2015). Comparison of the expression of prognostic biomarkers between primary tumor and axillary lymph node metastases in breast cancer. International journal of clinical and experimental pathology, 8(5), 5744-8.**
Study type	Case series

<table>
<tr><td>Bibliographic reference</td><td>Zhao S, Xu L, Liu W, et al. (2015). Comparison of the expression of prognostic biomarkers between primary tumor and axillary lymph node metastases in breast cancer. International journal of clinical and experimental pathology, 8(5), 5744-8.</td></tr>
<tr><td>Aim</td><td>To compare expressions of ER, PR, HER-2 between primary tumour and axillary lymph node metastases of female breast cancer patients.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
Diagnosis of breast cancer with ALN metastases by pathological examination

Exclusion criteria
Not reported

Baseline characteristics
Age – median (range) : 47 years (29 – 79)
Gender : 54 (100%) female
Ethnicity : Not reported
Treatment at baseline : preoperative neoadjuvant chemotherapy (24), no chemotherapy (30)
Biopsy site : axillary lymph nodes (54)
Biopsy type : tumour blocks
Hormone status : ER+ (34) / ER- (20) : PR+ (46) / PR- (8) : HER-2 + (12) / HER-2- (42).
Disease stage : Not reported
Survival/time to recurrence or progression Not reported</td></tr>
<tr><td>Number of Patients</td><td>54</td></tr>
<tr><td>Intervention</td><td>Immunohistochemical analysis
Fluorescence in situ hybridization</td></tr>
<tr><td>Length of follow up</td><td>NA</td></tr>
<tr><td>Location</td><td>China</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
<table>
<tr><td>Change in receptor expression direction for HER-2*
• Negative to negative
• Negative to positive
• Positive to negative
• Positive to positive</td><td>
41/54 (75.9%)
1/54 (1.9%)
4/54 (7.4%)
8/54 (14.8%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Zhao S, Xu L, Liu W, et al. (2015). Comparison of the expression of prognostic biomarkers between primary tumor and axillary lymph node metastases in breast cancer. International journal of clinical and experimental pathology, 8(5), 5744-8.</td></tr>
<tr><td></td><td>*This additional data was extracted as a post-hoc analysis to feed into the health economic model.</td></tr>
<tr><td>Source of funding</td><td>Shandong Provincial Nature Funds</td></tr>
<tr><td>Comments</td><td>Tumour classified as positive with a score of more than ‘+’ (immunohistochemistry) for ER and PR (-, 0% positive tumour cells; +,0 to 25%; ++, 26% to 50%; +++, more than 50%)..
HER-2 was classified as positive with a score of +++ (uniform, intensive membrane staining of more than 30% of invasive tumour cells) and negative with an IHC staining of 0, +. Besides, some patients bearing HER-2 ++ were retested with fluorescence in situ hybridization (FISH), and were classified as positive or negative according to FISH results.

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)
<table>
<tr><td>Were there clear criteria for inclusion in the case series?</td><td>YES</td></tr>
<tr><td>Was the condition measured in a standard, reliable way for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Were valid methods used for identification of the condition for all participants included in the case series?</td><td>YES</td></tr>
<tr><td>Did the case series have consecutive inclusion of participants?</td><td>YES</td></tr>
<tr><td>Did the case series have complete inclusion of participants?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the demographics of the participants in the study?</td><td>NO – demographic data was reported poorly</td></tr>
<tr><td>Was there clear reporting of clinical information of the participants?</td><td>YES</td></tr>
<tr><td>Were the outcomes or follow up results of cases clearly reported?</td><td>YES</td></tr>
<tr><td>Was there clear reporting of the presenting site(s)/clinic(s) demographic information?</td><td>YES</td></tr>
<tr><td>Was statistical analysis appropriate?</td><td>YES</td></tr>
</table></td></tr>
</table>

G.3.51 Idrisinghe 2010

Bibliographic reference	**Idirisinghe PK. A, Thike AA, Cheok PY, et al. (2010). Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. American journal of clinical pathology, 133(3), 416-29.**
Study type	Case series
Aim	To compare ER, PR, and c-ERBB2 status in series of primary breast carcinomas with their locoregional recurrences and distant metastases.
Patient characteristics	**Inclusion criteria** Patients with primary breast carcinoma with subsequent histologically proven local recurrences and distant metastases **Exclusion criteria** None reported **Baseline characteristics** Age – mean (range) : 52.2 years (29 – 85) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : ipsilateral breast, chest wall Biopsy type : paraffin sections of the formalin-fixed tissue Hormone status : ER+ (72) / ER- (45) : PR+ (59)/PR- (58) : HER-2 + (22)/HER-2- (95) Disease stage : Not reported Survival/time to recurrence or progression – mean (range) : 46.1 months (0.7 – 175.4)
Number of Patients	117 of which 45 were local recurrance.
Intervention	Immunohistochemical analysis
Length of follow up	NA
Location	Singapore
Outcomes measures and effect size	Change in receptor expression direction for HER-2* • Negative to negative: 36/45 (80%) • Negative to positive: 1/45 (2%)

Bibliographic reference	**Idirisinghe PK. A, Thike AA, Cheok PY, et al. (2010). Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. American journal of clinical pathology, 133(3), 416-29.**
	• Positive to negative: 0/45 (0%) • Positive to positive: 8/45 (18%) ***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**
Source of funding	Singapore Cancer Syndicate
Comments	**JBI critical appraisal checklist for case series** (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES
Were valid methods used for identification of the condition for all participants included in the case series?	YES
Did the case series have consecutive inclusion of participants?	YES
Did the case series have complete inclusion of participants?	YES
Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
Was there clear reporting of clinical information of the participants?	YES
Were the outcomes or follow up results of cases clearly reported?	YES
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
Was statistical analysis appropriate?	YES

1

G.3.62 Santinelli 2008

Bibliographic reference	**Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.**
Study type	Case series

Bibliographic reference	**Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.**
Aim	To determine HER-2 status in primary breast invasive carcinomas and in the paired lymph node metastases, locoregional recurrence and distant metastases,
Patient characteristics	**Inclusion criteria** Patients with metachronous breast cancer metastases (local and distant) **Exclusion criteria** Not reported **Baseline characteristics** Age – mean (range) : 50.4 years (31 – 76) Gender : Not reported Ethnicity : Not reported Treatment at baseline : Not reported Biopsy site : Bone (4), cervical (1), CNS (5), colon (2), liver (4), lung (3), ovary (1), peritoneum (1), pleura (9), retroperitoneum (1), skin (3), stomach (1) Biopsy type : paraffin-embedded blocks Hormone status : ER+ (9) / ER- (16) / unknown (10) : PR+ (11) / PR- (14) / unknown (0) : HER-2 + (12) / HER-2- (42). Disease stage : Not reported Survival/time to recurrence or progression : Not reported
Number of Patients	Synchronous lymph n = 45, metachronous lymph node metastases N = 9 and local recurrence N = 30.
Intervention	Immunohistochemical analysis Fluorescence in situ hybridization
Length of follow up	NA
Location	Italy
Outcomes measures and effect size	Synchronous lymph n = 45

Change in receptor expression direction for HER-2* • Negative to negative • Negative to positive	 21/45 1/45

Bibliographic reference	**Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.**

• Positive to negative • Positive to positive	2/45 21/45

Metachronous lymph node metastases N = 9

Change in receptor expression direction for HER-2*	
• Negative to negative	4/9
• Negative to positive	1/9
• Positive to negative	0/9
• Positive to positive	4/9

Local recurrence N = 30

Change in receptor expression direction for HER-2*	
• Negative to negative • Negative to positive • Positive to negative • Positive to positive	21/304/300/305/30

***This additional data was extracted as a post-hoc analysis to feed into the health economic model.**

Source of funding	None reported
Comments	Data on 30 cases with local recurrence only used in analyses. HER-2 positivity defined as 2+ or 3+ in IHC analysis

JBI critical appraisal checklist for case series (http://joannabriggs.org/research/critical-appraisal-tools.html)

Were there clear criteria for inclusion in the case series?	YES
Was the condition measured in a standard, reliable way for all participants included in the case series?	YES

Bibliographic reference	Santinelli A, Pisa E, Stramazzotti D et al. (2008). HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. International journal of cancer, 122(5), 999-1004.	
	Were valid methods used for identification of the condition for all participants included in the case series?	YES
	Did the case series have consecutive inclusion of participants?	YES
	Did the case series have complete inclusion of participants?	YES
	Was there clear reporting of the demographics of the participants in the study?	NO – demographic data was reported poorly
	Was there clear reporting of clinical information of the participants?	YES
	Were the outcomes or follow up results of cases clearly reported?	YES
	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	YES
	Was statistical analysis appropriate?	YES

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2

Appendix H: GRADE profiles

H.1 Studies examining distant recurrences

Quality assessment							No of patients	Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Number discordant /total	Median (range)	
Change in ER receptor expression between the two samples									
18	Case series	Serious[1]	No serious[2]	n/a[3]	Not assessed[4]	None	259 / 1378	18.6% (0, 55.6)	Very low
Change in PR receptor expression between the two samples									
17	Case series	Serious[1]	No serious[2]	n/a[3]	Not assessed[4]	None	472 / 1302	30.6% (4.17. 48.6)	Very low
Change in HER-2 receptor expression between the two samples									
22	Case series	Serious[5]	No serious[2]	n/a[3]	Not assessed[4]	None	153 / 1573	9.5% (0, 22.6)	Very low
Change in management in those with ER discordance									
1 (Aurilio et al 2013)	Case series	Very serious[6]	No serious[2]	n/a[3]	Not assessed[4]	None	ER: 22/107 (20.5%)	ER: 13/22 (59.1%)	Very low
Change in management in those with HER-2 discordance									
1 (Aurilio et al 2013)	Case series	Very serious[6]	No serious[2]	n/a[3]	Not assessed[4]	None	6/86 (6.9%)	4/6 (66.7%)	Very low
1 (Zidan et al 2005)	Case series	Serious[8]	No serious	n/a[3]	Not assessed[4]	None	8/58 (13.8%)	4/8 (50)[9]	Very low
Change in management in those with ER/PR/HER-2 discordance									
1 (Curiglia	Case series	Very serious[6]	No serious[2]	n/a[3]	Not assessed[4]	None	ER: 37/255 (14.5%) PR: 124/255 (48.6%)	31/255 (12.1)[10]	Very low

Quality assessment							No of patients	Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Number discordant /total	Median (range)	
no et al 2011)							HER-2: 24/172 (14.0%)		
1 (Yonemori 2008)	Case series	Serious[8]	No serious	n/a[3]	Not assessed[4]	None	ER: 3/24 (12.5%) PR: 1/24 (4.2%) HER-2: 3/24 (12.5%)	6/24 (25%)	Very low
Change in management in those with ER and/or PR discordance									
1 (Karagoz Ozen et al 2014)	Case series	Very serious[7]	No serious[2]	n/a[3]	Not assessed[4]	None	27/58 (46.5%)	11/27 (40.7)	Very low
Adverse events - haematoma in the left iliac biopsy site									
1 (Amir 2008)	Case series	Serious[8]	No serious	n/a[3]	Not assessed[4]	None	ER: 5/9 (56%) PR: 4/9 (44%)	1/9 (11.1%)	Very low

[1] Demographics were poorly reported in 14 studies and therefore not possible to assess how homogenous populations were – downgraded one level
[2] No serious indirectness as all distant metastases.
[3] Inconsistency not assessed as median (range) were the specified outcome.
[4] Imprecision not assessed as change in receptor expression judged clinically significant could not be defined – downgraded two levels
[5] Demographics poorly reported in all 20 studies and therefore not possible to assess how homogenous populations were - downgraded one level
[6] Demographics poorly reported and not all eligible patients had tissues samples for both primary tumour and locoregional recurrence / distant metastases. Change in management details not reported – downgraded 2 levels.
[7] Data on receptor status was not available for all patients, demographic data was reported poorly and site of distant metastases was not reported. Change in management details not reported – downgraded 2 levels.
[8] Demographics poorly reported and therefore not possible to assess how homogenous populations were - downgraded one level
[9] Reported as “treated with trastuzumab due to HER-2 evaluation in the metastases”
[10] 255 refers to total number of subjects as total discordant across all 3 receptor types not reported

H.21 Studies examining mixed locoregional and distant metastases

Quality assessment							No of patients	Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Number discordant /total	Median (range)	
Change in ER receptor expression between the two samples									
26	Case series	Serious[1]	Serious[2]	n/a[3]	Not assessed[4]	None	689/3890	20.9% (3.2, 53.6)	Very low
Change in PR receptor expression between the two samples									
19	Case series	Serious[1]	Serious[2]	n/a[3]	Not assessed[4]	None	617/1979	26.1% (16.3, 54.2)	Very low
Change in HER-2 receptor expression between the two samples									
23	Case series	Serious[1]	Serious[2]	n/a[3]	Not assessed[4]	None	135/1398	9.9% (0, 22.4)	Very low
Change in ER/PR receptor expression between the two samples									
1	Case series	Very serious[5]	Serious[2]	n/a[3]	Not assessed[4]	None	11 / 35	31.4%	Very low
Change in management in those with ER/PR/HER-2 discordance									
1 (Amir 2012)	Case Series	Very serious[5]	Serious[2]	n/a[3]	Not assessed[4]	None	ER: 15 / 94 (16.0%) PR: 38 / 84 (45.2%) HER-2: 8 / 83 (9.6%)	17/83 (20.5%)[6]	Very low
1 (Thompson 2010)	Case series	Serious[7]	Serious[2]	n/a[3]	Not assessed[4]	None	ER: 14/137 (10.2) PR: 34/137 (24.8) HER-2: 4/137 (2.9)	24/137 (17.5)[8]	Very low
1 (Amir 2012b)	Case series	Serious[7]	Serious[2]	n/a[3]	Not assessed[4]	None	ER: 29/231 (12.6%) PR: 72/231 (31.2%) HER-2: 12/220 (5.5%)	41/220 (18.8%)[8]	Very low
Adverse events - bleeding from a punch biopsy of the skin leading to admission									
1 (Amir 2012)	Case Series	Very serious[5]	Serious[2]	n/a[3]	Not assessed[4]	None	ER: 15 / 94 (16.0%) PR: 38 / 84 (45.2%) HER-2: 8 / 83 (9.6%)	1/83 (1.2%)	Very low

[1] Demographics poorly reported in 14 studies and therefore not possible to assess how homogenous populations were – downgraded one level
[2] Site of metastases includes locoregional and distant recurrences
[3] Inconsistency not assessed as median (range) were the specified outcome.
[4] Imprecision not assessed as change in receptor expression judged clinically significant could not be defined – downgraded two levels
[5] Demographics poorly reported, not all samples produced results and not all eligible patients had tissue samples for both primary tumour and local recurrence/distant metastases – downgraded two levels.
[6] Changes in management included the addition of trastuzumab in women with gain of HER-2 overexpression (n=6), the use of chemotherapy in place of endocrine therapy in those with loss of ER (n=5), no change to previous treatment in those with benign disease or second primary (n=4), and provision of endocrine therapy in place of chemotherapy for those gaining ER (n=2).
[7] Demographics poorly reported and therefore not possible to assess how homogenous populations were – downgraded one level
[8] Change in management details not reported.

Appendix I: Post-hoc analysis – direction of HER-2 receptor status change

I.1 Distant metastases

Table 15: HER-2 receptor status change from primary to distant metastases

Study	neg to neg	neg to pos	pos to neg	pos to pos	Total number
Aurilio 2013	74	4	2	6	86
Curigliano 2011	111	7	17	37	172
Duchnowska 2012	51	10	7	51	119
Fabi 2011	100	12	2	23	137
Gancberg 2002	49	3	2	14	68
Idirisinghe 2010	57	1	4	10	72
Karagoz Ozen 2014	31	5	4	5	45
Lorincz 2006	19	0	2	2	23
Okita 2013	30	4	3	21	58
Omoto 2013	11	3	1	6	21
Santinelli 2008	20	6	4	5	35
Shen 2015	19	1	0	16	36
Tapia 2007	80	3	5	17	105
Vincent Salomon 2002	33	0	2	9	44
Wu 2008	9	1	0	0	10
Yonemori 2008	14	1	2	7	24
Zidan 2005	37	7	1	13	58

I.21 Locoregional metastases

2 **Table 16: HER-2 receptor status change from primary to locoregional metastases**

Study	neg to neg	neg to pos	pos to neg	pos to pos	Total number
Aitken 2010	148	14	3	25	190
Carlsson 2004	21	0	0	26	47
Xiang 2011	16	2	3	14	35
Zhao 2015	41	1	4	8	54
Idrisinghe 2010	36	1	0	8	45
Santinelli 2008a (synchronous lymph)	21	1	2	21	45
Santinelli 2008b (metachronous lymph)	4	1	0	4	9
Santinelli 2008c (local recurrance)	21	4	0	5	30

3

Appendix J: Forest plots

None

Appendix K: Economic search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 17. The Medline search strategy is shown in Table 18. The same strategy was translated for the other databases listed.

Table 17: Economic search summary

Database	Date searched	Number retrieved
MEDLINE (Ovid)	30/08/2016	181
MEDLINE In-Process (Ovid)	30/08/2016	8
EMBASE (Ovid)	30/08/2016	296
NHS Economic Evaluation Database - NHS EED (Wiley)	30/08/2016	2
HTA (Wiley)	30/08/2016	0
PubMed	26/08/2016	1293

Table 18: Economic search strategy (Medline)

Line number/Search term/Number retrieved
Database: Ovid MEDLINE(R) <1946 to August Week 3 2016> Search Strategy: --- 1 exp Breast Neoplasms/ (248079) 2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ (32836) 3 1 or 2 (258469) 4 exp Breast/ (40576) 5 breast$.tw. (324795) 6 4 or 5 (335785) 7 (breast adj milk).tw. (9569) 8 (breast adj tender$).tw. (475) 9 7 or 8 (10042) 10 6 not 9 (325743) 11 exp Neoplasms/ (2886766) 12 10 and 11 (247311) 13 (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)).tw. (240632) 14 (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)).tw. (29895) 15 Paget's Disease, Mammary/ (694) 16 (paget$ and (breast$ or mammary or nipple$ or areola*)).tw. (999) 17 or/12-16 (286303) 18 3 or 17 (331174) 19 Receptor, erbB-2/ (19459) 20 Genes, erbB-2/ (2912) 21 (HER-2 or HER-2 or erbb-2 or erbb2 or c erbB2 or c-erbB2 or human epidermal growth factor receptor$ or cd340 antigen* or neu proto-oncogene protein or neu proto oncogene protein or neu receptor).tw. (27378) 22 exp Receptors, Estrogen/ (43693) 23 ((oestrogen$ or estrogen* or EgR or ER) adj3 (status or test$ or level$ or receptor$ or express* or hormone*)).tw. (67787)

Line number/Search term/Number retrieved
24 ((ER adj2 positiv$) or (ER adj2 negativ$) or (EgR adj2 positiv$) or (EgR adj2 negativ$) or (oestrogen$ adj2 positiv$) or (oestrogen$ adj2 negativ$) or (estrogen adj2 negativ$) or (estrogen adj2 positiv$)).tw. (12913)
25 Receptors, Progesterone/ (17204)
26 ((progesteron$ or progestin or PgR or PR) adj3 (status or test$ or level$ or receptor$ or express* or hormone*)).tw. (33912)
27 ((PR adj2 positiv$) or (PR adj2 negativ$) or (PgR adj2 positiv$) or (PgR adj2 negativ$) or (progesteron$ adj2 positiv$) or (progesteron$ adj2 negativ$) or (progestin adj2 negativ$) or (progestin adj2 positiv$)).tw. (3959)
28 or/19-27 (120466)
29 18 and 28 (48871)
30 ((change or alter or acquire$ or alter$ or conserve$ or lost or unchange$ or revert$ or reassess*) adj2 (status or express$)).tw. (44448)
31 ((concordan$ or discordan$) adj5 (status or express$)).tw. (2267)
32 ((primary or primitive) adj (tumo?r or disease or breast cancer or invasive breast cancer or focus* or diagnos* or lesion$ or site* or tissue* or region*)).tw. (67142)
33 Disease Progression/ (124847)
34 (tumo?r progress$ or cancer progress$ or disease progress$ or breast cancer progress$ or exacerbation).tw. (118285)
35 Neoplasm metastasis/ or Neoplasm recurrence, local/ (179654)
36 (distant metast* or local* recur$ or minimal residual disease or locoregional).tw. (60024)
37 ((metast* or recur*) adj (focus* or site$ or lesion$ or breast cancer or tissue$ or disease$ or tumo?r or region* or invasive breast cancer or diagnos*)).tw. (66834)
38 or/30-37 (547211)
39 29 and 38 (13110)
40 exp Biopsy/ (247761)
41 biops*.tw. (303243)
42 (re-biops* or rebiops* or re-test* or retest*).tw. (25852)
43 (tissue adj4 confirm*).tw. (4163)
44 Immunohistochemistry/ (269228)
45 (immunohistochem* or immunocytochem* or immunohistocytochem* or immunogold* or immunolabel*).tw. (338262)
46 In Situ Hybridization, Fluorescence/ (38540)
47 fluorescen*.tw. (334487)
48 (FISH adj4 (technic* or technique*)).tw. (1903)
49 Cytodiagnosis/ (15105)
50 cytodiagnos*.tw. (2270)
51 or/40-50 (1208271)
52 39 and 51 (3997)
53 animals/ not humans/ (4268987)
54 52 not 53 (3920)
55 limit 54 to english language (3673)
56 Economics/ (26766)
57 exp "Costs and Cost Analysis"/ (201681)
58 Economics, Dental/ (1889)
59 exp Economics, Hospital/ (21788)
60 exp Economics, Medical/ (13939)
61 Economics, Nursing/ (3940)
62 Economics, Pharmaceutical/ (2643)
63 Budgets/ (10559)
64 exp Models, Economic/ (12027)
65 Markov Chains/ (11532)
66 Monte Carlo Method/ (23110)

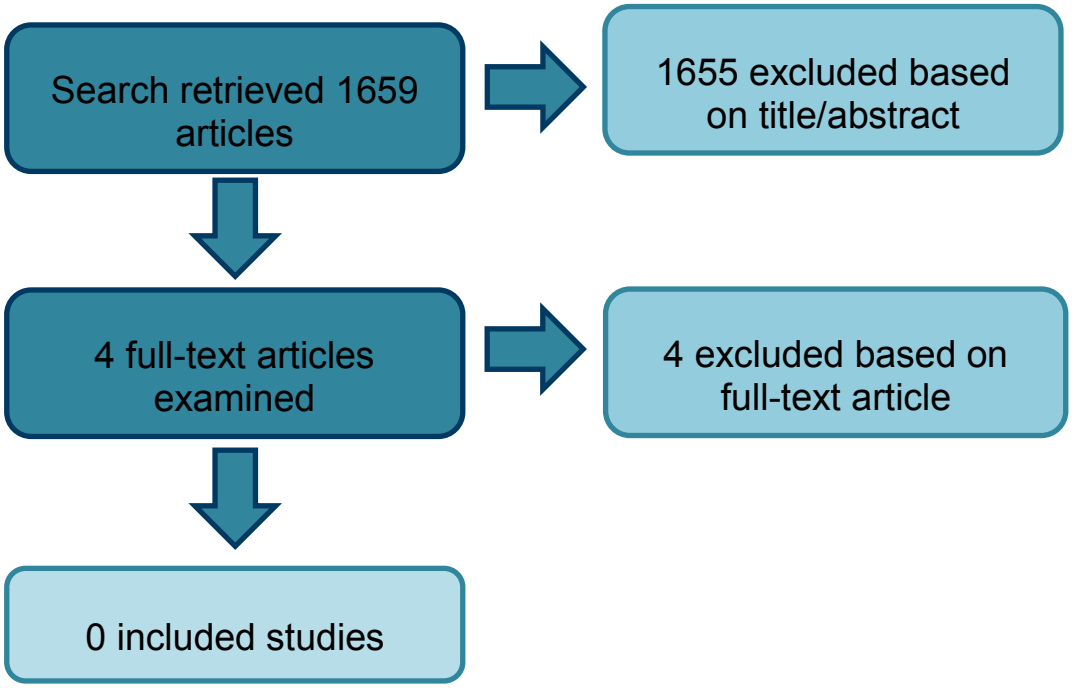
Line number/Search term/Number retrieved
67 Decision Trees/ (9662)
68 econom$.tw. (181368)
69 cba.tw. (9200)
70 cea.tw. (17898)
71 cua.tw. (846)
72 markov$.tw. (13801)
73 (monte adj carlo).tw. (24018)
74 (decision adj3 (tree$ or analys$)).tw. (9733)
75 (cost or costs or costing$ or costly or costed).tw. (355215)
76 (price$ or pricing$).tw. (26261)
77 budget$.tw. (19367)
78 expenditure$.tw. (39609)
79 (value adj3 (money or monetary)).tw. (1561)
80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3019)
81 or/56-80 (741854)
82 "Quality of Life"/ (142174)
83 quality of life.tw. (166585)
84 "Value of Life"/ (5518)
85 Quality-Adjusted Life Years/ (8778)
86 quality adjusted life.tw. (7529)
87 (qaly$ or qald$ or qale$ or qtime$).tw. (6152)
88 disability adjusted life.tw. (1634)
89 daly$.tw. (1549)
90 Health Status Indicators/ (21784)
91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (17884)
92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1095)
93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3399)
94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)
95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (348)
96 (euroqol or euro qol or eq5d or eq 5d).tw. (5168)
97 (qol or hql or hqol or hrqol).tw. (30385)
98 (hye or hyes).tw. (54)
99 health$ year$ equivalent$.tw. (38)
100 utilit$.tw. (130992)
101 (hui or hui1 or hui2 or hui3).tw. (1008)
102 disutili$.tw. (262)
103 rosser.tw. (72)
104 quality of wellbeing.tw. (7)
105 quality of well-being.tw. (351)
106 qwb.tw. (187)
107 willingness to pay.tw. (2824)
108 standard gamble$.tw. (699)
109 time trade off.tw. (837)
110 time tradeoff.tw. (216)
111 tto.tw. (684)
112 or/82-111 (374476)
113 81 or 112 (1064781)

Line number/Search term/Number retrieved	
114	55 and 113 (181)

1

2

Appendix L: Economic review flowchart



1 Appendix M: Economic excluded studies

2

Reference	Reason for exclusion
Ferrusi IL, Marshall DA, Kulin NA et al. (2009). Looking back at 10 years of trastuzumab therapy: What is the role of HER-2 testing? A systematic review of health economic analyses. Personalized Medicine, 6(2), 193-215.	Incorrect population, not recurrent tumour
Lux M P, Hildebrandt T, Bani M et al. (2013). Health economic evaluation of different decision aids for the individualised treatment of patients with breast cancer. Geburtshilfe und Frauenheilkunde, 73(6), 599-610.	Narrative review only
Vyberg M, Nielsen S, Roge R et al. (2015). Immunohistochemical expression of HER-2 in breast cancer: socioeconomic impact of inaccurate tests. BMC health services research, 15, 352.	Narrative review only
Ward S, Scope A, Rafia R et al. (2013). Gene expression profiling and expanded immunohistochemistry tests to guide the use of adjuvant chemotherapy in breast cancer management: A systematic review and cost-effectiveness analysis. Health Technology Assessment, 17(44), V-302.	Incorrect population, not recurrent tumour

3