NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Diagnostics Assessment Programme

Intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer

Final scope

June 2012

1 Introduction

The RD100i OSNA system is manufactured by Sysmex UK Limited. The Medical Technologies Advisory Committee identified the RD100i OSNA system as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note that included a description of the purpose of the technology as detailed in section 2.1. A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technology

This section describes the properties of the diagnostic technology based on the manufacturer's notification to NICE. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

The RD100i OSNA system is an automated molecular test that uses one-step nucleic acid amplification (OSNA) technology to indicate if cancer has spread to the lymph nodes in people diagnosed with breast cancer. The test analyses and amplifies genetic material (mRNA) from solubilised biopsy samples of sentinel lymph node tissue and detects the presence of the Cytokeratin 19 (CK19) gene, a biological marker associated with breast cancer. It is claimed

that the RD 100i OSNA test will provide a result within a short time and therefore, can be used during breast surgery to determine if other lymph nodes should be removed at the same time as the initial tumour. This could avoid a second operation for the patient and enable subsequent treatments such as chemotherapy to begin earlier.

2.2 Product properties

The RD-100i OSNA system analyses and amplifies mRNA from solubilised biopsy samples of sentinel lymph node tissue. It detects the level of expression of the CK19 gene, an epithelial marker associated with breast cancer. CK19 is normally not present in healthy lymph node tissue. The OSNA technology involves the homogenisation of sentinel lymph node tissue followed by analysis of the CK19 mRNA using the process of reverse transcription loop mediated isothermal amplification (RT-LAMP) on the automated analyser, RD100i. OSNA does not require the mRNA to be extracted and purified from the tissue before being analysed. The expression level of CK19 mRNA correlates with the size of the metastatic foci. Since the metastatic foci may not be evenly distributed throughout the node, the system provides more accurate results if more of the node is analysed because there is less risk of tissue allocation bias (sample bias). The result is most accurate if the entire node is used, but then no follow-up histopathology is possible. The system can be used with half of the lymph node (one piece or alternate slices), allowing for the possibility of follow-up histopathology but potentially decreasing the accuracy of the results due to the increased risk of tissue allocation bias. The time to results is dependent on the number of lymph nodes analysed, but the test takes approximately 30 - 45 minutes. The OSNA test result is expressed both quantitatively and qualitatively; - for lymph node negative test results, + (> 250 copies of CK19 m RNA / µl) for lymph nodes with a micro-metastatic tumour burden and ++ (>5000 copies of CK19 m RNA / µl) for lymph nodes with a macro-metastatic tumour burden. The analyser amplifies and detects the CK19 mRNA by using 6 different primers which have been specifically designed to avoid the amplification of CK19 pseudogenes or their transcripts; amplification of these would lead to false

positive results. Undesired amplification of genomic DNA is avoided by precipitation of DNA at low pH during sample preparation and the isothermal reaction temperature of 65°C.

The manufacturer estimates that 1% of breast tumours do not express CK19 mRNA and therefore, if cancer spreads to the lymph nodes from these tumours, CK19 mRNA will not be detected even though the lymph nodes are metastatic. Pre-screening of tumour biopsies for CK19 expression could be carried out before using the RD100i OSNA test to reduce the small risk of false negative results for metastatic sentinel lymph nodes.

2.3 Potential alternative technologies

The Metasin test is an intraoperative molecular test developed within the NHS at the Princess Alexandra Hospital in Harlow, Essex. The test has similarities to a discontinued commercial test (Veridex Genesearch BLNA assay) and uses the technique of quantitative reverse transcriptase PCR (qRT-PCR) to detect 2 predictive markers of metastases, CK19 and mammaglobin. Mammaglobin is expressed mainly by breast epithelial cells and high levels of mammaglobin are associated with breast cancer. A reference gene, PBGD, is used to confirm the validity of the mRNA used in the test and two other controls, positive and negative, are also included. The test uses reagents that can be purchased from Roche and Qiagen and can be used on any platform (PCR machine). This in-house test differs from the discontinued commercial test by using distinctly different and unique primer-probe combinations to detect the CK19 and mammaglobin genes. The test is reported to take 26 minutes to results after 6-10 minutes for extracting and purifying mRNA from the tissue. This Metasin test is currently available as an in-house test within the NHS.

Pre-screening of tumour biopsies for CK19 mRNA and mammaglobin mRNA expression may be carried out before using the Metasin test because like the CK19 biomarker, mammaglobin is not expressed in all breast tumours. The proportion of breast cancer tumours that do not express mammaglobin mRNA is not known.

3 Target conditions / indications

3.1 Background – breast cancer

Breast cancer is one of the most common cancers for women in England and Wales, with about 46,000 new cases diagnosed and 10,900 deaths recorded each year. Around one in nine women develop breast cancer at some stage in their life. Most develop in women over the age of 50, but younger women, and in rare cases men, can also get breast cancer. In men, there are around 260 cases of breast cancer diagnosed and 68 deaths in England and Wales each year. Of new cases in women, around 11,000 require additional surgery each

year to manage the spread of breast cancer to the lymph nodes. A small proportion of new cases in women and men are diagnosed in the advanced stages, when the tumour has spread significantly within the breast or to other organs of the body. In addition, a number of women who have been previously treated with curative intent subsequently develop either a local recurrence or metastases[1,2,3,4].

The main ways in which breast cancer can spread are by local spread to nearby tissues, or by regional or distant spread through the circulatory system or through the lymphatic system. Of particular relevance for this evaluation is the spread of breast cancer through the lymphatic system, which occurs when cancer cells become detached from the main breast tumour and are usually carried in the lymph to the axillary lymph nodes. The cancer cells can grow in the lymph node(s) and cause swelling, although not all metastatic lymph nodes are morphologically abnormal.

The treatment of breast cancer can cause many side-effects including significant pain, persistent fatigue, a reduction in fertility and osteoporosis. Emotionally, a diagnosis of breast cancer and subsequent treatment can cause long-term anxiety, depression and isolation in both the individual and their relatives. Hair loss and changes to the body from a mastectomy for example, are associated with social stigma, and can significantly impact on quality of life and reduce self-esteem.

One side-effect of lymph node surgery is lymphoedema, which is more likely after axillary lymph node dissection than sentinel lymph node biopsy. The most common symptom is swelling of the arm, hands and fingers on the side of the body that was operated on, which can persist for months or years. Swelling can also affect the breast, chest and shoulder[6]. Lymphoedema does not affect all individuals who undergo lymph node surgery but in some individuals it can develop soon after treatment or years later precipitated by inflammation, infection and scarring.

Axillary lymph node dissections result in minor and major complications for 80% of women. The incidence of lymphoedema in women following axillary

lymph node dissection is estimated to be 7-8%. Other complications can include pain, limited mobility, arm oedema, seroma and numbness or sensory loss[7].

3.2 Diagnostic pathway

NICE Clinical Guideline 80 'Early and locally advanced breast cancer: Diagnosis and treatment' outlines the current care pathway[1].

This guideline recommends that ultrasound evaluation of the axilla (armpit) is performed for all patients being investigated for early invasive breast cancer. If morphologically abnormal lymph nodes are identified, ultrasound-guided needle sampling is offered pre-operatively.

For patients who have no evidence of abnormal lymph nodes on ultrasound images or aspiration cytodiagnosis, minimal surgery is performed to stage the axilla at the same time as breast surgery to confirm that the cancer hasn't spread. Sentinel lymph node biopsy (SLNB) is the preferred technique in which the first lymph node(s) is removed to see if the cancer has spread from the original site. A radioactive solution and a blue dye are injected into the breast before surgery to help identify the sentinel lymph node(s) during surgery. Identifying the sentinel lymph node(s) during surgery can be difficult and there is a widely-recognised learning curve for performing SLNB. The Royal College of Surgeons, Cardiff university and the Department of Health established a surgical training programme (New Start) for performing SNLB and set standards for surgeons to achieve; greater than 90% localisation rate (ability to locate sentinel node(s)) and less than 10% false negative rate. One study reported that the localisation rate achieved for SNLB was around 98%[8]

The fresh biopsy tissue from SLNB is currently analysed by post-operative histopathology, which involves slices of the lymph node being stained and viewed by a consultant histopathologist to identify any abnormalities in the tissue. There is a risk of tissue allocation bias in histopathology because only a few slices of the lymph node are examined and metastatic foci are not evenly distributed through a lymph node. The time to receive results from histopathology is usually between 5 and 15 working days in the NHS. If the

results are positive, the patient will undergo a second operation to remove the remaining lymph nodes which may be technically more challenging than performing the axillary dissection as part of the initial surgery.

Two pathological methods that can be used intraoperatively are frozen section and touch imprint cytology. Frozen section involves a section of the lymph node being snap-frozen, stained and sliced before being viewed by a consultant histopathologist. Touch imprint cytology involves the lymph node being sliced and the cut surface of the node imprinted on to a slide, which is then stained and viewed by a consultant histopathologist or cytopathologist. Both intraoperative pathological methods can be used to help determine if axillary lymph node dissection is to be performed at the same time as the first surgery. Post-operative histopathology analysis is usually carried out on the remaining tissue to reduce the risk of a false negative result. However, in practice, these intraoperative methods are rarely used because they have low accuracy and pathology resources are very limited within the NHS.

The RD100i OSNA system and other intraoperative molecular tests can analyse the whole lymph node so there is no risk of tissue allocation bias and post-operative analysis using histopathology may not be necessary. This is decided by clinical judgement because no histopathology can be performed if the whole lymph node is used.

Individuals who have macrometastases or micrometastases detected in their sentinel lymph node are regarded as lymph node- positive, and axillary lymph node dissection is usually performed. Individuals who have isolated tumour cells in their sentinel lymph node are regarded as lymph node-negative and will not receive axillary lymph node dissection.

All information on the sentinel nodes, axillary nodes and primary breast tumour is typically discussed at a multidisciplinary team (MDT) meeting to determine the appropriate systemic adjuvant therapy. NICE Clinical guideline 80 states that adjuvant chemotherapy and radiotherapy should be started as soon as clinically possible within 31 days of completion of surgery in patients with early breast cancer having these treatments. The use of intraoperative

molecular tests and a potential consequent reduction in the number of second surgeries performed may result in patients starting adjuvant therapy earlier

4 Scope of the evaluation

4.1 Decision question

Are the RD100i OSNA system and any alternative technologies identified during scoping, clinically effective and cost effective if used in the NHS in England?

4.2 Populations

- Individuals with invasive breast cancer who undergo a sentinel lymph node biopsy.

4.3 Intervention(s)

- The RD100i OSNA system using a whole node sample.
- The RD100i OSNA system using a half node sample with postoperative histopathology confirmation.

4.4 Alternative diagnostic technologies

- The Metasin test using a whole node sample (Intraoperative in-house molecular test developed at Princess Alexandra Hospital, Harlow, Essex).
- The Metasin test using a half node sample with postoperative histopathology confirmation.

4.5 Comparators

- Post-operative standard histopathology alone.

4.6 Healthcare setting

- Secondary and tertiary care settings.

4.7 Health outcomes

4.7.1 Clinical considerations

The intermediate measures for consideration include:

- Diagnostic test accuracy
- Test failure rate
- Discordant test results
- Time to test result
- Duration of anaesthesia

The clinical outcomes for consideration include:

- Patient anxiety associated with waiting time for result and not knowing extent of surgery prior to operation
- Number of repeat operations (except for re-excision of positive margins)
- Time in operating theatre
- Time to start and nature of adjuvant therapy
- Morbidity and mortality from biopsies, axillary dissections, first and second operations and treatment of cancer
- Adverse events from false test results including patient distress and sequelae.

Data on these outcomes are likely to be used along with clinical utility scores to estimate Quality-Adjusted Life Years (QALYs).

4.7.2 Cost considerations

The cost analysis will be based on the UK NHS setting and comprise both NHS and Personal Social Services (PSS) costs.

The costs for consideration include:

- Cost of equipment, any additional tests (pre-screening), reagents and consumables
- Staff and training of staff
- Maintenance of equipment

- Costs associated with surgeon time and the management of operating theatre time
- Medical costs arising from on-going care following test results including those associated with surgery, time spent in hospital, and treatment of cancer.
- Medical costs arising from adverse events including those associated with biopsies, surgery, cancer treatment and false test results.

The cost of the hardware for the RD100i OSNA system is approximately £70,000 (excluding VAT). The consumable cost is approximately £150 - £250 per patient (excluding VAT). This consumable cost is dependent upon the number of tests performed per theatre day and the number of patient samples tested. The maintenance cost is £6,180 per annum (excluding VAT) following the expiry of the 1 year warranty.

5 Modelling approach

The aim and structure of the economic model will depend upon the final scope.

5.1 Existing models

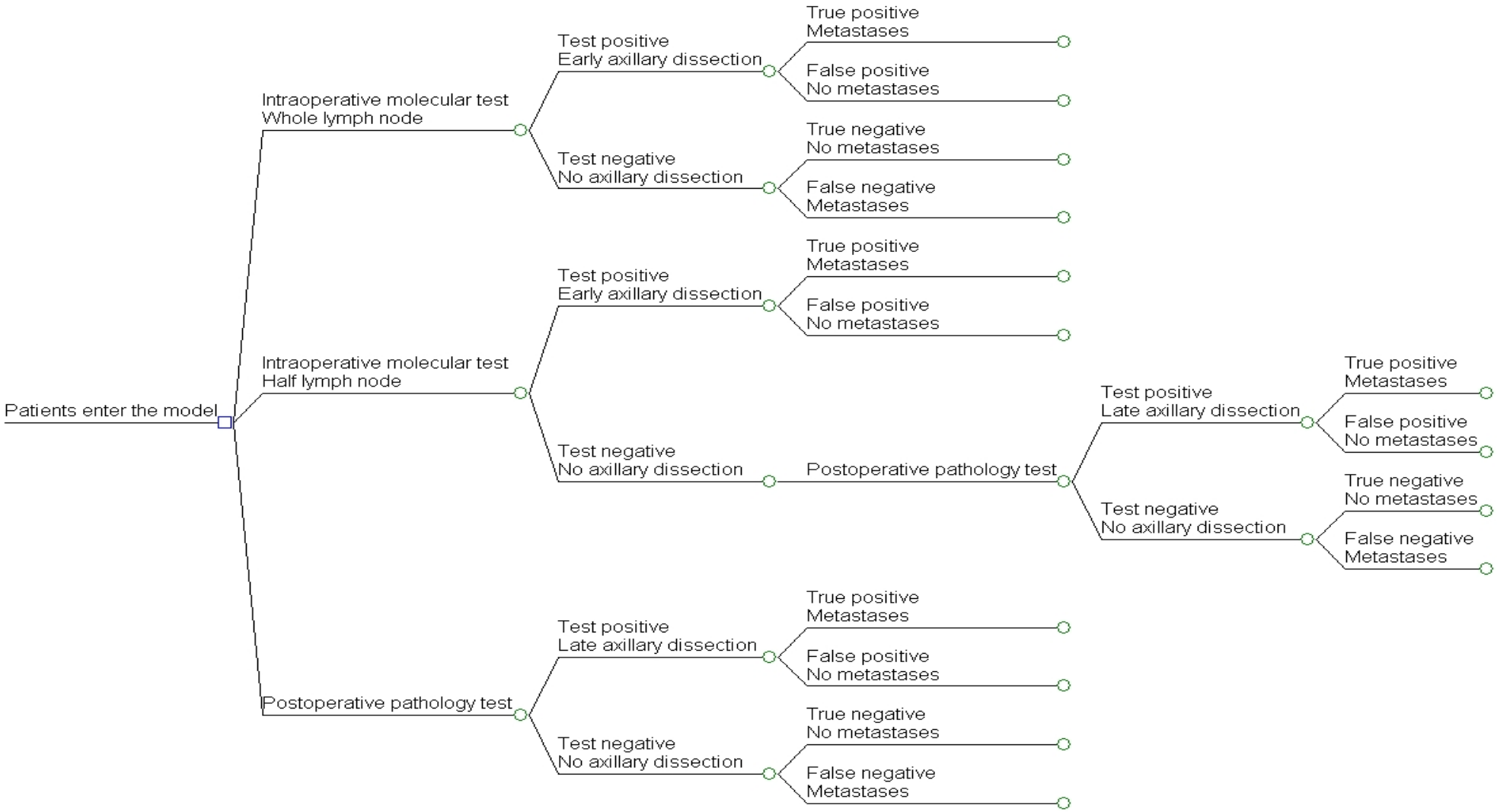
One study in the published literature has considered the cost-effectiveness of introducing intraoperative molecular diagnosis of metastatic sentinel lymph nodes[9]. Sensitivity analyses showed that the costs are dependent on the number of operations performed rather than the cost of the operation. The main savings were from hospital bed utilisation and theatre time due to the reduction in the need for second operations. Resulting direct costs but no QALYs were reported. A cost impact report from York Health Economics Consortium reported that intraoperative testing reduces the number of operations and length of hospital stay, and provides overall cost savings to the NHS[10].

5.2 Modelling possibilities

The issues that will need to be addressed, through modelling if necessary, include the short term outcomes from potentially extended time in surgery (taking into account the primary operation, be it conservation, ablation or reconstruction), side-effects of axillary lymph node dissection and the long-term outcomes associated with breast cancer. The potential variations in test accuracy, owing to the size of the lymph node sample and whether the biomarkers are present in all patients will need to be determined and modelled to identify resulting changes in final health outcomes. Assumptions about the test accuracy will also have to be made with regard to discordant results between the molecular and pathological classification of regional lymph node metastasis in patients.

5.3 Model structure

Potential decision tree for intraoperative molecular tests for sentinel lymph node analysis:


Patients enter the model
Intraoperative molecular test
Whole lymph node
Test positive
Early axillary dissection
True positive
Metastases
False positive
No metastases
Test negative
No axillary dissection
True negative
No metastases
False negative
Metastases
Intraoperative molecular test
Half lymph node
Test positive
Early axillary dissection
True positive
Metastases
False positive
No metastases
Test negative
No axillary dissection
Postoperative pathology test
Test positive
Late axillary dissection
True positive
Metastases
False positive
No metastases
Test negative
No axillary dissection
True negative
No metastases
False negative
Metastases
Postoperative pathology test
Test positive
Late axillary dissection
True positive
Metastases
False positive
No metastases
Test negative
No axillary dissection
True negative
No metastases
False negative
Metastases

5.4 Outcomes

Final health outcomes in the form of QALYs will need to be calculated in the economic modelling.

6 Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

The prevalence of breast cancer is significantly more common in women than in men. People with a diagnosis of cancer are protected under the Equality Act 2010 from the point of diagnosis.

7 Implementation issues

Biomedical scientists can carry out the molecular intraoperative tests although a level of molecular biology expertise may be needed. This expertise may not be available in all hospitals performing breast surgery.

For efficient use of intraoperative testing, surgical theatre lists need to be carefully scheduled and multiple analysers may be needed for sentinel lymph node testing if breast operations occur in parallel.

Appendix A Glossary of terms

Axillary lymph node
Lymph node located in the armpit

Frozen section
A technique, in which a section of tissue is snap-frozen, stained and sliced before being viewed by a consultant histopathologist.

Lymphoedema
Swelling caused by a build-up of lymph fluid in the tissues of the body

Lymph node
Small round mass of supported lymphatic tissue that is filled with white blood cells (lymphocytes) and acts as a filter to trap bacteria and foreign particles from lymph fluid. Lymph nodes are critical for the immune system and are principal sites where many immune reactions are initiated.

Messenger RNA
Messenger RNA is transcribed from a DNA template and carries coding information to sites of protein synthesis, at which the messenger RNA is translated into protein.

One step Nucleic Acid Amplification
A technique that uses a process called reverse-transcription-loop-mediated-isothermal-amplification (RT-LAMP) to rapidly amplify genes without extracting or purifying the genes from tissue.

Pseudogene
A DNA sequence that resembles a gene but lacks essential components that are necessary for function.

Polymerase chain reaction
A scientific technique that amplifies a few copies of a segment of DNA into millions of copies.

Quantitative reverse transcriptase polymerase chain reaction
A technique in which RNA is reverse transcribed into DNA and the resulting DNA is amplified using the polymerase chain reaction.

Reverse Transcription Loop Mediated Isothermal Amplification
A technique that enables amplification and detection of the target sequence to be completed in a single step.

Sentinel lymph node
The first lymph node to which cancer cells are most likely to have spread from the primary tumour

Touch Imprint Cytology
A technique in which tissue is sliced and the cut tissue surface imprinted on to a slide. The sample slide is then stained and viewed by a consultant histopathologist.

Appendix B Abbreviations

mRNA	messenger RNA
OSNA	One Step Nucleic Acid Amplification
PCR	Polymerase Chain Reaction
qRT-PCR	Quantitative Reverse Transcriptase Polymerase Chain Reaction
RT-LAMP	Reverse Transcription Loop Mediated Isothermal Amplification
SLNB	Sentinel Lymph Node Biopsy

Appendix C Related NICE guidance

- Eribulin for the treatment of locally advanced or metastatic breast cancer. NICE Technology Appraisal TA250, Issued: April 2012

- Breast reconstruction using lipomodelling after breast cancer treatment. NICE Interventional Procedure guidance IPG417. Issued: January 2012.

- Fulvestrant for the treatment of locally advanced or metastatic breast cancer. NICE Technology Appraisal TA239, Issued: December 2011.

- Early and locally advanced breast cancer. NICE Pathways, May 2011

- Early and locally advanced breast cancer: diagnosis and treatment. NICE clinical guideline CG80. Issued February 2009 *(currently being looked at by Guideline Reviews)*

- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline CG81. Issued February 2009 *(currently being looked at by Guideline Reviews)*

- Image-guided radiofrequency excision biopsy of breast lesions. NICE Interventional Procedure guidance IPG308. Issued July 2009.

- Familial breast cancer: The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. NICE Clinical Guideline CG41. Issued: October 2006

- Improving outcomes in breast cancer. Cancer Service guidance, CSGBC. Issued: August 2002

- Eribulin for the treatment of locally advanced or metastatic breast cancer. NICE Technology Appraisal TA250, Issued: April 2012

- Breast reconstruction using lipomodelling after breast cancer treatment. NICE Interventional Procedure guidance IPG417. Issued: January 2012.

- Fulvestrant for the treatment of locally advanced or metastatic breast cancer. NICE Technology Appraisal TA239, Issued: December 2011.

Under development

- Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care -update of CG41. NICE clinical guideline**.** Anticipated publication date: TBC

- Gene expression profiling and expanded immunohistochemistry tests to guide selection of chemotherapy regimes in breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat. NICE Diagnostics Guidance. Anticipated publication date: TBC

Appendix D References

1 Early and locally advanced breast cancer: diagnosis and treatment. NICE clinical guideline CG80. Issued February 2009;

2 Breast Cancer (Dec 2009) Patient UK;

3 Breast cancer (female) (August 2010) NHS Choices;

4 Breast-Lymph Node Assay - Executive-Summary (NTAC)

5 Cancer Research UK website

6 Breast Cancer Care website

7 D'Angelo-Donovan D., Dickson-Witmer D. and Petrelli N.J. (2012) Sentinel lymph node biopsy in breast cancer: A history and current clinical recommendations. *Surgical Oncology* 1-5

8 Mansel R.E., Fallowfield L., Kissin M., Goyal A., Newcombe R.G., Dixon M.J., Yiangou C., Horgan K., Bundred N., Monypenny I., England D., Sibbering M., Abdullah T.I., Barr L., Chetty U., Sinnett D.H., Fleissig A., Clarke D and Ell P.J. (2006) Randomized Multicenter Trial of Sentinel Node Biopsy Versus Standard Axillary Treatment in Operable Breast Cancer: The ALMANAC Trial. *Journal of the National Cancer Institute* **98**: 599-609

9 Cutress R.I., McDowell A., Gabriel F.G., Gill J., Jeffrey M.J., Agrawal A., Wise M., Raftery J., Cree I.A. and Yiangou C. (2010) Observational and cost analysis of the implementation of breast cancer sentinel node intraoperative molecular diagnosis. *J. Clin. Path*. **63**: 522-529

10 Burke M., and Patton T. (2010) The Cost Impact of Implementing Intra-Operative Testing for the Diagnosis of Patients with Metastatic Breast Cancer in England. York Health Economics Consortium. NTAC Report.