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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Diagnostics Advisory Committee

## Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer

**Contents:**


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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# DIAGNOSTICS ASSESSMENT PROGRAMME

# Diagnostics consultation document

## Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer

The National Institute for Health and Care Excellence (NICE) is producing guidance on using tumour profiling tests (EndoPredict, MammaPrint, Oncotype DX Breast Recurrence Score, Prosigna and IHC4+C) to guide adjuvant chemotherapy decisions in people with early breast cancer in the NHS in England. The diagnostics advisory committee has considered the evidence base and the views of clinical and patient experts.

**This document has been prepared for public consultation.** It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report and the diagnostics assessment report addendum).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

**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. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:



 

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such effects and how they could be avoided or reduced.

**Note that this document is not NICE's final guidance on tumour profiling tests to guide adjuvant chemotherapy decisions in people with breast cancer. The recommendations in section 1 may change after consultation.**

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the Diagnostics Assessment Programme manual.

**Key dates:**

Closing date for comments: 11 May 2018

Third diagnostics advisory committee meeting: 13 June 2018

# 1 Draft recommendations

1.1 EndoPredict, Oncotype DX Breast Recurrence Score and Prosigna are recommended as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative early breast cancer, only if:

- they have an intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic Index
- information provided by the test would help them and their clinicians make a shared decision on whether or not to have adjuvant chemotherapy



 

- the companies provide the tests to the NHS with the discounts agreed in the access proposals and
- clinicians and companies make timely, complete and linkable record-level test data available to the National Cancer Registration and Analysis Service under a data collection agreement with NICE (see section 5.24).

1.2 MammaPrint is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because it is not cost effective.

1.3 IHC4+C is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because the analytical validity of the test is uncertain.

# 2 Clinical need and practice

## *The problem addressed*

2.1 The tumour profiling tests EndoPredict, MammaPrint, Oncotype DX Breast Recurrence Score, Prosigna and IHC4+C provide information on the activity of genes in tumour samples from people with early breast cancer. The results provide a risk profile of a person's breast cancer, which can be used with other routinely assessed clinical risk factors, such as nodal status and tumour size. It is claimed that the risk profile can be used to better predict the risk of disease recurrence. Some tests also claim to predict relative treatment effects for chemotherapy. This information is intended to help decision-making about adjuvant chemotherapy use.

2.2 It is also claimed that the tumour profiling tests may improve the identification of early breast cancer in people who may not benefit



 

from adjuvant chemotherapy because there is a low risk of disease recurrence. For these people unnecessary treatment could be avoided, and therefore the comorbidities and negative effects of chemotherapy on quality of life. Also, for people with early breast cancer at low risk of disease recurrence based on clinical and pathological features, the tests could confirm whether their risk is correct. If reclassified as being at high risk of recurrence, those people may benefit from chemotherapy. People with breast cancer and clinicians may also have more confidence that the treatment they are having or recommending is appropriate.

2.3 This assessment evaluates the clinical and cost effectiveness of EndoPredict, MammaPrint, Oncotype DX Breast Recurrence Score, Prosigna and IHC4+C when used to guide adjuvant chemotherapy decisions. The population was people with oestrogen receptor (ER)-positive (or progesterone receptor-positive or both), human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (stages 1 or 2) with 0 to 3 positive lymph nodes.

2.4 This is a full update of NICE's diagnostics guidance 10 on gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat, which was published in 2013. This recommended Oncotype DX as an option for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and lymph node-negative early breast cancer if the person was assessed as being at intermediate risk and the company provided Oncotype DX to NHS organisations according to the confidential arrangement agreed with NICE. The guidance also encouraged data collection on the use of Oncotype DX in the NHS, and further research on MammaPrint, IHC4 and Mammostrat. Since publication of the original guidance,



 

Mammostrat is no longer available and a new test, EndoPredict, has become available.

## *The condition*

2.5 Breast cancer is the most common cancer and the third most common cause of UK cancer-related deaths. One in 8 women and 1 in 870 men will be diagnosed with breast cancer during their lifetime (Cancer Research UK 2016). In 2014, 46,085 women and 332 men were newly diagnosed with breast cancer in England (Office for National Statistics 2016). Most breast cancer develops in women who are over the age of 50 (Cancer Research UK 2016).

2.6 Breast cancer survival depends on the stage of the disease at diagnosis, the treatment received and the biology of the tumour. More than 90% of women diagnosed with early breast cancer survive for at least 5 years, and 78% survive for 10 years (Cancer Research UK 2016). In contrast, only 13% of those diagnosed with advanced disease survive for more than 5 years.

## *The diagnostics and care pathways*

### Diagnosis

2.7 Breast cancer may be diagnosed following an abnormal result in the NHS breast cancer screening programme, or after referral for further investigation because of signs or symptoms that could be associated with breast cancer. The referral criteria are described in NICE's guideline on suspected cancer.

2.8 When cancer cells have been detected in a biopsy sample, further tests are done to provide more information on the characteristics of the tumour. The results of these tests are used to categorise breast cancer into molecular subtypes and determine which types of treatment it is most likely to respond to. Recommendations on tumour testing are in NICE's guideline on early and locally



 

advanced breast cancer. This guideline is being updated. Tumour tests can include hormone receptor and HER2 tests. Although not routinely done, some laboratories may also test for Ki67, a marker of cell proliferation.

**Care**

2.9 NICE's guideline on early and locally advanced breast cancer describes the care pathway. Surgery is often the initial treatment. Neoadjuvant treatment may be used before surgery, to reduce the size of the tumour and enable breast-conserving surgery.

2.10 After surgery, further treatment (adjuvant treatment) may be needed and this can include radiotherapy, chemotherapy, hormone therapy, biological therapy or a combination of these. The decision to offer adjuvant therapy, and the treatments to use, is made taking into account the clinical history, the stage of disease, the likely course of the disease (prognosis), the molecular characteristics of the tumour and the person's preferences.

2.11 A variety of tools are available that can help to predict the likelihood of breast cancer recurrence based on clinical and pathological features. These may be used to provide prognostic information for patients and to guide the selection of adjuvant therapy. Expert advice suggests that the PREDICT tool version 2.0, an online prognostic and treatment benefit calculator, is the most widely used tool in the NHS in England to calculate risk of recurrence. Adjuvant! Online is not currently available to the NHS.

# 3 The diagnostic tests

3.1 The assessment compared 5 intervention tests with 1 comparator.



 

## *The interventions*

### EndoPredict (Myriad Genetics)

3.2 EndoPredict is a CE-marked assay that is designed to predict the likelihood of metastases developing within 10 years of an initial breast cancer diagnosis. The test is for pre- and postmenopausal people with early breast cancer with oestrogen receptor (ER)-positive, human epidermal growth factor 2 (HER2)-negative and lymph node (LN)-negative or LN-positive disease (up to 3 positive nodes).

3.3 EndoPredict measures the expression of 12 genes: 3 proliferation-associated genes, 5 hormone receptor-associated genes, 3 reference (normalisation) genes and 1 control gene.

3.4 EndoPredict needs RNA extracted from a formalin-fixed, paraffin-embedded (FFPE) breast cancer tissue sample. The test can be done in a local laboratory or the Myriad Genetics pathology laboratory in Germany. It takes approximately 2 days to get the results from a local laboratory, and longer if samples are sent to Germany.

3.5 The test involves a reverse transcription-quantitative polymerase chain reaction. Online evaluation software calculates an EP score and an EPclin score. An EP score of 0 to less than 5 indicates low risk of distant disease recurrence in the next 10 years. An EP score of 5 to 15 indicates high risk of distant disease recurrence in the next 10 years.

3.6 The EPclin score estimates the probability of metastases developing within 10 years (assuming 5 years of endocrine therapy). It is calculated by adding clinical data about tumour size and nodal status to the EP score. An EPclin score of less than 3.3 indicates low risk (less than 10%) of metastases in the next



 

10 years. An EPclin score of 3.3 or more indicates high risk of metastases in the next 10 years.

3.7 During consultation on the first diagnostics consultation document, NICE accepted an access proposal from the company in line with the Diagnostics Assessment Programme's interim addendum on access proposals. This provides a simple discount to the list price of EndoPredict, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.

**MammaPrint (Agendia)**

3.8 MammaPrint is a CE-marked assay that is designed to assess the risk of distant recurrence within 5 and 10 years and whether a person would benefit from chemotherapy. The test is for pre- and postmenopausal people with stage 1 or 2 breast cancer, with a tumour size of 5 cm or less, and LN-negative or LN-positive disease (up to 3 positive nodes). The test can be used irrespective of ER and HER2 status.

3.9 MammaPrint measures the expression of 70 genes, including genes associated with 7 different parts of the metastatic pathway: growth and proliferation, angiogenesis, local invasion, entering the circulation, survival in the circulation, entering organs from the circulation, and adaption to the microenvironment at a secondary site.

3.10 The MammaPrint test needs RNA extracted from an FFPE breast cancer tissue sample. The test is offered as an off-site service. In Europe, samples are analysed at the Agendia laboratory in the Netherlands. Results are available within 10 days of submitting the sample.

3.11 The test is based on diagnostic microarray. Software is used to calculate the MammaPrint result on a scale of −1 to +1. The score



 

indicates the risk of developing distant metastases over the next 10 years without any adjuvant endocrine therapy or chemotherapy. A MammaPrint result of 0 or less indicates high risk of metastases in the next 10 years and a result of more than 0 indicates low risk (10% or less) of metastases in the next 10 years.

**Oncotype DX Breast Recurrence Score (Genomic Health)**

3.12 Oncotype DX Breast Recurrence Score (hereafter referred to as Oncotype DX) is designed to quantify the 10-year risk of distant recurrence and predict relative treatment effects for chemotherapy. The test also reports the underlying tumour biology: ER, progesterone receptor and HER2 status. The test is for pre- and postmenopausal people with stage 1 or 2 breast cancer and ER-positive, HER2-negative, LN-negative or LN-positive disease (up to 3 positive nodes). The assay does not have a CE mark because it is provided as a service by Genomic Health.

3.13 Oncotype DX quantifies the expression of 21 genes: 16 cancer-related genes correlated with distant recurrence-free survival, and 5 reference (normalisation) genes.

3.14 The Oncotype DX test needs RNA extracted from a FFPE breast cancer tissue sample. Samples are processed centrally at a Genomic Health laboratory in the US. Results are usually available 7 to 10 days after the sample is received.

3.15 The test is based on a reverse transcription-quantitative polymerase chain reaction. It gives a recurrence score of between 0 and 100, which is used to quantify the 10-year risk of distant recurrence, assuming 5 years of endocrine therapy. A score below 18 indicates low risk of distant recurrence and claims to predict little to no effect of chemotherapy on patient outcomes. A score between 18 and 30 indicates intermediate risk of recurrence and claims to predict no substantial effect of chemotherapy on patient



 

outcomes. A score of 31 or more indicates high risk of recurrence and claims to predict a large effect of chemotherapy on patient outcomes.

3.16 The breast recurrence score can be combined with clinical and pathological factors using the recurrence score-pathology-clinical (RSPC) calculator. However, this calculator has not been validated in a cohort independent of that used to derive Oncotype DX.

3.17 During consultation on the first diagnostics consultation document NICE accepted the company's commitment to maintain the current confidential discount, which is in line with the Diagnostics Assessment Programme interim addendum on access proposals. This provides a simple discount to the list price of Oncotype DX, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.

**Prosigna (NanoString Technologies)**

3.18 Prosigna is a CE-marked assay designed to provide information on breast cancer subtype and to predict distant recurrence-free survival at 10 years. The test is for postmenopausal peoplewith early breast cancer that is ER-positive, HER2-negative and LN-negative or LN-positive (up to 3 positive nodes).

3.19 Prosigna measures the expression of 50 genes used for intrinsic subtype classification, 8 housekeeping genes used for signal normalisation, 6 positive controls, and 8 negative controls.

3.20 The test needs RNA extracted from a FFPE breast tumour tissue sample. It is based on direct mRNA counting using fluorescent probes and an nCounter Digital Analyser.

3.21 Prosigna classifies the risk of distant recurrence within 10 years, assuming 5 years of endocrine therapy, based on the PAM50 gene signature, breast cancer subtype, tumour size, nodal status and



 

proliferation score. The proliferation score is determined by evaluating multiple genes associated with the proliferation pathway. The test gives a score between 0 and 100. Based on this score and the nodal status, samples are classified into risk categories:

- LN-negative: low risk (0 to 40), intermediate risk (41 to 60) or high risk (61 to 100).
- LN-positive (up to 3 positive nodes): low risk (0 to 15), intermediate risk (16 to 40), or high risk (41 to 100).

3.22 During consultation on the first diagnostics consultation document, NICE accepted an access proposal from the company in line with the Diagnostics Assessment Programme interim addendum on access proposals. This provides a simple discount to the list price of Prosigna, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence.

**IHC4 and IHC4+C**

3.23 The IHC4 test is a laboratory developed test that combines the results of 4 immunohistochemistry (IHC) measurements. The IHC4+C test combines the results of the 4 IHC4 tests with clinical and pathological features such as age, nodal status, tumour size, and grade. Both versions are designed to quantify the 10-year risk of distant disease recurrence, assuming 5 years of endocrine therapy. The test is for postmenopausal people with early breast cancer that is ER-positive and LN-negative or LN-positive (up to 3 positive nodes).

3.24 The IHC4+C test needs an FFPE breast tumour tissue sample. The 4 immunohistochemistry tests are: ER, progesterone receptor (PR), HER2 and the proliferation marker Ki67. ER and HER2 markers are commonly measured in NHS laboratories, but PR and Ki67 markers are not.



 

3.25 The IHC4+C test is in clinical use at 1 NHS centre (the Royal Marsden NHS Foundation Trust), which carries out the test with an average turnaround time of 1 week. The test could be run in local NHS laboratories providing that training and quality assurance programmes for the individual assays are in place.

3.26 The IHC4+C test uses a published algorithm to calculate a risk score for distant recurrence based on the results of the 4 assays and clinical factors. A calculator is available for use on request. A score of less than 10% is categorised as low risk for distant recurrence at 10 years. A score of more than 10% but less than 20% is intermediate risk, and a score of 20% or more is high risk for distant recurrence at 10 years.

### *The comparator*

3.27 The comparator is decision-making for adjuvant chemotherapy prescribing, based on clinical and pathological features or the results of tools used to assess risk without the tumour profiling tests. Features may include the stage of the disease, nodal status, ER or PR status, HER2 status and any previous treatment (for example, neoadjuvant therapy). Risk assessment tools include PREDICT, the Nottingham Prognostic Index (NPI) and Adjuvant! Online. However, Adjuvant! Online is currently unavailable because it is being updated. It is not certain when it will be reinstated, and the website directs people to the PREDICT tool.

3.28 These risk assessment tools can be used to define the level of clinical risk. For example, in LN-negative disease a NPI of 3.4 or less is classed as low risk, and a NPI of more than 3.4 is classed as intermediate risk. If using the PREDICT tool, an absolute 10-year survival benefit from chemotherapy of less than 3% is classed as low risk; between 3 and 5% is classed as intermediate risk; and more than 5% is classed as high risk.



 

# 4 Evidence

The diagnostics advisory committee (section 8) considered evidence on EndoPredict, MammaPrint, Oncotype DX, Prosigna and IHC4 or IHC4+C from several sources. Full details of all the evidence are in the committee papers.

## *Clinical effectiveness*

4.1 Evidence on the following outcomes was of interest in the clinical effectiveness review:

- Prognostic ability – the degree to which the test can accurately predict the risk of an outcome such as disease recurrence.
- Prediction of relative treatment effect – the ability of the test to predict which patients have disease that will respond to chemotherapy. It can be assessed by considering whether the relative treatment effect of chemotherapy or no chemotherapy on patient outcomes differs according to the test score.
- Clinical utility – the ability of the prospective use of the test to affect patient outcomes such as recurrence and survival compared with current practice.
- Decision impact – how the test influences decision-making in terms of which patients will be offered chemotherapy.

4.2 A total of 153 references were included in the review. Studies assessing prognostic ability and prediction of relative treatment effect were quality assessed using relevant criteria from the draft prediction model study risk of bias assessment tool (PROBAST). Clinical utility studies were quality assessed using the Cochrane risk of bias tool for randomised controlled trials (RCTs).

### Prognostic ability

4.3 Studies providing information on prognostic ability were retrospective analyses of RCT data or routinely collected data. Most of the studies excluded patients who did not have a large



 

enough tissue sample for testing, which leaves the evidence base at potential risk of spectrum bias, because patients with smaller tumours (who may be systematically different to those with large tumours) are likely to be under-represented. In many studies patients had chemotherapy, which could affect event rates and therefore potentially reduce the apparent prognostic performance of a test. In other studies, patients who had chemotherapy were excluded from analyses, which may also lead to spectrum bias. Therefore studies in which all patients had endocrine monotherapy were preferable.

4.4 Results for prognostic ability were generally presented as unadjusted or adjusted analyses. Unadjusted analyses look at differences in the event rates among low-, intermediate- and high-risk groups without adjusting for clinical and pathological variables. Adjusted analyses show whether the test has prognostic value over clinical and pathological variables.

***Distribution of patients across risk categories***

4.5 Among studies of patients with lymph node (LN)-negative disease who had endocrine monotherapy, in each group around 70% to 80% had disease that was categorised as low or low/intermediate risk across all tests (11 studies). Most MammaPrint studies had mixed endocrine and chemotherapy use, mixed hormone receptor status with or without mixed human epidermal growth factor receptor 2 (HER2) status, so results may not be comparable with results from other tests. In these studies 20% to 61% of patients had disease that was categorised as low risk (6 studies). Most IHC4 or IHC4+C studies used quartiles or tertiles to define risk groups. These studies do not provide useful information on the distribution of patients across risk categories.



 

4.6 The proportion of patients with low and intermediate risk was generally much lower in groups with LN-positive disease than in groups with LN-negative disease who had endocrine monotherapy (7 LN-positive studies). For Oncotype DX, however, the proportion of patients with low and intermediate risk was only slightly lower in the LN-negative group than in the LN-positive group. Studies of MammaPrint in patients with LN-positive disease were all done in groups with mixed hormone receptor status and mixed or unknown HER2 status, so results may not be comparable with results from other tests. In these studies 38% to 41% of patients had disease that was categorised as low risk (2 studies).

***Oncotype DX***

4.7 There were 11 data sets that provided information on the prognostic ability of Oncotype DX: 7 reanalyses of RCT data and 4 retrospective studies of routinely collected data. All studies were validation studies, and in 4 studies patients had endocrine monotherapy. Three of the studies were done in East Asia and may not be generalisable to England because usual clinical practice may differ between countries enough to affect prognostic outcomes. Also, it is possible that people of different ethnicities have different underlying risk profiles and natural history of disease.

4.8 Unadjusted analyses indicated that Oncotype DX had prognostic accuracy (there were statistically significant differences between low-risk and high-risk groups) across various recurrence outcomes, regardless of lymph node status. However, hazard ratios between the intermediate-risk group and the high- or low-risk groups were not always statistically significant, particularly in the group with LN-positive disease.

4.9 In adjusted analyses, Oncotype DX provided statistically significant additional prognostic information over most commonly used clinical



 

and pathological variables (age, grade, size, nodal status), regardless of lymph node status. A bespoke analysis of TransATAC study data also showed that Oncotype DX provided additional prognostic information over clinical and pathological tools to assess risk.

### *MammaPrint*

4.10 There were 10 data sets that provided information on the prognostic ability of MammaPrint: 1 reanalysis of RCT data and 9 retrospective studies of routinely collected data. In addition, a further 4 studies pooled data on specific patients from the same 10 data sets. All studies were validation studies, and in 5 studies patients had endocrine monotherapy. Most studies included some patients who were out of scope (with HER2-positive or hormone receptor-negative disease or both).

4.11 In 6 of 7 unadjusted analyses, MammaPrint had prognostic accuracy (there were statistically significant differences between low-risk and high-risk groups) for 10 year distant recurrence-free survival or interval, regardless of LN status.

4.12 In adjusted analyses, a pooled analysis of patients with LN-negative and LN-positive disease showed that MammaPrint had statistically significant prognostic accuracy for 10-year distant recurrence-free survival after adjusting for clinical and pathological variables. In patients with LN-negative disease, MammaPrint had statistically significant prognostic accuracy for 10-year distant recurrence-free interval when adjusted for Adjuvant! Online or Nottingham Prognostic Index (NPI). In patients with LN-positive disease, MammaPrint had borderline statistically significant prognostic accuracy for 10-year distant recurrence-free survival when adjusted for clinical and pathological variables.



 

### *Prosigna*

4.13 There were 8 data sets that provided information on the prognostic ability of Prosigna: 6 reanalyses of RCT data and 3 retrospective analyses of 2 prospective cohort studies. All studies were validation studies, and in 5 studies patients had endocrine monotherapy. Some studies included some patients who were out of scope (with HER2-positive or hormone receptor-negative disease or both).

4.14 Prosigna had statistically significant prognostic accuracy for 10-year distant recurrence-free survival and interval in all unadjusted analyses of patients with LN-negative and LN-positive disease.

4.15 In analyses adjusted for clinical and pathological variables or tools, Prosigna had prognostic accuracy for 10-year distant metastasis-free survival and distant recurrence-free survival. In patients with LN-negative disease the results were statistically significant. In patients with LN-positive disease the results were statistically or borderline significant.

### *EndoPredict*

4.16 There were 3 data sets that provided information on the prognostic ability of EndoPredict; all were reanalyses of RCT data. All studies were validation studies, and in 2 of the 3 studies patients had endocrine monotherapy.

4.17 In unadjusted analyses, EndoPredict had statistically significant prognostic accuracy for 10-year distant recurrence-free survival and interval in patients with LN-negative and LN-positive disease.

4.18 Results from the bespoke analysis of TransATAC, which reported adjusted analyses on the EPclin score part of EndoPredict were academic in confidence. Two studies reported adjusted analyses on the EP score part of EndoPredict, showing that it provided



 

statistically significant additional information over clinical and pathological variables regardless of LN status.

### *IHC4 and IHC4+C*

4.19 There were 12 data sets that provided information on the prognostic ability of IHC4 and IHC4+C: 6 reanalyses of RCT data and 6 reanalyses of routinely collected data. Most of the data related to the IHC4 score alone, without including clinical factors. One of the studies was based on the derivation cohort for IHC4, and therefore may have overestimated prognostic ability. The remaining studies were validation studies. Patients had endocrine monotherapy in only 2 studies, 1 of which was the derivation cohort study.

4.20 In unadjusted analyses, IHC4 had statistically significantly better prognostic performance in groups with high risk than in groups with low risk (defined by quartiles or tertiles) regardless of lymph node status. However, no studies reported survival or recurrence outcomes by risk group. Also, many used laboratory methods that differed from the derivation study methodology. In adjusted analyses, IHC4 had additional prognostic value over clinical and pathological factors in 3 studies, but patients had endocrine monotherapy in only 1 of these studies.

4.21 Data on IHC4+C came from the derivation cohort and 1 validation cohort. These studies showed that IHC4+C had prognostic value in unadjusted analyses. In adjusted analyses IHC4+C provided statistically significantly more information than the NPI in LN-negative, but not LN-positive, disease.

### Prediction of relative treatment effect

4.22 In addition to estimating the risk of recurrence, the ability of Oncotype DX and MammaPrint to predict which patients have disease that will respond to chemotherapy was explored in studies.



 

The external assessment group (EAG) reviewed evidence in support of this.

### *Oncotype DX*

4.23 In 5 data sets (2 reanalyses of RCT data and 3 observational studies) reported across 11 published references and 1 confidential manuscript, analyses assessed the ability of Oncotype DX to predict relative treatment effects for chemotherapy.

4.24 The 2 reanalyses of RCTs suggest that Oncotype DX may predict differences in relative treatment effects for chemotherapy. Hazard ratios for disease-free survival for patients having chemotherapy compared with those having no chemotherapy suggested that the greatest relative treatment effect was for patients in the Oncotype DX high-risk category. Unadjusted interaction tests between Oncotype DX risk group and relative treatment effects were mainly statistically significant, but adjusted interaction tests were not always statistically significant, particularly in the group with LN-positive disease.

4.25 Results from the 3 observational studies were mixed and at high risk from confounding. One reported a statistically significant interaction test but this was only adjusted for a limited number of factors. Two others reported hazard ratios for chemotherapy compared with no chemotherapy; 1 study in patients with intermediate risk, and another in patients with high risk. Both of these studies reported statistically non-significant results.

4.26 The recurrence score-pathology-clinical (RSPC) algorithm incorporates Oncotype DX plus age, tumour size and grade. There was a non-significant interaction test result between relative chemotherapy treatment effects and RSPC risk group.



 

### *MammaPrint*

4.27 Two studies reported the ability of MammaPrint to predict the relative treatment effects for chemotherapy. In a pooled analysis including patients with LN-negative and LN-positive disease, the effect of chemotherapy compared with no chemotherapy was statistically significant in the MammaPrint high-risk group but not in the low-risk group in unadjusted and adjusted analyses. Further, the interaction test for chemotherapy treatment and risk group was non-significant. In a pooled analysis of patients with LN-positive disease, there was a non-significant interaction between chemotherapy treatment and risk group.

## Clinical utility

4.28 There were no clinical utility data available for EndoPredict, Prosigna or IHC4+C.

### *Oncotype DX*

4.29 Five data sets, reported across 9 published references and 1 confidential manuscript, reported evidence on the clinical utility of Oncotype DX. One further study did not meet the inclusion criteria (because of insufficient follow-up length), but presented subgroup data according to age, lymph node status and ethnicity, and was therefore discussed by the EAG. Studies generally reported different outcomes, making comparisons across studies difficult. The EAG noted that the best evidence for clinical utility is an RCT of treatment guided by the test compared with treatment guided by the comparator, and that this type of evidence is not currently available for Oncotype DX. All studies reporting on the clinical utility of Oncotype DX are judged to be of poor quality using the Cochrane risk of bias tool for RCTs.

4.30 In patients with LN-negative disease, using the test in clinical practice appeared to result in low rates of chemotherapy in patients



 

with low risk (2% to 12%), with acceptable outcomes (distant recurrence-free survival, distant recurrence-free interval or invasive disease-free survival 96% to 99.6%). Rates of chemotherapy increased with increasing risk category, and were generally higher in patients with LN-positive disease. It was not possible to conclude whether patients in intermediate and high-risk categories had better outcomes as a result of using Oncotype DX to guide treatment because there were no comparator groups (patients who had treatment without Oncotype DX testing).

***MammaPrint***

4.31 Two studies reported evidence relating to the clinical utility of MammaPrint. MINDACT was a prospective, partially randomised study in which clinical risk was determined using a modified version of Adjuvant! Online. Patients with risk scores that disagreed from MammaPrint and modified Adjuvant! Online were randomised to chemotherapy or no chemotherapy. Of patients included in the study, 88% had HR-positive disease and 90% HER2-negative disease, therefore some patients were outside of the scope for this assessment. For the group who were high risk with modified Adjuvant! Online and low risk with MammaPrint, 5-year distant metastasis-free survival was 95.9% with chemotherapy and 94.4% without chemotherapy, a non-statistically significant absolute difference of 1.5% (adjusted hazard ratio for distant metastasis or death with chemotherapy compared with no chemotherapy, 0.78; 95% CI 0.50 to 1.21; p=0.27). For the group who were low risk with modified Adjuvant! Online and high risk with MammaPrint, 5-year distant metastasis-free survival was 95.8% with chemotherapy and 95.0% without chemotherapy, a non-statistically significant absolute difference of 0.8% (adjusted hazard ratio for distant metastasis or death with chemotherapy compared with no chemotherapy, 1.17; 95% CI 0.59 to 2.28; p=0.66). The EAG judged MINDACT to be at



 

low risk of bias in terms of randomisation, allocation concealment and reporting. However, no details of blinding were reported.

4.32 Results from the RASTER study suggested that distant recurrence-free interval rates were sufficiently low in the MammaPrint low-risk group for these patients to avoid chemotherapy. The 5-year distant recurrence-free interval rate for LN-negative disease was 97.0% for patients with low risk (15% had chemotherapy) and 91.7% for patients with high risk (81% had chemotherapy). In addition, MammaPrint provided additional prognostic information over Adjuvant! Online and the NPI, but not over the NHS PREDICT tool. The EAG judged RASTER to be at high risk of bias using the Cochrane risk of bias tool for RCTs.

**Comparison of the tests with each other**

4.33 There were 6 studies that compared more than 1 test: 4 reanalyses of RCTs and 2 observational studies. Evidence shows that generally when a test placed more patients in a low-risk category than another test, the event-free survival in the low-risk group was reduced. Also, the tests generally performed differently in patients with LN-negative and LN-positive disease.

4.34 Thirteen studies reported data from microarray analyses on more than 1 test, however, these studies had methodological limitations. The comparability of test algorithms applied to microarray data with the commercial assays was unknown, so the generalisability of findings from microarray studies to the decision problem was uncertain. All the studies reported data on Oncotype DX and MammaPrint, and 2 also reported data on EndoPredict. The microarray studies generally supported the conclusions from studies using the commercial versions of the assays in suggesting that Oncotype DX, MammaPrint and EndoPredict can discriminate between patients with high and low risk regardless of LN status. In



 

terms of additional prognostic performance of the tests over clinical and pathological variables, EndoPredict appeared to have the greatest benefit, followed by Oncotype DX and then MammaPrint. However, because of the methodological limitations, the EAG judged that these studies did not provide conclusive evidence of the superiority of 1 test over others.

4.35 The OPTIMA Prelim study, a UK-based feasibility phase of an RCT, analysed concordance between different tests. The study included Oncotype DX, MammaPrint, Prosigna and IHC4 plus 2 other tests. Out of the 4 in-scope tests, MammaPrint assigned the most patients to the low-risk category, but unlike the other 3 tests it does not have an intermediate category. When the low and intermediate categories were treated as 1 category for the 3 tests that have 3 risk groups, Oncotype DX assigned the most patients to this category, and MammaPrint the least. Kappa statistics indicated modest agreement between tests, ranging from 0.33 to 0.53. Also, across 5 tests in the study, only 39% of tumours were uniformly classified as either low/intermediate risk or high risk by all 5 tests. Of these, 31% were classified as low/intermediate risk by all tests and 8% were high risk by all tests. The study authors concluded that although the tests assigned similar proportions of patients to low/intermediate-risk and high-risk categories, test results for an individual patient could differ markedly depending on which test was used.

### Decision impact

4.36 The review of decision impact focused on studies done in the UK or the rest of Europe:

- Oncotype DX: 6 UK studies and 12 other European studies
- EndoPredict: 1 UK study and 3 other European studies
- IHC4+C: 1 UK study and 0 other European studies



 

- Prosigna: 0 UK studies and 3 other European studies
- MammaPrint: 0 UK studies and 8 other European studies.

4.37 The percentage of patients with any change in treatment recommendation or decision (either to or from chemotherapy) in UK studies was 29% to 49% across 4 Oncotype DX studies, 37% in 1 EndoPredict study and 27% in 1 IHC4+C study. Ranges across European (non-UK) studies were 5% to 70% for Oncotype DX, 38% to 41% for EndoPredict, 14% to 41% for Prosigna and 13% to 51% for MammaPrint.

4.38 The net change in the percentage of patients with a chemotherapy recommendation or decision (pre-test to post-test) among UK studies was a reduction of 8% to 23% across 4 Oncotype DX studies, an increase of 1% in 1 EndoPredict study, and a reduction of between 2% and 26% in 1 IHC4+C study. Net changes across European (non-UK) studies were a reduction of 0% to 64% for Oncotype DX, a reduction of 13% to 26% for EndoPredict, a reduction of 2% to an increase of 9% for Prosigna, and a reduction of 31% to an increase of 8% for MammaPrint.

### Anxiety and health-related quality of life

4.39 There were 6 studies that reported outcomes relating to anxiety (including worry and distress) and health-related quality of life. The lack of a comparator in the studies made it difficult to tell whether changes in anxiety experienced with the use of tumour profiling tests would also have occurred if patients received a definitive decision based on clinical risk factors alone. Overall, evidence suggests that tumour profile testing may reduce anxiety in some patients in some contexts, but generally there was little effect on health-related quality of life.



 

## *Cost effectiveness*

### Review of economic evidence

4.40 The EAG reviewed existing studies investigating the cost effectiveness of tumour profiling tests to guide treatment decisions in people with early breast cancer, and also did a detailed critique of the economic models and analyses provided by Agendia (MammaPrint), Genomic Health (Oncotype DX), and the chief investigator of a UK decision impact study (EndoPredict).

4.41 From the review, 26 studies were identified that had been published since the original assessment for diagnostics guidance 10. The models reported in the studies assessed the cost effectiveness of tumour profiling tests across different countries including the UK, the US, Canada, Mexico, Japan, Austria, Germany, France and the Netherlands. Most studies compared Oncotype DX (18 studies), MammaPrint (8 studies) or EndoPredict (1 study) with comparators such as Adjuvant! Online, the St Gallen guidelines, standard practice or other conventional diagnostic tools. There was variation between the analyses in the populations evaluated, the disease type and other patient characteristics.

4.42 There was a high level of consistency in the general modelling approach and structure, and several studies were based on a previously published model. Most of the models used a Markov or hybrid decision tree–Markov approach, 2 studies used a partitioned survival approach and 1 study used a discrete event simulation approach. The time horizons ranged from 10 years to the patient's remaining lifetime, with cycle lengths ranging from 1 month to 1 year when reported. Most of the models that evaluated Oncotype DX assumed that the test could predict relative treatment effects for chemotherapy.



 

## Economic evaluation

4.43 None of the models identified in the literature review included all of the tests identified in the scope. Therefore, the EAG developed a de novo economic model designed to assess the cost effectiveness of Oncotype DX, MammaPrint, Prosigna, IHC4+C and EndoPredict compared with current practice without the use of the tumour profiling tests. The model used a lifetime time horizon (42 years) from the perspective of the UK NHS and personal social services. All costs and health outcomes were discounted at a rate of 3.5% per year. Unit costs were valued at 2015/16 prices. The main source of evidence used to inform the analyses of Oncotype DX, Prosigna, IHC4+C and EndoPredict was a bespoke analysis of TransATAC provided by the study investigators. This was limited to UK data on patients with hormone receptor-positive, HER2-negative disease with 0 to 3 positive lymph nodes to match the scope for this assessment. Because this study did not include MammaPrint, MINDACT was used as the basis for evaluating the cost effectiveness of MammaPrint. PREDICT scores were not available in either data set, and so this tool could not be considered as a comparator or used to determine different risk subgroups. Therefore, the comparator for Oncotype DX, Prosigna, IHC4+C and EndoPredict was current practice (various tools and algorithms), and the comparator for MammaPrint was a modified version of Adjuvant! Online.

### *Model structure*

4.44 The hybrid decision tree–Markov model was based on the model previously developed by Ward et al. (2013). The decision tree component of the model classified patients in the current practice group (no test) and the tumour profiling test group as high, intermediate and low risk. For EndoPredict and MammaPrint, the intermediate-risk category was excluded because the test provides



 

results in terms of high and low risk only. In both the test group and the current practice group, the decision tree determined the probability that a patient would be in 1 of 6 groups: low risk, chemotherapy; low risk, no chemotherapy; intermediate risk, chemotherapy; intermediate risk, no chemotherapy; high risk, chemotherapy, and high risk, no chemotherapy. For EndoPredict and MammaPrint, 4 groups were used because there was no intermediate-risk category. Each group was linked to a Markov model which predicted lifetime quality-adjusted life-years (QALYs) and costs according to the patient's risk of distant recurrence and whether or not they had chemotherapy.

4.45 Each Markov node included 4 health states: distant recurrence-free; distant recurrence; long-term adverse events (acute myeloid leukaemia [AML]); and dead. Patients entered the model in the distant recurrence-free health state. A health-related quality of life decrement was applied during the first model cycle to account for health losses associated with short-term adverse events for patients having adjuvant chemotherapy. The treatment effect for adjuvant chemotherapy was modelled using a relative risk reduction for distant recurrence within each risk classification group. The benefit of the test was therefore captured in the model by changing the probability that patients with each test risk classification had adjuvant chemotherapy.

***Model inputs***

4.46 The risk classification probabilities used in the model for Oncotype DX, Prosigna, IHC4+C and EndoPredict were from the bespoke data analysis of TransATAC, which only included postmenopausal women. For MammaPrint, they were from MINDACT.

4.47 The probability of developing distant metastases in each group and risk category was based on 10-year recurrence-free interval data



 

from the bespoke data analysis of TransATAC for Oncotype DX, Prosigna, IHC4+C and EndoPredict. For MammaPrint the probability of developing distant metastases was based on an adjusted analysis of 5-year distant metastasis-free survival data from MINDACT. The model assumed that the risk of distant metastases between 10 and 15 years was halved, and after 15 years was zero.

4.48 The probability of having chemotherapy in the current practice group and in the tumour profiling test groups was taken from the sources in table 1.



 

**Table 1 Source for post-test probability of having chemotherapy**

| Population | Source | Proportion of patients having chemotherapy | | |
|---|---|---|---|---|
| | | Low risk | Intermediate risk | High risk |
| **Current practice group** | | | | |
| LN-negative, NPI≤3.4 | NCRAS data set | 0.07 | | |
| LN-negative, NPI>3.4 | Genomic Health access scheme data set[1] | 0.43 | | |
| LN-positive (1–3 nodes) | NCRAS data set | 0.63 | | |
| Overall population (MammaPrint) | Expert opinion | 0.47 | | |
| **3-level tests (Oncotype DX, Prosigna and IHC4+C)** | | | | |
| LN-negative, NPI≤3.4 | UKBCG survey data | 0.00 | 0.20 | 0.77 |
| LN-negative, NPI>3.4 | Genomic Health access scheme data set | 0.01 | 0.33 | 0.89 |
| LN-positive (1–3 nodes) | Loncaster et al. (2017) node-positive estimates | 0.08 | 0.63 | 0.83 |
| **2-level tests (EndoPredict and MammaPrint)** | | | | |
| EndoPredict: all 3 subgroups | Bloomfield et al. (2017) study | 0.07 | – | 0.77 |
| MammaPrint: all subgroups | Bloomfield et al. (2017) study | 0.07 | – | 0.77 |

Abbreviations: LN, lymph node; NCRAS, National Cancer Registration and Analysis Service; NPI, Nottingham Prognostic Index; UKBCG, UK breast cancer group

[1] The Genomic Health access scheme data set is based on the access scheme operated by NHS England and is a result of the research recommendation from NICE's original diagnostics guidance 10

4.49 In the base-case analysis, the relative treatment effect for chemotherapy was assumed to be the same across all test risk groups, that is, all tests were assumed to be associated with prognostic benefit only. For Oncotype DX, Prosigna, IHC4+C and



 

EndoPredict a 10-year relative risk of distant recurrence was estimated as 0.76 for chemotherapy compared with no chemotherapy (Early breast cancer trialists' collaborative group 2012), and was assumed to apply to the groups with LN-negative and LN-positive disease. For MammaPrint the 10-year relative risk of distant recurrence was estimated to be 0.77 (MINDACT) for chemotherapy compared with no chemotherapy.

4.50 In sensitivity analyses the effect of assuming that Oncotype DX could predict relative treatment effects for chemotherapy was explored, based on the B20 study by Paik et al. (2006) and the SWOG-8814 study by Albain et al. (2010). For the group with LN-negative disease, the 10-year relative risks of distant recurrence with chemotherapy compared with no chemotherapy were 1.31, 0.61 and 0.26 for the low-, intermediate- and high-risk categories respectively. For the group with LN-positive disease, the 10-year relative risks of relapse with chemotherapy compared with no chemotherapy were 1.02, 0.72 and 0.59 respectively. It is possible that the no-chemotherapy arm of B20 may have overestimated the difference in response rates between low- and high-risk patients, because this arm was the derivation set for Oncotype DX. Therefore, additional sensitivity analyses in the group with LN-negative disease explored the impact of varying the relative chemotherapy treatment effect between risk groups on the incremental cost-effectiveness ratios (ICERs). Hazard ratios were based on naive indirect comparisons of the chemotherapy arms from the B20 study and the no-chemotherapy arms from the B14 study (hazard ratios for treatment effects with chemotherapy compared with no chemotherapy were 0.64, 0.75 and 0.35 for the low-, intermediate- and high-risk categories respectively), and the chemotherapy arms of the B20 study and the no-chemotherapy arms of the TransATAC study (hazard ratios for treatment effects with chemotherapy compared with no chemotherapy were 0.86,



 

0.88 and 0.49 for the low-, intermediate- and high-risk categories respectively).

4.51 Survival following distant recurrence was based on a median of 40.1 months from Thomas et al. (2009). From this, the 6-month probability of death following distant recurrence was estimated to be 0.098, assuming a constant rate. The rate of death following distant metastases was assumed to be the same across the different subgroups and across each test risk group.

4.52 The model assumed that 10.5% of patients entering the distant recurrence health state had previously had local recurrence, based on de Bock et al. (2009). The 6-month probability of developing AML was estimated to be 0.00025, based on Wolff et al. (2015). Survival following the onset of AML was estimated to be approximately 8 months; assuming a constant event rate gave a 6-month probability of death following AML of 0.53. Additional sensitivity analyses explored the effect of including congestive heart failure (average net lifetime QALY loss of 0.0385 and average net lifetime cost saving of £2 from Hall et al. 2017, using an excess congestive heart failure risk relative to that of the general population), permanent hair loss (disutility of 0.04495 from Nafees et al. 2008 applied to 15% of all patients having chemotherapy) and peripheral neuropathy (disutility of 0.02 from Shiroiwa et al. 2009 applied to 12% of all patients having chemotherapy) in the model.

### *Costs*

4.53 The costs of the tumour profiling tests were based on company prices (see table 2).



 

**Table 2 Test prices**

| Test | List price | Comments |
|---|---|---|
| Oncotype DX | £2,580 | Tests carried out in Genomic Health laboratory in US. Cost includes sample handling and customer service. A commercial-in-confidence discounted test cost was used in the model. |
| Prosigna | £1,970 | Based on doing the test in an NHS laboratory, which includes the laboratory costs (£240), the Prosigna kit (£1,650) and the nCounter system (£194,600) and is based on 2,500 samples per lifetime of the nCounter system).<br>A commercial-in-confidence discounted test cost was used in a scenario analysis to account for the access proposal. |
| EndoPredict | £1,500 | Tests carried out in Myriad's laboratory in Munich.<br>A commercial-in-confidence discounted test cost was used in a scenario analysis to account for the access proposal. |
| IHC4 | £203 | The cost was based on 2014 prices. The total cost of the test (£198) was uplifted using the HCHS indices to current prices. |
| MammaPrint | £2,326 | Converted from Euros to UK pounds sterling, assuming an exchange rate of 1 British pound to 1.15 Euros. |
| Abbreviations: HCHS, hospital and community health services | | |

4.54 The costs associated with adjuvant chemotherapy were from a previous costing analysis of the OPTIMA Prelim trial (Hall et al. 2017). The weighted mean cost of adjuvant chemotherapy acquisition, delivery and toxicity was estimated to be £3,145 per course.

4.55 All surviving patients had endocrine therapy for a period of between 5 and 8 years. Costs of endocrine therapy were taken from the British national formulary (2017). In addition, 30% of women with early breast cancer had 4 mg of bisphosphonates (zoledronic acid) by intravenous infusion every 6 months for up to 3 years, at a cost of £58.50, excluding administration.



 

4.56 All patients had 2 routine follow-up visits during the first year after surgery, with annual visits thereafter for 5 years. Patients were also assumed to have a routine annual mammogram for up to 5 years. The cost of a routine follow-up visit was estimated to be £162.84, and the cost of a mammogram was estimated to be £46.37.

4.57 Costs associated with treating local recurrence were taken from Karnon et al. (2007) and uplifted to current prices (£13,913). This was applied as a once-only cost to distant recurrence. Costs associated with treating distant metastases were derived from Thomas et al. (2009), and included visits, drugs, pharmacy, hospital admission and intervention, imaging, radiotherapy, pathology and transport. Cost components specifically associated with terminal care were excluded. The 6-monthly cost of treating metastatic breast cancer was estimated to be £4,541.

### *Health-related quality of life*

4.58 Health utilities were taken from published studies (see table 3).

**Table 3 Health utilities applied in the base case**

| Health state / event | Duration applied in model | Mean | Standard error | Source |
|---|---|---|---|---|
| Recurrence-free | Indefinite | 0.824 | 0.002 | Lidgren et al. 2007 |
| Disutility distant metastases | Indefinite | 0.14 | 0.11 | Calculated from Lidgren et al. 2007 |
| Local recurrence | Once-only QALY loss applied on transition to distant recurrence state | −0.108 | 0.04 (assumed) | Campbell et al. 2011 |
| Chemotherapy AEs | 6 months | −0.038 | 0.004 | Campbell et al. 2011 |
| AML | Indefinite | 0.26 | 0.04 (assumed) | Younis et al. 2008 |
| Abbreviations: AEs, adverse events; AML, acute myeloid leukaemia; QALY, quality-adjusted life year | | | | |



 

### *Base-case results*

4.59 The following key assumptions were applied in the base-case analysis:

- Clinicians interpreted each of the 3-level tests in the same way (for example, an Oncotype DX high-risk score would lead to the same chemotherapy decision as a Prosigna high-risk score).
- Clinicians interpreted each of the 2-level tests in the same way (for example, a MammaPrint high-risk score would lead to the same chemotherapy decision as an EndoPredict high-risk score).
- The treatment effect for adjuvant chemotherapy was the same across all risk score categories for all tests.
- The prognosis of patients with AML and the costs and QALYs accrued within the AML state were independent of whether they had previously developed distant metastases.
- A disutility associated with adjuvant chemotherapy was applied once during the first model cycle only (while the patient is taking the regimen).
- Costs associated with endocrine therapy, bisphosphonates, follow-up appointments and mammograms were assumed to differ according to time since model entry.
- The model assumed that people entered at an age of around 60 years.

4.60 In the subgroup with LN-negative disease and a NPI of 3.4 or less, compared with current practice, the probabilistic model gave ICERs of:

- £147,419 per QALY gained (EndoPredict)
- £122,725 per QALY gained (Oncotype DX)
- £91,028 per QALY gained (Prosigna)
- £2,654 per QALY gained (IHC4+C).



 

4.61 In the subgroup with LN-negative disease and a NPI of more than 3.4, compared with current practice, the probabilistic model gave ICERs of:

- £46,788 per QALY gained (EndoPredict)
- £26,058 per QALY gained (Prosigna)
- Oncotype DX was dominated by current practice (that is, it was more expensive and less effective)
- IHC4+C was dominant over current practice (that is, it was less expensive and more effective).

4.62 In the population with LN-positive disease, compared with current practice, the probabilistic model gave ICERs of:

- £28,731 per QALY gained (Prosigna)
- £21,458 per QALY gained (EndoPredict)
- Oncotype DX was dominated by current practice
- IHC4+C was dominant over current practice.

4.63 In the overall MINDACT population, MammaPrint compared with modified Adjuvant! Online had an ICER of £131,482 per QALY gained. In the modified Adjuvant! Online high-risk subgroup, MammaPrint was dominated by current practice, and in the modified Adjuvant! Online low-risk subgroup, MammaPrint compared with current practice had an ICER of £414,202 per QALY gained.

4.64 The risk classification probabilities and the probability of having chemotherapy were combined in the model to estimate chemotherapy use with and without tumour profiling. The modelled chemotherapy use in the base case is shown in table 4.



 

**Table 4 Modelled chemotherapy use with and without tumour profiling**

| Test, subgroup compared with current practice | Chemotherapy use | | |
|---|---|---|---|
| | Test | No test | Net change |
| **Oncotype DX** | | | |
| LN0 NPI≤3.4 | 0.076 | 0.072 | 0.004 |
| LN0 NPI>3.4 | 0.273 | 0.430 | −0.157 |
| LN+ (1–3 nodes) | 0.337 | 0.627 | −0.290 |
| **IHC4+C** | | | |
| LN0 NPI≤3.4 | 0.030 | 0.072 | −0.042 |
| LN0 NPI>3.4 | 0.355 | 0.430 | −0.075 |
| LN+ (1–3 nodes) | 0.554 | 0.627 | −0.073 |
| **Prosigna** | | | |
| LN0 NPI≤3.4 | 0.075 | 0.072 | 0.003 |
| LN0 NPI>3.4 | 0.435 | 0.430 | 0.005 |
| LN+ (1–3 nodes) | 0.709 | 0.627 | 0.082 |
| **EndoPredict** | | | |
| LN0 NPI≤3.4 | 0.140 | 0.072 | 0.068 |
| LN0 NPI>3.4 | 0.438 | 0.430 | 0.008 |
| LN+ (1–3 nodes) | 0.603 | 0.627 | −0.024 |
| **MammaPrint** | | | |
| MINDACT overall population | 0.319 | 0.466 | −0.148 |
| mAOL high risk | 0.445 | 0.772 | −0.327 |
| mAOL low risk | 0.191 | 0.159 | 0.033 |
| Abbreviations: LN0, lymph node negative; LN+, lymph node positive, mAOL, modified Adjuvant! Online; NPI, Nottingham Prognostic Index | | | |

### *Probabilistic sensitivity analyses*

4.65 The cost-effectiveness planes from the probabilistic sensitivity analyses showed considerable uncertainty in the cost-effectiveness estimates.

4.66 In the subgroup with LN-negative disease and a NPI of 3.4 or less, the only test with a non-zero probability of producing more net benefit than current practice at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained was IHC4+C.



 

4.67 In the subgroup with LN-negative disease and a NPI of more than 3.4, at a maximum acceptable ICER of £20,000 per QALY gained, IHC4+C had a probability of 0.69 of being cost effective compared with current practice. For all other tests, the probability that the test was cost effective compared with current practice at this threshold was 0.24 or less. In the same subgroup, at a maximum acceptable ICER of £30,000 per QALY gained, IHC4+C had a probability of 0.67 and Prosigna had a probability of 0.60 of being cost effective compared with current practice. Oncotype DX had a probability of 0.04 and EndoPredict had a probability of 0.26 of being cost effective compared with current practice.

4.68 In the subgroup with LN-positive disease, IHC4+C had probabilities of 0.95 and 0.94 of being cost effective compared with current practice at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained respectively. In the same subgroup at the same maximum acceptable ICERs, the probability of EndoPredict producing more net benefit than current practice ranged from 0.44 to 0.73. For Prosigna the range was 0.24 to 0.55. In this subgroup Oncotype DX had very low probabilities of producing more net benefit than current practice at the same maximum acceptable ICERs (0.01 or lower).

4.69 In the overall MINDACT population and in the subgroups, the probability that MammaPrint would be cost effective compared with current practice at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained was approximately zero.

### *Deterministic sensitivity analyses*

4.70 The EAG did deterministic sensitivity analyses, testing a wide range of plausible values of key parameters.

4.71 Deterministic sensitivity analysis results for Oncotype DX compared with current practice were:



 

- Subgroup with LN-negative disease and a NPI of 3.4 or less: ICERs remained over £34,000 per QALY gained across all analyses.
- Subgroup with LN-negative disease and a NPI of more than 3.4: Oncotype DX was either dominated or had an ICER of more than £35,000 per QALY gained across almost all analyses. The only exception was when Oncotype DX was assumed to predict relative treatment effects for chemotherapy. In this analysis, Oncotype DX dominated current practice.
- Population with LN-positive disease: Oncotype DX remained dominated across most analyses. The exceptions were when Oncotype DX was assumed to predict relative treatment effects for chemotherapy (it was dominant), and when the cost of chemotherapy was doubled (£3,700 saved per QALY lost).

4.72 Deterministic sensitivity analysis results for IHC4+C compared with current practice were:

- Subgroup with LN-negative disease and a NPI of 3.4 or less: ICERs remained below £16,000 per QALY gained across all analyses, except when post-test chemotherapy probabilities were derived from Holt et al. (2011; £36,259 per QALY gained). Also, IHC4+C dominated current practice when the cost of chemotherapy was doubled.
- Subgroup with LN-negative disease and a NPI of more than 3.4: IHC4+C dominated current practice or had an ICER below £6,000 per QALY gained across all scenarios.
- Population with LN-positive disease: IHC4+C dominated current practice across all but 1 scenario. When the probability of having chemotherapy was based on the UK breast cancer group (UKBCG) survey the ICER was £1,929 per QALY gained.



 

4.73 Deterministic sensitivity analysis results for Prosigna compared with current practice were:

- Subgroup with LN-negative disease and a NPI of 3.4 or less: ICERs were greater than £71,000 per QALY gained across all analyses.
- Subgroup with LN-negative disease and a NPI of more than 3.4: ICERs were below £34,000 per QALY gained across all analyses.
- Population with LN-positive disease: ICERs were below £38,000 per QALY gained across all analyses.

4.74 Deterministic sensitivity analysis results for EndoPredict compared with current practice were:

- Subgroup with LN-negative disease and a NPI of 3.4 or less: ICERs remained greater than £91,000 per QALY gained across all analyses.
- Subgroup with LN-negative disease and a NPI of more than 3.4: ICERs remained greater than £30,000 per QALY gained across all but 2 of the analyses. Exceptions were when the UKBCG survey was used to inform the probability of having chemotherapy (£25,250 per QALY gained), and when Cusumano et al. (2014) was used to inform the probability of having chemotherapy based on the EndoPredict test result (£26,689 per QALY gained).
- Population with LN-positive disease: ICERs remained below £30,000 per QALY gained across all scenarios.

4.75 Deterministic sensitivity analysis results for MammaPrint compared with current practice were:

- Overall MINDACT population: ICERs were estimated to be greater than £76,000 per QALY gained across all scenarios.



 

- Modified Adjuvant! Online high-risk subgroup: MammaPrint was dominated by current practice across almost all scenarios.
- Modified Adjuvant! Online low-risk subgroup: ICERs were greater than £161,000 per QALY gained across all analyses.

# 5 Committee discussion

5.1 The committee discussed current practice for making adjuvant chemotherapy prescribing decisions. The clinical experts explained that NHS clinical practice has changed since NICE's diagnostics guidance 10 was published in 2013. Also, the PREDICT tool is now used by many NHS trusts rather than the Nottingham Prognostic Index (NPI). Adjuvant! Online is not currently available. The committee also heard that Oncotype DX is currently used in NHS clinical practice and may be used for a broader group than the population defined in the original diagnostics guidance 10, that is, people with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative early breast cancer who are assessed as being at intermediate risk using existing risk assessment tools.

5.2 The committee discussed the potential benefits of the tumour profiling tests for people with early breast cancer who are deciding whether to have adjuvant chemotherapy. It heard that there is potential benefit for people with cancer identified as being at low clinical risk, when test results suggest a high risk of distant recurrence. These people would therefore benefit from chemotherapy. It also heard that there is potential benefit for people with cancer categorised as high clinical risk, when test results suggest a low risk of distant recurrence. The committee heard that these people could decide not to have chemotherapy, therefore avoiding toxic side effects and effects on fertility. They could potentially resume normal daily activities earlier, although



 

some may wish to have chemotherapy regardless of the test result. However, the committee noted that the claimed benefits of the tests depend on them having sufficient accuracy and discrimination to correctly classify risk and provide valid clinical information. The clinical experts explained that the additional clinical information provided by the tests may help people discuss further treatment options. This information is particularly helpful for people with cancers identified as intermediate clinical risk when the decision to offer chemotherapy is unclear. However, the final decision to recommend a course of adjuvant chemotherapy would always take into account the person's circumstances and preferences.

### *Clinical effectiveness*

5.3 The committee considered the prognostic ability of the tumour profiling tests. It noted that for people with LN-negative disease, all the tests had statistically significant prognostic accuracy over clinical and pathological features or risk assessment tools such as the NPI (see section 4). It also noted that for people with LN-positive disease, results for prognostic ability were more variable but all tests except IHC4+C showed statistically significant or borderline statistically significant prognostic ability over clinical and pathological features or risk assessment tools. The external assessment group (EAG) explained that there were concerns about patient spectrum bias in all studies reporting prognostic ability. This was because in many of the studies some or all patients had chemotherapy or patients who had not had chemotherapy were selected for analyses. Also, most studies excluded tumour samples with insufficient tissue, and some studies included patients who had hormone receptor-negative or HER2-positive disease. The committee concluded that despite the potential spectrum bias, the evidence suggested that all the tumour profiling tests have the ability to predict the risk of distant recurrence in the population



 

included in the assessment. It also concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease.

5.4 The committee considered the evidence on whether the tumour profiling tests can predict relative treatment effects associated with chemotherapy. The clinical experts stated that it is likely some patients could have a greater relative treatment effect from chemotherapy than others, for example, patients with hormone receptor-positive cancer that is not sensitive to endocrine therapy, but evidence is not available to support this. The EAG explained that the only evidence available to show a relative treatment effect for chemotherapy across different risk groups is for Oncotype DX, and this evidence is weak because it is at high risk of bias from potential confounding. The results of interaction tests (which show whether the tumour profiling test is able to predict a different treatment effect by risk group) in the adjusted analysis in the B20 study by Paik et al. (2006; LN-negative disease) remained statistically significant when adjusting simultaneously for clinical and pathological variables. However, the EAG also explained that the difference in relative treatment effects for chemotherapy in the B20 study may be overestimated because this was the Oncotype DX derivation data set. In the SWOG-8814 study by Albain et al. (2010; LN-positive disease) the results of the interaction tests remained statistically significant when adjusting for some individual clinical and pathological variables, but there was no analysis that adjusted for these simultaneously, and the test was non-significant when adjusting for Allred-quantified ER status. The clinical experts explained that hormone receptor status may also predict relative treatment effects for chemotherapy. The committee considered that if all known clinical and pathological variables were included in the analyses of the SWOG-8814 data then it was likely that the results of the interaction test would no longer be statistically significant.



 

This suggested highly uncertain relative treatment effects for chemotherapy according to the results of the tumour profiling tests for this group with LN-positive disease. The committee concluded that the evidence on the extent to which tumour profiling tests are able to predict relative treatment effects for chemotherapy is highly uncertain, but there may be some differences between Oncotype DX risk groups. The committee noted that no data were available to assess a difference in relative treatment effects for chemotherapy for EndoPredict, IHC4+C and Prosigna risk groups, and that data on MammaPrint suggest no difference in relative treatment effects for chemotherapy.

5.5 The committee considered the evidence on clinical utility, that is, data from studies which assessed the ability of the tumour profiling tests to affect patient outcomes. It noted that the only test with evidence from randomised controlled trials in which patients were randomised to treatment guided by either test result or usual clinical practice was MammaPrint. The committee noted that MINDACT was a well-designed study. The results suggested that patients with high clinical risk and MammaPrint low-risk scores can forgo chemotherapy without a statistically significant increase in the 5-year risk of distant recurrence. However, a clinical expert explained that the risk of recurrence often continues beyond 5 years and noted that the MINDACT authors (Cardoso et al. 2016) stated that long-term follow-up and outcome data will be essential. These data are being collected and a 10-year follow-up analysis is planned. The committee noted that none of the other tumour profiling tests had similar evidence of clinical utility, but it was aware that this evidence was being collected for Oncotype DX and Prosigna (see section 5.22). The committee concluded that none of the tests had strong enough evidence to demonstrate an effect on subsequent patient outcomes.



 

5.6 The committee was encouraged by the availability of the data set provided in confidence to NICE by Genomic Health. The data set was based on the access scheme operated by NHS England, which provided real world evidence on the use of adjuvant chemotherapy in the NHS following testing with Oncotype DX for the population included in the scope for this assessment. The committee noted that the total number of patients in the data set appeared to be much larger than the number of patients with complete data in the population of interest, and that the advice from clinical experts (see section 5.1) was that the test has been used on a wider group of patients in practice. The committee concluded that the access scheme data set was an important piece of real world evidence for use in the economic model, but that more complete data could have been collected and reported. It also concluded that future data collection should be done as part of a national database, rather than by individual companies, to increase transparency and link to outcome data (see section 5.24).

5.7 The committee discussed the analytical validity of IHC4+C. The EAG explained that the evidence has developed since diagnostics guidance 10 was published. The committee noted that the data showed good correlation between different centres when scoring and staining were assessed separately for measurement of the Ki67 marker, which had been achieved with training. But it also noted that when studies looked at staining and scoring combined, the correlation between centres decreased substantially. A clinical expert noted that different antibody clones are available for testing Ki67, ER and progesterone receptor (PR) status, and that different studies used different antibody clones which means that the studies are not directly comparable. The committee heard that different methods of assessing ER and PR receptors may be needed for IHC4+C compared with those already used routinely, which may introduce additional complexity. The committee concluded that



 

because of these issues, the reproducibility of IHC4+C is poor. It also concluded that if this test were to be developed further the antibody clones used in the assays for ER, PR and Ki67 should be specified, and there would need to be substantial investment in staff training and quality assurance.

### *Cost effectiveness*

5.8 The committee discussed the assumptions and inputs used in the model, and carefully considered the extensive stakeholder comments on the model and EAG responses to these comments. It noted that a specific analysis of the TransATAC data was used for risk classification probabilities and for distant recurrence rates based on test result for Oncotype DX, EndoPredict, Prosigna and IHC4+C. The results from this specific analysis of the data set have now been published. The EAG explained that this data source was chosen because it included data on 4 of the 5 tests of interest and was specific to the population included in the scope (patients with hormone receptor-positive, HER2-negative disease). The committee heard that although the TransATAC data were slightly older and some patients were not candidates for chemotherapy, the patient characteristics matched well with the more recent MINDACT study. The alternative would be to use different data sources for each test, which would have introduced additional uncertainty and complexity. Also, the group with LN-negative disease could not have been split according to level of clinical risk. The EAG also explained that the distant recurrence-free rates from the TransATAC analysis used in the model were consistent with results from other studies (B14, B20, TAILORx, MD Anderson, Clalit, Memorial Sloan Kettering, SEER and WSG PlanB) both when grouped separately by clinical risk and when all clinical risk groups were pooled together. The committee concluded that the



 

TransATAC analysis had some limitations, but was the best available data for use in the model.

5.9 The committee considered the data on pre- and post-test chemotherapy decisions used in the model. The EAG explained that for 3-level tests (tests with low, intermediate and high-risk categories [IHC4+C, Oncotype DX, Prosigna]), data on pre- and post-test chemotherapy decisions for the group with LN-negative disease and a NPI of more than 3.4 were taken from the Genomic Health access scheme data set (see section 5.6). For other clinical risk subgroups with the 3-level tests, and for all clinical risk subgroups with 2-level tests (tests with low and high-risk categories [EndoPredict, MammaPrint]), data on pre-test chemotherapy decisions were taken from different sources to data on post-test chemotherapy decisions. There were also very limited UK data for these groups. The committee considered the modelled impact of these data on chemotherapy use, and noted that although clinical and patient experts thought that the main benefit of the tests was in avoiding unnecessary chemotherapy, most tests were estimated to increase chemotherapy use at least in some subgroups (see section 4.48). The committee concluded that there was much more uncertainty around chemotherapy decision-making for the 2-level tests, and for the subgroups who were not included in the original NICE recommendation on tumour profiling tests (LN-negative disease and a NPI of 3.4 or less, and LN-positive disease).

5.10 The committee considered how adjuvant chemotherapy treatment effects had been applied in the economic model, particularly the relative treatment effects of chemotherapy between the risk groups predicted by the tumour profiling tests. It noted its earlier conclusion that the evidence on whether tumour profiling tests can predict relative treatment effects for chemotherapy is highly uncertain, but that there may be some differences between Oncotype DX risk



 

groups (see section 5.4). It agreed that for EndoPredict, IHC4+C and Prosigna, no evidence was available to show a difference in relative treatment effects of chemotherapy across risk groups, and that data on MammaPrint suggested no difference in relative treatment effects. Therefore for these tests it was appropriate to assume the same relative risk of distant recurrence across all test risk categories (0.76). The committee considered stakeholder comments submitted during the first consultation suggesting that Oncotype DX has the ability to predict which patients have disease that will respond to chemotherapy. The EAG noted that in response to the comments it had done additional exploratory analyses for Oncotype DX to show the impact on the incremental cost-effectiveness ratios (ICERs) if a smaller relative treatment effect than that taken from the B20 study (Paik et al. 2006) was applied in the model in the group with LN-negative disease and a NPI of more than 3.4 (see section 4.50). The EAG noted that the hazard ratios used in these analyses were from comparisons of independent arms of trials and were therefore very uncertain. The EAG also said that using hazard ratios calculated from the B20 (Paik et al. 2006) and the B14 (Paik et al. 2004) studies resulted in an ICER of around £24,000 per quality-adjusted life year (QALY) gained for Oncotype DX compared with current practice. Using hazard ratios calculated from the B20 and TransATAC studies resulted in an ICER of around £8,000 per QALY gained. The committee concluded that although these analyses were associated with considerable uncertainty, they gave an indication of Oncotype DX's likely cost effectiveness if the relative treatment effects for chemotherapy did differ between Oncotype DX risk groups, but not to the extent reported in the Paik et al. (2006) study.

5.11 The committee considered stakeholder comments submitted during the first consultation suggesting that adverse events had not been adequately captured in the economic model; in particular,



 

congestive heart failure, permanent hair loss and peripheral neuropathy. The EAG noted that in response to the comments it had done additional exploratory analyses to include these adverse events in the model. Congestive heart failure was added into the model by incorporating estimated lifetime QALY losses and costs taken from an alternative model (Hall et al. 2017). Hair loss and peripheral neuropathy were incorporated using a disutility applied to a proportion of the population for the lifetime of the model. The EAG highlighted the considerable limitations of these analyses, and noted that for tests that increased chemotherapy use in some subgroups, the ICERs became less favourable. The committee noted that including additional adverse events in the model did reduce some of the ICERs, but not enough to change the conclusions. It also noted a further EAG analysis, which suggested that for tests that reduced chemotherapy use but were not cost effective, the QALY gain from avoiding adverse events would have to be in the range of 1.1 to 1.3 to result in cost-effective ICERs. The committee concluded that it was important to consider potential adverse events that could be caused by chemotherapy. However, the reduction in adverse events from reduced chemotherapy use, while beneficial for patients, was unlikely to affect its conclusions on the cost effectiveness of the tumour profiling tests based on the EAG's analysis.

5.12 The committee considered other assumptions used in the model such as the cost of chemotherapy, how the risk of distant recurrence was applied over time, and adjuvant chemotherapy treatment effects if a different relative risk across risk groups is not assumed. The EAG explained that there was some uncertainty around these inputs, but all had been tested in sensitivity analyses. The committee concluded that the assumptions and inputs used in the model were reasonable, but they were associated with



 

considerable uncertainty because of the limitations in the data that underpinned them.

5.13 The committee noted its discussion on current practice (see section 5.1) and considered the absence of comparisons of the tumour profiling tests with the PREDICT tool. The EAG explained that in the model it was not possible to compare the tumour profiling tests with PREDICT, or to define the clinical risk groups using PREDICT, because relevant data were not available. The committee noted that the comparisons in the model do not fully reflect current NHS clinical practice, which leads to uncaptured uncertainty in the model results. The committee concluded that research on tumour profiling tests should include comparisons with PREDICT (see section 5.22) so that the cost effectiveness of the tests relative to current practice can be fully assessed in future.

5.14 The committee considered the subgroups that were included in the model, that is, people with LN-negative disease and a NPI of 3.4 or less, LN-negative disease and a NPI of more then 3.4, and LN-positive disease. It noted its earlier conclusion that the evidence suggested that all the tumour profiling tests have the ability to predict risk of distant recurrence (prognosis), but this ability was less certain in the group with LN-positive disease (see section 5.3). The committee also recalled that the test results are particularly helpful for people with cancers identified as intermediate clinical risk when the decision to offer chemotherapy is unclear (see section 5.2). The clinical experts explained that tumour profiling tests are also helpful for people with LN-positive cancer, who have comorbidities and therefore an additional reason to want to avoid chemotherapy. The EAG noted that this subgroup of the LN-positive population could not be modelled because of a lack of data. In addition, the committee noted that the EAG's systematic review had highlighted substantial lack of agreement between the



 

tests in risk categorising the group with LN-positive disease. The committee decided to consider the ICERs in the group with LN-negative disease only, but noted that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (see section 5.23).

5.15 The committee considered the results from the model. It noted that the differences in the QALYs were small, and that the ICERs for all tumour profiling tests were highly uncertain because of the available clinical data and the assumptions used in the modelling (see sections 5.8 to 5.12). It also noted that the base-case ICERs for many of the tumour profiling tests were higher than those normally considered to be cost effective. However, it heard that access proposals had been made by Myriad Genetics (for EndoPredict) and NanoString Technologies (for Prosigna). Genomic Health confirmed that the confidential discount for Oncotype DX would continue in the NHS. The committee concluded that the availability of the access proposals for EndoPredict and Prosigna may reduce the ICERs to a range that could be considered plausibly cost effective despite the clinical uncertainties.

5.16 The committee considered the EndoPredict and Prosigna access proposals. Compared with current practice, the ICERs for EndoPredict and Prosigna in the group with LN-negative disease and a NPI of 3.4 or less were still higher than those normally considered to be a cost-effective use of NHS resources. In the group with LN-negative disease and a NPI of more than 3.4, Prosigna compared with current practice had an ICER of less than £20,000 per QALY gained, and therefore could be considered cost effective. In the same group, EndoPredict compared with current practice had ICERs between £20,000 and £30,000 per QALY gained, and varied depending on whether the testing was done at a



 

local or a centralised laboratory. The committee noted that localised testing was more cost effective than centralised testing, and that testing became more cost effective as test throughput increased. It also recalled its conclusion that the data on post-chemotherapy decisions were more uncertain for 2-level tests than for 3-level tests (see section 5.9), and noted that the EAG's sensitivity analyses using plausible alternative sources for post-chemotherapy decisions resulted in ICERs that were lower than £20,000 per QALY gained. The committee decided that although there is uncertainty around the ICERs for EndoPredict compared with current practice, sensitivity analyses suggested that the ICER will be around £20,000 per QALY gained, and therefore it could be considered cost effective. The committee concluded that EndoPredict and Prosigna, when provided at the costs stated in the access proposals, were likely to be cost effective in the group with LN-negative disease and a NPI of more than 3.4, but evidence on clinical outcomes will be important to confirm this (see section 5.24).

5.17 The committee considered the ICERs for Oncotype DX compared with current practice. It heard that the proposed confidential test cost for Oncotype DX was the same as in current NHS practice, and that this cost had been used in the EAG's economic model. It noted that in the base-case analyses Oncotype DX was dominated by the comparator in the group with LN-negative disease and a NPI of more than 3.4. The committee recalled its earlier conclusions; Oncotype DX may be able to predict relative treatment effects for chemotherapy, and the ICERs for Oncotype DX compared with current practice when some relative treatment effect across different risk groups was applied in the model were most likely to be between £9,000 and £25,000 per QALY gained (see section 5.4). However, it noted that this was very uncertain. The committee concluded that Oncotype DX, when provided at the test



 

cost stated in the access proposal, was likely to be cost effective in the group with LN-negative disease and a NPI of more than 3.4, but evidence on clinical outcomes will be important to confirm this (see section 5.24).

5.18 The committee considered the ICERs for MammaPrint compared with modified Adjuvant! Online. It noted that in the base-case analyses, MammaPrint was dominated by the comparator in the modified Adjuvant! Online high-risk subgroup. In the modified Adjuvant! Online low-risk subgroup, the ICERs were much higher than those normally considered to be cost effective. The committee concluded that MammaPrint would not be a cost-effective use of NHS resources.

5.19 The committee considered the ICERs for IHC4+C compared with current practice. It noted that the ICERs were low or that IHC4+C dominated current practice in all subgroups. The committee felt that the test cost had been underestimated because it did not include any costs for training or for setting up a quality assurance programme. But even if these costs were included, IHC4+C may still be cost effective. However, the committee noted its earlier conclusion on the analytical validity of IHC4+C (see section 5.7) and concluded that it could not be recommended for use in the NHS until issues around reproducibility and implementation have been resolved.

5.20 The committee noted that the model for EndoPredict, IHC4+C, Oncotype DX and Prosigna related only to a postmenopausal population because TransATAC was used as the data source for these tests. It considered whether the model results could also apply to a premenopausal population. A clinical expert explained that the biology of a cancer and its molecular subtype, for example hormone receptor status and HER2 status, is more influential in



 

determining the risk of distant recurrence than menopausal status. Therefore the committee concluded that the model results apply to premenopausal and postmenopausal populations.

5.21 The committee discussed the generalisability of the data to men. It acknowledged that men make up a small proportion of people with breast cancer. The committee noted that all the clinical and economic evidence was based on trials with women, but that the general subtypes are identical in men and women, and in clinical practice men would have treatment in the same way as women. The committee concluded that the recommendations in this guidance should also apply to men.

### *Research considerations*

5.22 The committee noted that there are several ongoing studies which will provide evidence of long-term patient outcomes: further data collection from the MINDACT study on MammaPrint, the TAILORx trial on Oncotype DX and the OPTIMA trial on Prosigna. The committee concluded that these studies are relevant to this assessment and data from them may be important when the guidance is considered for updating in the future. But it noted that not all studies would provide UK-specific data and comparisons with the PREDICT tool, which would be important for future updates to fully assess the cost effectiveness of the tests compared with current practice.

5.23 The committee recalled its previous conclusion on the potential utility of the tests in the group with LN-positive disease (see section 5.14), particularly for people who have comorbidities and who may be particularly affected by the side effects of adjuvant chemotherapy. It noted that further research in this group would be welcome and heard from clinical experts that the ongoing OPTIMA



 

trial may help to reduce some of the uncertainties identified during this assessment.

### *Data collection arrangements*

5.24 The recommendations for EndoPredict, Oncotype DX and Prosigna are conditional on data collection agreements being put in place. NICE will be inviting Genomic Health, Myriad Genetics and NanoString Technologies to review the proposed data collection agreements during the consultation period for this draft guidance. It is anticipated that companies will be asked to make arrangements to collect timely and complete record-level test data, which can be submitted to the National Cancer Registration and Analysis Service, with the aim of linking test data to chemotherapy use, recurrence and survival outcomes.

## 6 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

## 7 Review

NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Mark Kroese
Chair, diagnostics advisory committee
April 2018



 

# 8 Diagnostics advisory committee members and NICE project team

## *Diagnostics advisory committee*

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

### Standing committee members

**Dr Mark Kroese**

Chair, diagnostics advisory committee

**Mr John Bagshaw**

In-vitro Diagnostics Consultant

**Professor Enitan Carrol**

Chair in Paediatric Infection, University of Liverpool

**Dr Owen Driskell**

Lead for Laboratory Medicine, National Institute for Health Research (NIHR) Clinical Research Network West Midlands

**Dr Steve Edwards**

Head of Health Technology Assessment, BMJ Evidence Centre

**Dr Simon Fleming**

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

**Dr James Gray**

Consultant Microbiologist, Birmingham Children's Hospital

**Professor Steve Halligan**

Professor of Radiology, University College London



 

**Mr John Hitchman**

Lay member

**Professor Chris Hyde**

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

**Mr Patrick McGinley**

Head of Costing and Service Line Reporting, Maidstone and Tunbridge Wells NHS Trust

**Dr Michael Messenger**

Deputy Director and Scientific Manager NIHR Diagnostic Evidence Co-operative, Leeds

**Mrs Alexandria Moseley**

Lay member

**Dr Peter Naylor**

GP, Wirral

**Dr Dermot Neely**

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

**Dr Shelley Rahman Haley**

Consultant Cardiologist, Royal Brompton and Harefield NHS Foundation Trust

**Dr Simon Richards**

VP Regulatory Affairs, EME, Alere Inc

**Professor Mark Sculpher**

Professor of Health Economics, Centre for Health Economics, University of York



 

**Professor Matt Stevenson**

Professor of Health Technology Assessment, School of Health and Related Research, University of Sheffield

**Professor Anthony Wierzbicki**

Consultant in Metabolic Medicine/Chemical Pathology, St Thomas Hospital

**Specialist committee members**

**Miss Maria Bramley**

Consultant Oncoplastic Breast Surgeon, Pennine Acute NHS Trust c/o Royal Oldham Hospital

**Dr John Graham**

Consultant Oncologist, Taunton & Somerset NHS Foundation Trust

**Linda Pepper**

Lay specialist committee member

**Dr Deirdre Ryan**

Consultant Cellular Pathologist, Barts Health NHS Trust

**Dr Britta Stordal**

Senior Lecturer, Middlesex University

**Ursula Van Mann**

Lay specialist committee member

**Professor Andrew Wardley**

Professor of Medical Oncology, The Christie NHS Foundation Trust

## *NICE project team*

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.



 

**Frances Nixon**

Topic Lead

**Rebecca Albrow**

Technical Adviser

**Donna Barnes**

Project Manager

ISBN:



 

NICE National Institute for Health and Care Excellence

**DIAGNOSTICS ASSESSMENT PROGRAMME**

**Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer**

**Diagnostics Consultation Document – Comments**

**Diagnostics Advisory Committee date: 13 June 2018**

**THEME: Micrometastases and lymph node positive disease**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| 1 | NHS Professional | General | Testing patients with micrometastases and 1-3 nodes is crucial to avoid patients being overtreated with un-necessary chemotherapy or undertreated due to the in accuracies of PREDICT | Thank you for your comment which the committee considered.<br><br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 2 | NHS Professional | General | We have also had access to oncotype in node positive patients via the PONDx platform. This has been very useful in guiding the decision making in the MDT. | Thank you for your comment which the committee considered. |

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| | | | | The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 3 | NHS Professional | General | (2) It would be helpful either at the same time, or at a planned later date, for NICE to address the use of diagnostic profiling in the population with low axillary nodal burden (such as those with isolated tumour cells/micrometastasis/one node positive disease). Emerging evidence suggests that this population behaves similarly to those with node negative disease (the attention of the current draft guidance) and that some diagnostic profiling tools might be similarly useful in selecting patients for chemotherapy benefits (or not). | Thank you for your comment which the committee considered.<br><br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease. |
| 4 | NHS Professional | General | Micro-metastases<br>There is plentiful evidence in the literature that the presence of micro-metastases or isolated tumour cells in a lymph node do not | Thank you for your comment which the committee considered. |

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| | | | effect prognosis and it is now accepted by Clinicians there is no need for an axillary clearance if a node is found to have a micro-metastases.<br><br>Decisions on treatment are then based on the molecular phenotypes of the tumour, not on the micro-metastasis in the node. There is no reason why micro-metastatic patients should therefore not be eligible for the Oncotype DX test as they represent a group of patients who were effectively node negative. In fact, patients with one node negative in the axilla have no difference in overall survival to node negative patients, so it is difficult to justify refusing to do Oncotype DX testing or any genomic testing on the basis of node status.<br><br>With regard to node positive patients, the Independent Southwestern Oncology Group SWOG-8814 trial found a recurrence score interaction with chemotherapy of p=0.029, indicating the predictive benefit of relapse recurrent score for predicting chemotherapy benefit in post-menopausal women. That trial was performed by an independent trial group in the United States and Canada, not by the company. | The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 5 | NHS Professional | General | I am concerned that patients with either micrometastases or macrometastases in the ipsilateral axillary nodes cannot access these tests. In my opinion, here is data for oncotype DX to support its use for 1-3 node positive breast cancer. | Thank you for your comment which the committee considered. |

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| | | | | The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 6 | NHS Professional | General | The greatest potential reduction in chemotherapy use would occur on expanding the role of Oncotype DX to those cases with minimal nodal disease. This we feel is the next step in its role and is supported by significant data. The evidence is sufficient enough that we do discuss this with our patients currently. If patients with minimal nodal disease were made eligible â€“ it | Thank you for your comment which the committee considered.<br><br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the |

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| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| | | | would significantly reduce the cost of chemotherapy to the individual and the health economy. | guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease. |
| 7 | NHS Professional | General | I would also strongly ask NICE to review their position on the use of genomic assays in patients with micrometastases and limited node involvement. If there is evidence to support sparing pN1 patients chemotherapy where endocrine treatment alone provides the key survival benefit that evidence should be considered. The Clalit dataset provides long term outcome data on patients er +ve, node negative and positive in the low and intermediate risk group using Oncotype DX who were spared chemotherapy. This showed that this group of patients have similar survival outcomes to node negative patients. Again I reiterate that a profound impact on the patient experience, journey and outcomes can be made if one can predict those who can be safely spared chemotherapy and if this is possible in the node positive group these patients should not be discriminated against by not valuing the evidence already published and the Tailor X data to be presented. | Thank you for your comment which the committee considered.<br><br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further |

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| | | | | studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 8 | NHS Professional | General | It would also be useful to examine results from the OPTIMA prelim trial to look at the benefit of genomic assays in women with lymph node positive breast cancer | Thank you for your comment which the committee considered.<br>The EAG noted that Optima prelim did not report long term outcomes. |
| 9 | NHS Professional | General | Whilst we welcome the 2nd draft consultation now considering the use of Oncotype Dx in patients with node negative disease, we believe there is a missed opportunity here to consider use of the test in patients with limited node positive breast cancer (1-3 nodes positive and micrometastases). This does not appear to have been addressed in the most recent consultation.<br><br>This is a group where the default in many cancer treatment centres is to offer chemotherapy, based on beliefs regarding clinical stage. However assessing the biology of the breast cancer clearly demonstrates that whilst some of these patients may be at higher risk of recurrence based on nodal involvement, their risk may be lower than anticipated when one takes into account biological factors by using a molecular test. Moreover in those patients with a low RS, not only is there risk of recurrence lower than anticipated, but also their chemotherapy sensitivity is | Thank you for your comment which the committee considered.<br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN- |

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| | | | lower than anticipated. Nonetheless in the absence of a molecular test the default will be to offer chemotherapy.<br><br>Our own experience of the PONDx access scheme where we have used Oncotype Dx in patients with node positive disease has been a very positive one., and we have managed to spare a number of patients chemotherapy because of minimal/no benefit whom previously would routinely have received such treatment. The impact of such treatment on day to day function, work productivity and long term impacts (on fertility, cardiac risk and secondary haematological malignancies) should not be underestimated. | negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 10 | NHS Professional | General | 3) We believe there is sufficient evidence for NICE to recommend Oncotype DX testing for patients with micromets to guide chemotherapy treatment decisions and avoid over-treatment. Studies have shown that micrometastases do not affect prognosis and our treatment guidelines state that treatment should be the same as for node-negative patients. Yet currently these patients may be excluded from genetic testing<br><br>4) The evidence for genetic testing for patients with low numbers of involved lymph glands is less clear, but should not be ignored. This remains an equality issue, as already many patients who are excluded from testing under the NHS have chosen to pay for the test to be carried out. This is clearly unfair, as only | Thank you for your comment which the committee considered.<br><br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an |

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| | | | patients who canâ€™t afford Â£3000 are unable to make a choice to have the testing done. We accept that the evidence for tumour profiling for node positive patients may not yet be strong enough to include this group for NHS funding, at least until further studies, such as the OPTIMA trial have been completed. We would hope that this will continue to be kept under review. | option for people with micrometastatic disease.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 11 | NHS Professional | General | There are also numerous studies with node positive patients and I do not understand why this cannot be considered in selected low risk patients. | Thank you for your comment which the committee considered.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |

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| 12 | NHS Professional | General | There is a body of evidence for patients with 1-3 lymph nodes, for some of whom chemotherapy is unnecessary, costly and toxic. The use of tumour profiling tests to identify N1-3 patients at low risk of relapse should be revisited | Thank you for your comment which the committee considered.<br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 13 | Private Sector Professional | General | We feel very strongly that genomic profiling has an important role in guiding Systemic therapy in early ER positive Her 2 negative node positive breast cancer. This support group of patients benefit most from this test. Although we agree that the volume of data is smaller for pla oh no we agree that the volume of data is smaller thab for node negative patients however the data for EPClin are sufficient to use this this test for women with 1â€“3 positive lymph nodes.<br>The vast majority of women with node negative disease do not require adjuvant chemotherapy and the challenge is to identify the subgroup of patients with node positive disease who can safely avoid chemotherapy. In the ABCSG 6 and 8 validation study for EPClin, more than 500 patients were node positive. We | Thank you for your comment which the committee considered.<br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |

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| | | | have also publish our data comparing EPClin with NHS Predict and the ministrative that the latter was inaccurate in predicting the genomic scores. We also demonstrated that a significant number of node (1-3) positive patients can avoid chemotherapy using the genomic a score as a guide. We obtain similar results when comparing the genomic the score with NPI in a cohort of 120 patients.<br><br>The guidance as it stands will subject a significant proportion of women with a low number of positive nodes to an expensive toxic therapy that is unnecessary. Expansion of the indications to include those with 1-3 positive lymph-node should be considered in the final revised guidance. | |
| 14 | NHS Professional | General | C. It is unfortunate that NICE do not address the use of these tests in breast cancer patients with micrometastatic disease. These are classified as node positive (by TNM) but behave as node negative and are clinically managed as such. I am aware that some centres in the UK are submitted these tumours for multiparametric testing (presently Oncotype Dx) by defining them a node negative whilst others are not including such patients, producing inequalities in availability of the tests and potentially in patient management. The inclusion of low volume metastatic disease would minimise such inequalities and be clinically valuable. | Thank you for your comment which the committee considered.<br><br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease. |

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| 15 | NHS Professional | General | To add to previous comments I wish to raise a point about Oncotype DX testing and extending it's indication to node positive disease. There is increasing data to support the use of Oncotype DX testing in node positive disease, but if the panel are not reconsidering extending the indication then can I ask them to consider the issue of micro metastases as a separate entity to 1-3 nodes. Prognostically we know patients with micro metastases behave similarly to those with node negative disease compared with those with definite macro metastases. Modern sentinel node techniques identify these tiny deposits in nodes that would have previously be called node negative, and indeed it is very likely that there would have been micro metastases in the 'node negative' patients that Oncotype as first validated on.<br><br>I urge you to consider extending your recommendation for Oncotype DX testing to those with micro metastases AND node negative patients as part of this guidance, even if node positive patients are not included. | Thank you for your comment which the committee considered.<br><br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 16 | Breast Cancer Now | 5.3, 5.14, 5.23 | • *Has all the relevant evidence been taken into account?* | Thank you for your comment which the committee considered. |

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| | | | It has been recognised in the consultation document that for people with LN positive disease results for prognostic ability were more variable and that evidence predicting the risk of distance recurrence in the population was weaker in the group with LN positive disease than the group with LN negative disease.<br><br>We are aware of real world evidence studies, such as evidence published in the European Journal of Oncology (Loncaster, J., Howell, S., et al 'Impact of Oncotype DX breast Recurrence Score testing on adjuvant chemotherapy use in early breast cancer: Real world experience in Greater Manchester, UK', January 2017) which states that the use of Oncotype DX in routine clinical practice, could be as influential in informing and helping with treatment decisions in LN positive patients, as it is in LN negative patients. It highlighted that it was effective in identifying some LN positive patients that could be spared chemotherapy and therefore helping to maintain patients' quality of life.<br><br>It has been noted in the NICE consultation document that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN positive disease. We are pleased that NICE has outlined in the research considerations that more research will be particularly welcomed on the potential utility of the tests in the group with LN positive disease, particularly for people who have comorbidities and may be particularly affected by the side effects of adjuvant chemotherapy. It has been | The EAG noted that Loncaster 2017 was included in the review, but as there was no long-term follow-up of patients, the study is classified as a decision impact study.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance).<br><br>NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. |

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| | | | recognised that the ongoing OPTIMA trial may help to reduce some of the uncertainties identified during the EAG's assessment.<br><br>It is now important that the necessary research and evidence can be gathered as quickly as possible and made available which may enable NICE to consider extending the recommendation and could potentially allow more patients to safely avoid overtreatment.<br><br>*How will NICE ensure any published research which could be influential in extending the recommendation to certain LN positive patients will be reviewed in a timely manner?* | |
| 17 | CM-PATH | Diagnostics Consultation Document, p38 Diagnostics Consultation Document, p49 | As practising clinicians, we are looking for tests that inform managing women with low metastatic nodal burden (certainly for micrometastasis and also for 1-3 positive nodes). Micrometastases are managed as node negative clinically and NICE guidance on the use of these tests in this setting would be helpful to the MDT teams. Clearly a proportion of those patients will not benefit from chemotherapy and NICE guidance on tests to help identify those patients and spare them unnecessary chemotherapy are needed. | Thank you for your comment which the committee considered.<br><br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease. |

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| 18 | Genomic Health | 1.1, 5.9, 5.14 | • **We urge the committee to include a recommendation for Oncotype DX testing of pNmic/pN1 patients**<br>• A wealth of evidence showcases independent-validation of Oncotype DX Breast Recurrence Score result's prognostic ability and ability to predict relative chemotherapy benefit, further confirmed by real-world patient outcome evidence based on follow-up of 8,000 patients, and UK-specific decision-impact data.<br>• The "substantial lack of agreement between the tests" is not a valid reason not to recommend the Breast Recurrence Score® test for pNmic/pN1 patients, which has far stronger supporting evidence. | Thank you for your comment which the committee considered.<br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 19 | Genomic Health | 1.1, 5.14, 5.23 | • The committee commented that "test results are particularly helpful for people with cancers identified as intermediate clinical risk when the decision to offer chemotherapy is unclear" | Thank you for your comment which the committee considered. |

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| | | | • A wealth of evidence shows that pNmic/pN1 patients are intermediate risk and not high risk, and many can be identified who have excellent prognoses. Indeed, pNmic and pN0 patients have similar outcomes.<br>• Many clinicians view the decision to offer chemotherapy to be similarly unclear for pN0 and pNmic/pN1 patients, considering that the Oxford Overview shows that only ~5-10% of patients benefit, but these patients cannot be identified using clinico-pathologic–based prognostic tools. | The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 20 | Genomic Health | 1.1 | • The evidence that patients with RS<18 derive no relative chemotherapy benefit is consistent across pN0, pNmic, pN1, and neoadjuvant patient cohorts.<br>• The Recurrence Score result provides independent predictive information based on underlying tumour biology. | Thank you for your comment which the committee considered. |

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| 21 | Genomic Health | 1.1 | • Particularly considering the access proposal for the lymph node positive (LN+) patient group, Oncotype DX testing in this patient group would allow the NHS to avoid substantial waste of healthcare resources and would be expected to be overall cost-saving | Thank you for your comment which the committee considered.<br>The committee concluded that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 22 | Genomic Health | 1.1, 5.23 | • **The current DCD will lead to inequity of care on the basis of node involvement**<br>• A large number of all newly diagnosed pNmic/pN1 breast cancer patients are not eligible or do not have access to participate in ongoing clinical trials of genomic signatures in the node positive setting.<br>• These patients will not have access to essential information needed to guide their treatment, or will be forced to pay out of pocket for Oncotype DX testing. | Thank you for your comment which the committee considered.<br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br>The committee also concluded that further studies would be helpful to assess the |

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| | | | | clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance).<br><br>The Committee considers the clinical and cost effectiveness of diagnostics to inform decisions on the efficient use of available NHS and PSS resources. The reference case perspective on costs is that of the NHS and PSS, and does not include private healthcare. |
| 23 | Genomic Health | 1.1 | [redacted] | Thank you for your comment which the committee considered.<br>The committee concluded that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |

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| 24 | Myriad Genetics | 1.1<br>5.3<br>5.14<br>5.23 | The diagnostics consultation document (DCD) states that the draft recommendations will apply to patients with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative early breast cancer when meeting a subset of clinical criteria. The Committee also noted its earlier conclusion that 'the evidence suggested that all tumour profiling tests have the ability to predict risk of distant recurrence (prognosis), but that this ability was less certain in the group with LN-positive disease (referencing 5.3 – which states that the Committee concluded that the evidence was weaker in the group with LN-positive disease) and called for more research on the utility of these test in this population.<br><br>Myriad Genetics appreciates the Committee's decision to include LN-negative disease but also believes strongly in the value of testing patients with node positive disease (1-3 nodes positive) and in the exceptional performance of EndoPredict in this group. Consequently, Myriad respectfully requests that the Committee reconsider the inclusion of this patient type in the FINAL guidance. We refer to the following points from the DCD which would support the inclusion of lymph node (LN)-positive patients:<br>• 4.17 states that in unadjusted analyses, EndoPredict had statistically significant prognostic accuracy for 10-year distant recurrence-free survival and interval in patients with LN-negative and LN-positive disease | Thank you for your comment which the committee considered.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |

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| | | | • 4.18 states that the results for the bespoke analysis of TransATAC- two studies reported adjusted analyses on the EP score part of EndoPredict, showing that it provided statistically significant additional information over clinical and pathological variables regardless of LN status<br>• 4.34 states that the microarray studies generally supported the conclusions from studies using the commercial versions of the assays in suggesting that EndoPredict can discriminate between patients with high and low risk regardless of LN status<br>• 4.62 states that in the population with LN-positive disease compared with current practice, the probabilistic model gave ICERs of £21,458 per QALY gained for EndoPredict<br>o Myriad notes that when the ICERs were recalculated using the confidential pricing proposed in the Patient Access Scheme (PAS) – LN-positive disease was modelled to be below £20,000 per QALY (final QALY calculation not provided in writing) gained for EndoPredict which indicates that treating these patients would be cost effective for the NHS<br>• 4.74 states that deterministic sensitivity analysis results for EndoPredict compared with current practice showed that in the population with LN-positive disease the ICERs | |

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| | | | remained below £30,000 per QALY gained across all scenarios | |
| 25 | Myriad Genetics | 1.1 | EndoPredict has been validated in the ABCSG6 and ABCSG8 cohorts as well as the TransATAC cohort. All three cohorts included node positive and node negative patients with **node positive patients comprising 31.6% of the ABCSG6/8 cohorts combined and 26.7% of the TransATAC cohort**.<br><br>• ABCG6 & ABCSG8 node positive cohorts<br>  ○ (n=537): Subgroup analyses in node negative and node positive patients were performed with combined data from the ABCSG6 and ABCSG8 cohorts. As shown by Kaplan-Meier statistics and log rank test (Appendix A) EPclin was highly prognostic in both node negative and node positive patient subgroups (Hazard ratios: 3.92 (p<0.001) for node negative and 4.70 (p<0.001) for node positive patients) (Appendix A -Fig. 1).<br>  ○ In both subgroups, EPclin could consistently identify patients with a low enough risk of distant recurrence, that chemotherapy could safely be avoided (distant recurrence-free survival after 10 years: 95.0% in node negative and 94.9% in node positive). In the node positive group, 30% of patients were identified as low risk. | Thank you for your comment which the committee considered.<br><br>The EAG noted that data from ABCSG6+8 were included in the assessment.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |

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| | | | • TransATAC node positive cohort (n=248):<br>  ○ In the clinical validation study with 928 total patients from the TransATAC cohort, the results regarding the node negative and node positive subgroups from ABCSG-6 and ABCSG-8 were confirmed. EPclin was highly prognostic in both node negative and node positive patient subgroups (Hazard ratios: 3.90 ($p<0.0001$) for node negative and 9.49 ($p=0.0001$) for node positive) (Appendix A - Fig. 2).<br>  ○ In both subgroups, EPclin consistently identified patients with a low enough risk of distant recurrence, that chemotherapy could safely be avoided (distant recurrence-free survival after 10 years: 94.1% in node negative and 95.0% in node positive disease). In the node positive group, 19% of patients were identified as low risk. | |
| 26 | Myriad Genetics | 1.1 | Additional literature to support the value of using tumour profiling testing in patients with LN-positive disease<br><br>• *Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor – Positive Breast Cancer. A Secondary Analysis of a Randomized Clinical Trial - Sestak I. et al., JAMA Oncology. Published online February 15, 2018. doi:10.1001/jamaoncol.2017.5524)* | Thank you for your comment which the committee considered.<br><br>The EAG noted that Sestak et al. 2018 is not new data as it relates to TransATAC and is a publication of an analysis that is almost identical to the analysis provided to the EAG. This analysis also excluded |

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| | | | ○ Sestak et al. is the most recent paper and excludes patients with more than 3 positive lymph nodes, therefore better representing the target population.<br>○ This paper compared the performance of prognostic signatures for breast cancer distant recurrence (DR) in years 0-10 and in years 5-10 using the TransATAC sample cohort<br>○ When compared to other prognostic signatures EndoPredict identified more LN-positive patients as low risk who may safely avoid chemotherapy (23.5% EPclin)<br>• Myriad will also reference the attached subgroup analysis of ABCSG6&8 which was provided to NICE academic in confidence during a previous comment period | patients with more than 3 positive lymph nodes.<br>The data relating to ABCSG 6+8 were also included in the EAG's assessment. |
| 27 | Myriad Genetics | General comment | Myriad respectfully requests clarification regarding micrometastasis. Would patients with micrometastasis be considered to have LN-positive or LN-negative disease? | Thank you for your comment which the committee considered.<br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour |

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| | | | | profiling tests should be available as an option for people with micrometastatic disease. |
| 28 | NHS England Breast Cancer Clinical Expert Group | General | 2. There is no basis for NICE's current recommendation that patients with nodal micrometastases should be excluded from genomic testing. There is a strong evidence base to suggest that their prognosis is the same as those with node negative disease, stage for stage. | Thank you for your comment which the committee considered.<br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease. |
| 29 | NHS England Breast Cancer Clinical Expert Group | General 5.3 | 3. The draft does not recommend the use of genomic testing for node positive patients. We feel this is an important missed opportunity. Evidence suggests that genomic testing is just as valid for prognostic outcome in patients with up to 3 nodes involved as for those with node negative disease (e.g. Dowsett et al J Clin.Oncol. 2010; 28;1829 ; Albain et al Lancet Oncol 2010 11:55; Petkov et al Br. Cancer 2016 2;1607; Gluz et al J Clin.Oncol. 2016 34:2341). Despite this, there is still a 'knee jerk' reaction amongst many UK oncologists to use node-positivity as | Thank you for your comment which the committee considered.<br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the |

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**THEME: Micrometastases and lymph node positive disease**

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| | | | a standalone indication for chemotherapy, based on historical practice. This offers a real opportunity for NICE. It is likely that a greater proportion of node-positive patients could be saved non-beneficial chemotherapy than in the node-negative group, with consequent patient quality of life benefit and resource savings. At the very least we ask that NICE review these data before finalising their recommendations. | group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 30 | Royal College of Pathologists | | More clarity on use of these tests in micrometastatic disease will be helpful. These are N1 while using NPI or TNM classification however treated by most clinical depts. as node negative. Will this fulfil criteria? | Thank you for your comment which the committee considered.<br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease. |
| 31 | Peony Breast Care Unit | General | NICE need to review their decision on testing in the micometasases and node 1-3 positive patients. Not allowing testing of this group contradicts their comment, "*The clinical experts explained that tumour profiling tests are also helpful for people with LN-positive cancer, who have comorbidities and* | Thank you for your comment which the committee considered.<br>The committee considered evidence on micrometastatic disease presented by the |

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| | | | *therefore an additional reason to want to avoid chemotherapy."* The justification for not considering further this question seems to be lack of correspondence between the 3 tests which is to be expected (see comment under section 4.35 and in any case EP and Prosigna are not predictive). Besides, the correspondence of the tests is little better in the node negatives, and testing has been approved.<br>It is very evident clinically that many node positive ER positive patients gain no benefit from the addition of chemotherapy. Many clinicians are persuaded of the benefit of OncoypeDX testing in this group and there is a very significant risk that testing will become restricted to those who are insured or who can afford to pay. | EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 32 | Peony Breast Care Unit | 4.8, 4.9 and 4.34 DCD | This is evidence that OncotypeDX is of value in node 1-3 positive disease and strongly suggests that the assessment should consider use of this test in this group of patients were chemotherapy is the standard of care. The economic benefits in this group are likely to be even greater than in the node negative patients. | Thank you for your comment which the committee considered.<br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further |

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| | | | | studies would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |

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**THEME: TAILORx study**

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| 33 | NHS Professional | General | I am very disappointed that the TailorX data is not considered in this draft document (due to report in the next month or so). | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 34 | NHS Professional | General | (1) I strongly advise NICE to await the report of the outcome of the TAILORx trial, which is imminent, and take that into account when finalising the recommendation. The TAILORx trial is the largest adjuvant trial ever conducted for early breast cancer, enrolling over 10,000 patients. It was independently designed and conducted by ECOG-ACRIN under the sponsorship of the National Cancer Institute (NCI). The primary objective of TAILORx is to more precisely determine the effect of chemotherapy, if any, for women with node-negative, hormone receptorâ€“positive disease and Oncotype DX recurrence score | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling |

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| | | | results of 11 to 25. The trial is expected to have the capability to produce extremely high level evidence for this specific context. It would be a shame for NICE to ignore this piece of evidence, which is available imminently, when drawing up their recommendation on this very topic. | to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 35 | NHS Professional | General | The TailorX study will be presented at ASCO in June 2018. This is a study of >10 000 women investigating risk of recurrence and benefit of chemo by Oncotype Dx recurrence score. NICE should delay their assessment to take account of this pivotal trial otherwise the NICE decision (whether positive or negative) will be out-dated within a few weeks | Thank you for your comment which the committee considered.<br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment (section 5.6 of the diagnostics guidance). |
| 36 | NHS Professional | General | In late May, early June, the TAILORx, the largest trial of over 10,000 patients recruited in international centres across the world will inform us of whether patients with a recurrence score | Thank you for your comment which the committee considered. |

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| | | | results 11-25 benefited from chemotherapy at all. If, as is widely expected (see NSABP statisticians comments), the results show no benefit for chemotherapy in any of these groups up to a recurrence score of 25, it will be clear that the RS test does predict for chemotherapy and it will demonstrate the biological assessment of a tumour is much more important than the anatomical assessment, which means that the Oncotype DX RS should be used in micro-metastatic and node positive disease as well, because if patients are not going to benefit with treatment, there is no point in poisoning them with that treatment, which is effectively what happens when chemotherapy is given to patients who will gain no benefit from the treatment.<br><br>I would strongly suggest that NICE awaits the TAILORx results because the landscape will change completely, both in terms of Clinicians being absolutely bought into the test because of the results and more importantly you will have randomised control trial evidence that the test predicts chemotherapy benefit and identifies a group with a score less than 25 who do not benefit from chemotherapy and equally a group over 31 who will have a substantial benefit from chemotherapy.<br><br>That data is already apparent from trials of node negative and node positive patients in a retrospect - prospect analysis of blocks(see NSABP B20 and SWOG 8819 trial results), but will now become clear in a prospective study. | The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance).<br><br>The EAG noted that TAILORx only recruited LN-negative patients. |

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| | | | In the German Plan-B trial, there was only a 3% distant recurrence at 5 years with a low recurrence score less than 12 node positive patients who were not given chemotherapy and TAILORx found a similar recurrence rate for RS<12. There was no benefit of chemotherapy on preventing relapse beyond 5 years from breast cancer as the EGCTCG meta-analysis shows.<br><br>NICE reviews have traditionally been welcomed as highly evidenced and unbiased. The mis-understanding and mis-interpretation of the data in this review will put NICEâ€™s reputation at high risk if they continue to ignore the evidence that is present and they do not take into account of the TAILORx results, given that you are not planning to publish the full DCD advice until September and the TAILORx results will be out in June, so the Oncology community Internationally will have already have made their mind up and it will be politically embarrassing to make a decision without having seen the TAILORx results and their impact on public and patient confidence in the test. | |
| 37 | NHS Professional | General | In addition, the TailorX clinical trial of 10000 women will report at ASCO in the first week of June 2018. I believe it would be prudent in light of such an important trial in this exact clinical area to postpone the decision of the DG to allow the results to be incorporated into your decision making. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The |

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| | | | | committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 38 | NHS Professional | General | The difficulty we have is in those cases with a recurrence score falling within the intermediate range. Because of this issue â€“ we would be grateful if you would consider waiting and incorporating the findings of the TAILORx trial (due early June) before publishing your definitive report. This publication should help in answering this issue of those individuals within the intermediate group.<br><br>If TAILORx shows no benefit of chemotherapy to those in the majority of this group, it could reduce significantly those undertaking chemotherapy with the significant side-effects and costs associated. If it shows a benefit for all in this group, it could ensure these individuals are not missed from important treatment. In summary, we can see the role of Oncotype DX in predicting chemotherapy benefit is increasing as more data | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |

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| | | | becomes apparent. (So please use the evidence from TAILORx). | |
| 39 | NHS Professional | General | Importantly with reference to patients who may be safely spared chemotherapy in this cohort the soon to be published TailorX study providing long term data on patients with intermediate risk scores should also be considered before any final recommendation should be made. | Thank you for your comment which the committee considered.<br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 40 | NHS Professional | General | Results of TAILORx study are going to be presented at ASCO annual meeting in Chicago, 1-5 June 2018 (abstract LBA1). I would strongly recommend these are reviewed and considered in the final version of these guidelines. | Thank you for your comment which the committee considered.<br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although |

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| | | | | TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 41 | NHS Professional | General | It is imperative that NICE look at the evidence from the TailorX study which is a large randomised trial examining the utility of OncotyeDX in the intermediate risk population prior to making a final recommendation regarding the availability of genomic assays in the NHS. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |

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| 42 | NHS Professional | General | Fortunately the TAILORx study will directly address the question of chemotherapy benefit according to Oncotype Dx recurrence score in a contemporary population. These data will be presented and simultaneously published in a high-impact peer-reviewed journal on the 3rd June 2018. These data are absolutely key to the interpretation of chemotherapy benefit in the intermediate risk group (RS score 11-25), and to publish guidance without incorporating these data would mean the guidance is out of date on the date of publication. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 43 | NHS Professional | General | 2) The TAILORx study, which will provide strong evidence about the benefit of genetic testing in patients with an intermediate recurrence score, has been selected for presentation at the â€˜practice changingâ€™ plenary session of ASCO on the 3rd June, with simultaneous publication in a major clinical journal. This would not happen unless the results are conclusive, yet the guidance does not plan to take these results into account. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling |

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| | | | | to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 44 | NHS Professional | General | Tailor x trial is going to be published at ASCO in early June 2018 and is a prospective study in intermediate risk breast cancer. It would be sensible to include these results otherwise it will be 4 years before this important result can be considered. | Thank you for your comment which the committee considered.<br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 45 | NHS Professional | General | The results of TAYLOR X study for intermediate risk patients will be presented at the ASCO meeting in June this year. I believe | Thank you for your comment which the committee considered. |

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| | | | NICE needs to wait with the final decision until we'll have the study results | The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 46 | NHS Professional | General | The TAILORx trial is being presented as a plenary at ASCO in 3 weeks. It would seem prudent to wait until we have this additional data before making a final decision. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer |

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| | | | | in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 47 | NHS Professional | General | The TAILORx study will provide the largest evidence to inform this topic and is a randomised trial which passes the highest level of scrutiny. It is to be presented at ASCO on 3/6/18 with simultaneous peer-reviewed publication. This is an academic-led study. The results will be out by the time the committee next meets and not to use this (whatever it may show) would be unwise.<br><br>If the TAILORx trial supports the omission of chemotherapy for a recurrence score up to 25 then there would be an enormous and appropriate reduction in chemotherapy given (for many units we are already doing this on recurrence score, so any change would lead to increase of chemotherapy inappropriately) but only using recurrence score. the use of the other two tests would mean a higher number of patients would receive chemotherapy. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 48 | NHS Professional | General | I am writing on behalf of the Sheffield breast MDT. As a collective group, we feel it is important to collate all relevant data before making decisions that may alter current use of Oncotype Dx. This should include data that is earmarked for release in the very near future, such as TailorX results. Ignoring this fact will render the consultation immediately out of date. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The |

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| | | | The current consultation is seeking comments on whether all relevant data has been taken into account. Our view is that this is not the case. | committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 49 | NHS Professional | General | B. The TAILOR-X trial question of chemotherapy benefit for patients with intermediate risk node-negative breast cancer is to be presented on the 3rd June at ASCO; oncologists anticipate that these will significantly affect practice internationally. The timing of the present guidance document is therefore unfortunate, as potentially it will be out of date, even before it is finalised. Is it not possible to defer this review until the manuscript is produced (it is expected that a concurrent manuscript/publication will be available)? | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |

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| 50 | NHS Professional | General | We have excellent data from the first report of the prospective randomised trial TAILORx trial showing that patients with a low Oncotype RS <11 do not need chemotherapy and the data from the Intermediate risk group is being presented at ASCO Saturday 3rd June at a Plenary session. Surely is important to introduce a slight delay in the output of this consultation to include this data, as it will answer the fundamental question that the panel have been addressing in this guidance hopefully with clarity and in a large prospective randomised clinical trial. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 51 | Association of Breast Surgery | Whole document | ABS is concerned about the timing of the publication of this review by NICE.<br><br>The TAILORx study has recruited tens of thousands of women and will examine exactly the question that this NICE review is trying to assess ie, women with intermediate risk of breast cancer recurrence (as assessed by tumour profiling) have been randomised into receiving hormone therapy or hormone therapy plus chemotherapy. The TAILORx randomised controlled trial | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling |

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| | | | will present results at the American Society of Clinical Oncology meeting in June 2018 likely followed by an immediate publication in a high profile peer reviewed journal. It has the potential to provide practice changing data that could immediately render this NICE review redundant.<br><br>ABS would like to see the publication of this NICE review delayed to incorporate the findings of the TAILORx study. It makes no sense to publish this guidance beforehand | to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 52 | Breast Cancer Now | 5.3, 5.14, 5.23 | We are also aware that the TAILORx trial is likely to be published shortly, before NICE's final recommendations are made. Whilst at this stage without seeing this data it is not possible to comment on the impact it could have on the current draft recommendations, if the research does prove significant and it would have wide-reaching implications for patients and clinical practice, it is crucial that NICE has transparent and robust mechanisms in place to consider this in a timely manner. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |

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| 53 | CM-PATH | Diagnostic Assessment Report, p365 | We believe that data of the TAILORx trial that will be presented in June 2018 at ASCO and published simultaneously should be considered by NICE. This will be the largest adjuvant trial to date addressing chemotherapy use in the intermediate risk group and whatever the results may be, they should inform clinical guidance. It is likely that the results will inform clinical practice across the world. | Thank you for your comment which the committee considered. |
| 54 | Genomic Health | 1.1, 5.22 | • **We urge NICE to incorporate the results of TAILORx into the current assessment.**<br>• Results of the independently-conducted, prospective TAILORx trial are confirmed for presentation by Dr. Joseph Sparano, the Study Chair, at the Plenary Session in the ASCO Annual Meeting on 3rd June 2018. Because of the significance of the TAILORx results, publication in a major medical journal is expected either simultaneously or very soon after presentation.<br>• TAILORx is the largest randomised adjuvant breast cancer treatment trial ever conducted, and enrolled 10,273 women with early-stage breast cancer across approximately 1,200 sites in six countries.<br>• The trial was independently designed and conducted by ECOG-ACRIN Cancer Research Group under the sponsorship of the National Cancer Institute (NCI), part of the National Institutes of Health | Thank you for your comment which the committee considered.<br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |

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**THEME: TAILORx study**

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| 55 | Genomic Health | 1.1, 5.22 | • The primary objective of TAILORx is to more precisely determine the effect of chemotherapy, if any, for women with node-negative, hormone receptor-positive disease and Oncotype DX Breast Recurrence Score® (RS) results of 11 to 25.<br>• Investigators used the Oncotype DX Breast Recurrence Score test on every patient to quantify individual risk of recurrence and assign treatment to determine whether chemotherapy would be beneficial or not. Based on previous studies, such as NSABP B-20, TAILORx participants with RS<11 were treated with hormonal therapy alone while those with RS>25 were treated with chemotherapy plus hormonal therapy.<br>• To more precisely define the effect of chemotherapy for women considered to be at intermediate risk for recurrence, more than 6,700 women with RS11-25, the primary study group, were randomized to receive hormonal therapy with or without chemotherapy. These randomized patients comprised about two-thirds of all TAILORx patients and were followed for approximately nine years on average. | Thank you for your comment which the committee considered. Details of the TAILORx study have been added to the diagnostics guidance (see section 4.31). |
| 56 | Genomic Health | 1.1, 5.10, 5.22, DAR addendum | • **Considering the three tests recommended in the current DCD classify patients very differently into risk groups and lead to different chemotherapy allocation, the benefits and harms of using each of the tests in clinical practice should be reconsidered in light of the TAILORx results.** | Thank you for your comment which the committee considered.<br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The |

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| | | | • **To avoid the risk of the final NICE guidance leading to many patients being over- or under-treated with chemotherapy, with the associated survival and quality of life impact and waste of NHS resources, it is crucial that the ground-breaking evidence from TAILORx is incorporated into the final NICE DG10 & CG80 guidance**<br>• Currently, the EAGs analysis is based on a central assumption that all patients allocated chemotherapy by tumour profiling tests, derive a substantial benefit. The results from TAILORx are expected to definitively inform this assumption in the analysis.<br>• Furthermore, of UK patients tested according to the current NICE criteria (NPI>3.4), approximately 77% have RS<25 (Blohmer et al. 2017). TAILORx will provide greater precision regarding the proportion of these patients, if any, who benefit from chemotherapy. | committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 57 | Genomic Health | 1.1, 5.22 | • **The committee should not wait for a future update of the guidance before considering this ground-breaking evidence**<br>• This would risk guidance being published that is known to be inconsistent with that of an independently-conducted randomised clinical trial, the highest quality of evidence, which will be available before the committee meeting on 13th June and several months prior to the guidance being released, and which the committee has acknowledged the importance of: | Thank you for your comment which the committee considered.<br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling |

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| | | | • 5.17: "The committee concluded that Oncotype DX…was likely to be cost effective…but evidence on clinical outcomes will be important to confirm this"<br>• 5.22: "The committee noted that there are several ongoing studies which will provide evidence of long-term patient outcomes…the TAILORx trial on Oncotype DX"<br>• TAILORx is expected to have a substantial impact on treatment guidelines and clinical practice, creating a new standard of care. | to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |
| 58 | Genomic Health | 1.1, 5.22 | • A large number of patients enrolled in the TAILORx trial are expected to align with patients tested under the current NICE recommendation of 'intermediate-risk'. In addition, planned secondary analyses will investigate the significance of classical clinical and pathologic information with the Recurrence Score® result. The trial will further refine the evidence from the Oxford Overview and NSABP B-20 trial finding that relative chemotherapy benefit is little associated with clinical-pathologic features. Therefore, the TAILORx results are highly relevant to this NICE assessment.<br>• Truly landmark evidence from large, multi-country, prospective randomized clinical trials designed to answer a critical clinical question such as this comes around very infrequently. NICE has the opportunity to produce guidance based on this latest and best evidence and lead the way in advancing clinical | Thank you for your comment which the committee considered.<br>NICE contacted the author of the TAILORx study to request a subgroup analysis relating to the performance of Oncotype DX in predicting chemotherapy benefit for patients eligible for chemotherapy in the UK, but no response was received (section 5.6 of the diagnostics guidance). |

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| | | | practice, allowing new levels of precision in the treatment of early breast cancer patients.<br>• **Genomic Health would encourage NICE to engage with the independent Study Chair Prof. Joseph Sparano at ECOG-ACRIN to discuss the importance and relevance of the imminent findings to the NICE DG10 & CG80 guidance.** | |
| 59 | NHS England Breast Cancer Clinical Expert Group | General | 1.The NICE draft guidelines still make the assumption that all patients have the same potential benefit from adjuvant chemotherapy proportional to risk of recurrence. This is a highly controversial viewpoint, and the arguments for and against have already been rehearsed. However there is no need to go over these again because the question of chemotherapy benefit for patients with intermediate risk node-negative breast cancer has now been directly addressed by the large TAILOR-X randomised trial which is to be reported imminently at the American Association of Clinical Oncologists annual meeting on 2 June 2018. A concurrent publication in a major journal is anticipated, and the results of TAILOR X will influence practice worldwide. It is essential therefore that NICE awaits the outcome of this trial and takes its results into account before finalising its recommendation. Otherwise there is the risk that the Guidelines recommendations could be directly refuted as soon as they are published by the largest major trial ever | Thank you for your comment which the committee considered.<br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |

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| | | | conducted to address this issue, with a potential loss of confidence in the NICE process. | |
| 60 | Peony Breast Care Unit | General | TailorX is a widely anticipated trial to which 10,000 patients worldwide have been recruited. Follow up is approaching 10 years. At least 1700 of these patients are in the intermediate risk group as defined by NICE. It is supported by some of the best and most rigorous research organisations including NCI, ECOG and Susan G Komen. It is being run wholely independently from GHI. It is likely to be the highlight of ASCO when it is presented on 3 June 2018. The primary aim of the trial is show whether endocrine therapy alone is inferior to ET plus chemotherapy (RFI and OS) in the RS 11 to 25. Planned secondary end points look at the influence of tumour size, menopausal status, taxane v non-taxane therapy, type of radiation therapy, degree of receptor positivity, grade, and it will divide down the intermediate group into RS 11-15, 16- 20 and 21-25. The degree of discordance in central v. local pathologists will be looked at. Finally, there is a quality of life assessment included for a subset of about 1000 patient comparing those who receive and avoid chemotherapy.<br><br>These results are likely to have an immediate impact on breast cancer management in the US and around the world. For NICE to dismiss these imminent results until the next review in 4 years time and exclude them from the current DG10 risks significant political, media, professional and patient backlash. It will | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |

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| | | | undermine the credibility of NICE not only in the UK but around the world where NICE is regarded as timely and independent of bias.<br><br>If TailorX shows that there is little value to chemotherapy in patients with an RS below 26, then, since 85% of patients tested are below this level, in future only 15% of patients will need adjuvant chemotherapy. This will have a major effect on the current cost analysis. | |
| 61 | Royal College of Pathologists | | NICE committee should take into consideration the impending release of TailoRx data at ASCO in June 2018. While the results are not known, this could potentially be practice-changing (either way) and not including this data when the deadline is this close would mean that we could potentially miss an opportunity for several years (when its being reviewed again) | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment. (section 5.6 of the diagnostics guidance). |

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| 62 | Patient | General | I am a patient who self-funded Oncotype DX following a diagnosis of breast cancer with one involved lymph node. I am submitting comments because I would like to make sure the Committee are aware of how difficult and finely balanced treatment choices patients can be from a patient perspective, and how helpful it is to have access even to less than perfect additional information. It is perhaps relevant that Iâ€™m a clinical professor who has been an expert member of a NICE GDG - hence my decision making, throughout very much a collaborative process with a very supportive and understanding oncologist, was also informed by reading as much as I could of the relevant scientific literature.<br><br>I was diagnosed in early 2017 with a small, screening-detected, oestrogen-dependent cancer with one involved sentinel node. The PREDICT tool estimated my 5-year overall survival with hormone therapy alone as 96%, rising to 97% with chemotherapy; corresponding 10 year figures were 90% and 92%. I am a mother, and my first instinct was to do all I could to survive, so I provisionally agreed to have chemotherapy.<br><br>I went away and thought further, and immersed myself in relevant literature. I began to worry that chemotherapy risks might not be justified by the small predicted survival increase. My work is very important to me, and there is much I still wish to do, both in my own research and developing the next generation of researchers. I donâ€™t think I could function effectively with even a small loss of intellectual sharpness, and my combination of roles requires considerable energy. There seem to be | Thank you for your comment which the committee considered.<br><br>The committee decided to add extra detail to section 5.2 of the diagnostics guidance to emphasise the adverse effects associated with chemotherapy. |

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| | | | many unresolved questions regarding long-term chemotherapy effects, but I found the literature on cognitive, neurological and cardiovascular effects, as well as on accelerated ageing, concerning. To me, these risks would have been readily justified by a 10 or even 5 percentage point mortality drop, but I felt very conflicted as to whether a reduction in risk of dying over 5 years of 1 percentage point justified the risk of potentially life-altering long-term effects. I am doubtful as to whether in other branches of medicine this trade-off between risks and benefits would be seen as justified - would people take risks like those involved in chemotherapy for a 2 percentage point reduction in 10 year risk of dying of a heart attack, for instance?<br><br>With such a challenging decision for high stakes, I very much welcomed the possibility of access to additional biologically based and individualised information, even though I am aware of the imperfections in the Oncotype DX evidence in relation to my situation. The test result predicted a low recurrence risk, with no predicted chemotherapy benefit, and this tipped the balance sufficiently that I felt, and my oncologist agreed, it was reasonable to forego chemotherapy. Because of substantial DCIS, I have had a mastectomy, axillary clearance and subsequent reconstruction. Nonetheless, a year on, I do not feel I have been impaired in any significant way by treatment â€“ I am living life to the full and my working life has been little disrupted. A change is that my lifestyle is significantly healthier before: a further concern I had about chemotherapy was that it might make it harder for me to achieve weight loss and exercise goals that I felt to be important. I have considered how I may feel if I do progress to Stage IV disease â€“ I do think I would still believe that I made the best informed decision feasible at the time, and indeed that the recurrence would probably have occurred even with | |

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| | | | chemotherapy. I hope the Committee will consider enabling other patients in my situation to make such challenging and marginal decisions on the best evidence now available, pending a time when it becomes more definitive. | |
| 63 | The University of Edinburgh – Cancer and Society in the 21st century research team | 1.1 | We are investigating women's experiences of gene expression profiling (Onco*type* DX) for chemotherapy decision-making using qualitative interview methods. This work is part of a larger programme of medical sociological research on cancer patienthood in the post genomics era, funded by the Wellcome Trust and involving acaedmics at the University of Edinburgh and Leeds (http://www.cancerandsociety.ac.uk/). The PIs are Professor Sarah Cunningham-Burley, University of Edinburgh and Professor Anne Kerr, University of Leeds. The research team comprises Dr Emily Ross and Dr Tineke Broer (U of Edin) and Dr Julia Swallow and Dr Choon Key Chekar (U of Leeds).<br><br>We wish to add support to the recommendation that tumour profiling tests to guide chemotherapy decision making are made available to women as part of standard care (under the conditions described). In cases where tools such as NHS PREDICT identify women as at intermediate risk of recurrence, clinicians may be unable to advise patients as to whether or not to proceed to adjuvant chemotherapy, and those we interviewed felt that the decision had been left to them. This was described as difficult to manage; participants have not felt knowledgeable enough to make this decision alone. | Thank you for your comment which the committee considered.<br><br>The committee thought that this is important research and made reference to it in section 5.28 of the diagnostics guidance. |

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| | | | Our research has found that gene expression profiling offers additional information to women and their families that aids decision making at this difficult time.<br><br>Women interviewed however, had not received 'intermediate' results (as defined by Onco*type* DX). Our observations of online forum discussions of Onco*type* DX testing have demonstrated that this categorisation can produce further uncertainty, and potential anxiety, for women. | |
| 64 | The University of Edinburgh – Cancer and Society in the 21st century research team | 2.2 | Having researched women's experiences of gene expression profiling (Onco*type* DX) for chemotherapy decision-making using qualitative interview methods, we wish to add support to claims that gene expression profiling provides people with breast cancer confidence that the treatment they are having is appropriate.<br><br>One interviewee described that the results of gene expression profiling made her options "more understandable". Another described gene expression profiling results as providing a "second opinion". Two women who had wanted to avoid chemotherapy, but were subsequently identified as at high risk of recurrence, felt that the test legitimised the need for them to go through this feared treatment. One said that this made this decision more "informed". For the other, the three or four percent increase in likelihood of increased survival, as identified by gene expression profiling, provided justification for her decision to have chemotherapy. | Thank you for your comment which the committee considered.<br><br>The committee thought that this is important research and made reference to it in section 5.28 of the diagnostics guidance. |

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| 64 | The University of Edinburgh – Cancer and Society in the 21st century research team | 4.39 | Having researched women's experiences of gene expression profiling (Onco*type* DX) for chemotherapy decision-making using qualitative interview methods, we wish to add support to claims that gene expression profiling may "reduce anxiety for some patients in some contexts".<br><br>For those women designated as 'intermediate risk of distant recurrence' by NHS PREDICT, the decision as to whether or not to proceed to chemotherapy – which had an unknown potential to reduce recurrence risk, but entailed several weeks of toxic side effects - was described as difficult and fraught. The results of gene expression profiling were described as "making the decision easier", and giving "peace of mind". | Thank you for your comment which the committee considered.<br><br>The committee thought that this is important research and made reference to it in section 5.28 of the diagnostics guidance. |
| 66 | Peony Breast Care Unit | 4.39 DCD | The considerable anxiety and distress of having to receive chemotherapy, often unnecessarily, needs to be taken into account and is likely to be much more significant when compared to the possible increased anxiety of testing. | Thank you for your comment which the committee considered.<br><br>The committee decided to add extra detail to section 5.2 of the diagnostics guidance to empahsise the adverse effects associated with chemotherapy. |

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**THEME: Data collection**

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| 67 | Genomic Health | 1.1, 5.24 | • **Genomic Health supports further evidence generation but for several reasons do not agree with this being made a condition of NICE's recommendation.**<br>• It seems that the committee may be grouping all evaluated tests together, when commenting on the perceived uncertainties. Less evidence is available for tests other than Oncotype DX, thus subjecting them to greater uncertainty.<br>• A substantial body of evidence already exists for the Oncotype DX test related to each of the areas of uncertainty mentioned in the draft data collection arrangement. Multiple decision-impact studies are available, including UK-focused decision-impact data, in addition to the NHS Access Scheme data on the use and impact of Oncotype DX testing in NHS clinical practice. Multiple independently-conducted validation trials and many long-term patient outcome studies involving both 5 and 10 years of follow-up clearly demonstrate low rates of distant recurrence without chemotherapy for patients with a low-Recurrence Score result. Furthermore, the results of the NSABP B-20 trial will be cemented by the imminent TAILORx RCT results, which definitively address the ability of Oncotype DX to affect patient outcomes. | Thank you for your comment which the committee considered.<br>The committee noted that it will be important to continue the data collection to capture the influence of TAILORx. It concluded that future data collection should be done as part of a national database, rather than by individual companies, to increase transparency and link to outcome data (section 5.8 of the diagnostics guidance). |
| 68 | Genomic Health | 1.1, 5.24 | • NICE seems to be suggesting that for Oncotype DX to be recommended as clinically and cost-effective for use in NHS practice, the company must also provide a data collection service for the NHS, which was not part of the scoping for this assessment. | Thank you for your comment which the committee considered.<br>When developing its recommendations, the Committee has the option to make adoption recommendations on the basis |

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| | | | • The proposed mandated extra service would involve collecting and reporting data that the patient/NHS owns and the NHS is already able to access. | that additional research is performed as the technology is adopted.<br><br>The arrangements for data collection involve clinicians and companies making timely, complete and linkable record-level test data available to the National Cancer Registration and Analysis Service as described in the data collection arrangements agreed with NICE. |
| 69 | Genomic Health | 1.1, 5.24 | • The effect on NICE's assessment of the data collection required is far from clear. While Genomic Health believes that observational studies are useful and informative, the EAG has disregarded the large body of observational outcomes evidence already available for the Oncotype DX test, due to the 'potential for spectrum bias'. Observational data collected in the UK would likewise be devalued if the EAG maintains this position. | Thank you for your comment which the committee considered.<br><br>The committee noted that the access scheme data set provided in confidence to NICE by Genomic Health was an important piece of real world evidence and noted that it was used in the economic model. It also noted that the publication on TAILORx (Sparano et al. 2018) may influence chemotherapy decision-making in people with a recurrence score of 11 to 25, and therefore the data set may not represent clinical decision-making in this group. It concluded that more complete data could |

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| | | | | have been collected and reported, and that it will be important to continue the data collection to capture the influence of TAILORx (section 5.8 of the diagnostics guidance). |
| 70 | Genomic Health | 1.1, 5.24 | • There is inequity in the fact that Genomic Health already invested substantial resources in data collection within the NHS following the publication of DG 10 in 2013. | Thank you for your comment which the committee considered.<br>The committee noted that it will be important to continue the data collection to capture the influence of TAILORx. It concluded that future data collection should be done as part of a national database, rather than by individual companies, to increase transparency and link to outcome data (section 5.8 of the diagnostics guidance). |
| 71 | Genomic Health | 1.1, 5.24 | • We would like to reiterate that Genomic Health supports further evidence generation and is willing to discuss a mutually beneficial collaboration with Public Health England to develop further UK-specific evidence about the Oncotype DX test.<br>• We request that the committee remove this condition and instead consider making a clear recommendation for further evidence to be developed, taking into account the evidence now available for each test evaluated. | Thank you for your comment which the committee considered.<br>The committee concluded that the recommendations for EndoPredict, Oncotype DX and Prosigna are conditional on data collection agreements being in |

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| | | | | place (section 5.29 of the diagnostics guidance). |
| 72 | Royal College of Pathologists | | More clarity is needed about how data/information will be gathered by NICE to accurately evaluate the use of these tests in practice in the NHS | Thank you for your comment which the committee considered.<br>The data collection agreements will be published on the NICE website alongside the final guidance. |

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**THEME: Differences between EndoPredict, Oncotype DX and Prosigna**

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| 73 | NHS Professional | General | Whilst improved from the first consultation, the latest DCD remains fatally flawed by misunderstandings by the authors and the lack of evidence, particularly for EndoPredict and the Prosigna ROR. Neither of these tests have evidence or data predicting chemotherapy benefit and their prognostic data is mainly in post-menopausal women, so the claims by the DCD is not evidence based and completely lacking prognostic data for premenopausal women.<br><br>Of greater concern, is that in the OPTIMA pilot trial, both of these tests produced results markedly different to the Genomic Health Oncotype DX test and would classify more patients to receive chemotherapy. In fact the Prosigna ROR test in node negative patients would only identify 27% of the patients who were at low risk and the Endopredict would only identify 47% of patients who were low risk, whereas in the Manchester pilot study 69% of node negative cases were low or low-intermediate risk and avoided chemotherapy. Thus the advice from NICE would end up with more patients being subject to chemotherapy then would be currently in the node negative group and would increase the cost to the NHS because patients would not be avoiding a treatment. Quite how NICE have ignored this fact and supported the use of Endopredict and Prosigna ROR is flabbergasting and likely to lead to considerable political and press opprobrium.<br><br>It appears that both Prosigna and Endopredict have been thrown into the DCD because their companies offered to reduce the cost of | Thank you for your comment which the committee considered.<br><br>The Committee noted that for people with LN-negative disease, all the tests had statistically significant prognostic accuracy over clinical and pathological features or risk assessment tools such as the NPI (section 5.3 of the diagnostics guidance) A clinical expert explained that the biology of a cancer and its molecular subtype, for example hormone receptor status and HER2 status, is more influential in determining the risk of distant recurrence than menopausal status. Therefore the committee concluded that the model results apply to premenopausal and postmenopausal populations, but noted that Prosigna is not indicated for use in premenopausal people (section 5.24 of the diagnostics guidance)<br><br>The committee considered how EndoPredict, Oncotype DX and Prosigna compare with each other, and heard from the EAG that because of limitations in the clinical evidence tests were not compared incrementally against one another. The |

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| | | | the assays but in view of the lack of patient predictive data for chemotherapy and any quality assurance for either assay, both will cost the NHS more and it is a false economy to include them in the DCD. | committee noted that since the publication of TAILORx (Sparano et al. 2018) evidence on clinical utility was strongest for Oncotype DX. It also noted that it was not possible to determine which test was the most cost-effective use of NHS resources, and that it may not be the test with the lowest acquisition price (section 5.21 of the diagnostics guidance). |
| 74 | NHS Professional | General | We are also confused by the recommendation of the two other predictive genomic tools. The benefit on Oncotype DX is its role in determining chemotherapy benefit. This is a different question to predicting survival. We should only give treatment that will benefit the patient and this is why genomics is becoming so important. The model described in your initial report appeared flawed in suggesting there is a whole scale benefit of chemotherapy to all. | Thank you for your comment which the committee considered.<br><br>The committee noted that no data were available to assess a difference in relative treatment effects for chemotherapy for EndoPredict, IHC4+C and Prosigna risk groups, but that it would be considered unethical to do a randomised controlled trial to look at the benefit of chemotherapy compared with endocrine therapy in patients with a clinically low or high risk of distant recurrence (section 5.5 of the diagnostics guidance). |
| 75 | NHS Professional | General | Following on from my response to the previous consultation on genomic assays, I am pleased to see NICE have reviewed their | Thank you for your comment which the committee considered. |

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| | | | recommendations. However I have continued reservations with regards to the current NICE position.<br><br>Firstly the review has recommended the use of either Oncotype DX, EPClin or Prosigna as equivalent assays to be used to further assess the benefit of chemotherapy in the intermediate prognostic group as described in the NICE statement (ER+ve Her 2 â€“ve node â€“ve). The value of any assay in this group where there is an intermediate risk of recurrence and so uncertain benefit on survival and disease specific recurrence by recommending chemotherapy is actually in selecting those who would not benefit from chemotherapy.<br><br>It is therefore surprising that EPClin and Prosigna are included as equivalent assays in the decision making process in this cohort of patients when it has been presented in the NICE document that they would actually increase the proportion of patients in this cohort who receive chemotherapy (diagnostics consultation document pg 36 table 4). | The committee considered how EndoPredict, Oncotype DX and Prosigna compare with each other, and heard from the EAG that because of limitations in the clinical evidence tests were not compared incrementally against one another. The committee noted that since the publication of TAILORx (Sparano et al. 2018) evidence on clinical utility was strongest for Oncotype DX. It also noted that it was not possible to determine which test was the most cost-effective use of NHS resources, and that it may not be the test with the lowest acquisition price (section 5.21 of the diagnostics guidance). |
| 76 | NHS Professional | General | The implication of the change from the first to second draft is that EndoPredict and Prosigna have been included as much on the discount as the evidence base. No additional evidence has been added from the first draft when they weren't going to be recommended. The most important factor for clinicians is the 'predictive value of tests' for the use of chemotherapy, only Oncotype DX even claims this. Your document acknowledges that | Thank you for your comment which the committee considered.<br><br>The committee considered how EndoPredict, Oncotype DX and Prosigna compare with each other, and heard from the EAG that because of limitations in the clinical evidence tests were not compared |

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| | | | for EndoPredict and Prosigna there are not long-term outcomes. My concern is that if all three are recommended that economics will push us towards the cheapest test not the most and best evidence based. | incrementally against one another. The committee noted that since the publication of TAILORx (Sparano et al. 2018) evidence on clinical utility was strongest for Oncotype DX. It also noted that it was not possible to determine which test was the most cost-effective use of NHS resources, and that it may not be the test with the lowest acquisition price (section 5.21 of the diagnostics guidance). |
| 77 | NHS Professional | General | Whilst several genomic test are being proposed for approval in this document, which is always welcome, these tests are not interchangeable and give different information, and this is not made clear in the document. The concern is that commissioning groups may see that approval of one tests is enough (and likely to be the cheapest). Endopredict and Prosigna currently give PROGNOSTIC information, whereas Oncotype Dx has clearly been shown to be prognostic AND PREDICTIVE of benefit to adjuvant chemotherapy. All these tests should be made available to clinicians for circumstances where they can be helpful to patients and some clarity in this document would be helpful.<br><br>The aim of this guidance document is to use these genomic tests to provide predictive and more importantly predictive information to guide decisions on the need for adjuvant chemotherapy and potentially identifying those patients with ER positive, HER-2 | Thank you for your comment which the committee considered.<br><br>The committee considered how EndoPredict, Oncotype DX and Prosigna compare with each other, and heard from the EAG that because of limitations in the clinical evidence tests were not compared incrementally against one another. The committee noted that since the publication of TAILORx (Sparano et al. 2018) evidence on clinical utility was strongest for Oncotype DX. It also noted that it was not possible to determine which test was the most cost-effective use of NHS resources, and that it may not be the test with the lowest |

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| | | | negative disease who gain little from chemotherapy, to spare all the toxic effects and consequences of this on patients and their families. | acquisition price (section 5.21 of the diagnostics guidance). |
| 78 | CM-PATH | Diagnostics Consultation Document, p36 | The draft recommends the use of 3 tests in clinical practice. This implies the tests are equal and may cause confusion for the clinical teams deciding on which one to use. It would be useful to highlight the pros and cons of each, if all are regarded as predictive/prognostic. It is recognised that patients would not be necessarily classified into the same risk groups using each individual test and there is a concern that the current recommendations will lead to an increase in the use of chemotherapy rather than sparing patients who are unlikely to benefit from it. | Thank you for your comment which the committee considered.<br>The committee considered how EndoPredict, Oncotype DX and Prosigna compare with each other, and heard from the EAG that because of limitations in the clinical evidence tests were not compared incrementally against one another. The committee noted that since the publication of TAILORx (Sparano et al. 2018) evidence on clinical utility was strongest for Oncotype DX. It also noted that it was not possible to determine which test was the most cost-effective use of NHS resources, and that it may not be the test with the lowest acquisition price. (section 5.21 of the diagnostics guidance). |
| 79 | CM-PATH | | The laboratory QA issues have not been addressed. One of those tests (Oncotype Dx) is done at one laboratory with stringent quality assurance criteria. The other tests two tests can be done by individual laboratories. It is important to ensure that QA is robust | Thank you for your comment which the committee considered. |

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| | | | and that testing will provide reliable and consistent results. This is particularly important for pathology laboratories setting up the service for testing. | |
| 80 | Genomic Health | 1.1, 5.9, 5.15, 5.16 | • **Could the committee confirm whether any new evidence or analyses have been considered since the first consultation which has led the committee to now believe that there is sufficient evidence about whether Prosigna and Endopredict would have a positive effect on patient outcomes?**<br>• In recommendation 1.1 of the first DCD, the committee stated that more evidence is needed to prove that tests have a positive effect on patient outcomes, but then provisionally recommend Prosigna and Endopredict in DCD#2<br>• The access proposals from the test providers do not of course address evidence gaps and uncertainties about whether these tests will have a positive effect on patient outcomes<br>• Section 5.9: "…although clinical and patient experts thought that the main benefit of the tests was in avoiding unnecessary chemotherapy, most tests were estimated to increase chemotherapy use…". As the Oxford Overview highlights that only ~10% of patients benefit from chemotherapy, we would suggest the importance of the clinical and patient experts' advice should be reconsidered<br>• Most importantly, benefits and harms of using other tests in clinical practice will need to be greatly revised in light of the TAILORx results | Thank you for your comment which the committee considered.<br>The committee noted that access proposals had been made by Myriad Genetics (for EndoPredict) and NanoString Technologies (for Prosigna). The committee concluded that the availability of the access proposals for EndoPredict and Prosigna may reduce the ICERs to a range that could be considered plausibly cost effective despite the clinical uncertainties (section 5.18 of the diagnostics guidance). The committee concluded that EndoPredict (EPclin) and Prosigna, when provided at the costs stated in the access proposals, were likely to be cost effective in the group with LN-negative disease and a NPI of more than 3.4, but evidence on clinical outcomes will be important to confirm this (section 5.19).<br>The committee considered how EndoPredict, Oncotype DX and Prosigna |

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| | | | | compare with each other, and heard from the EAG that because of limitations in the clinical evidence tests were not compared incrementally against one another. The committee noted that since the publication of TAILORx (Sparano et al. 2018) evidence on clinical utility was strongest for Oncotype DX. It also noted that it was not possible to determine which test was the most cost-effective use of NHS resources, and that it may not be the test with the lowest acquisition price (section 5.21 of the diagnostics guidance). |
| 81 | Genomic Health | DAR, 1.1, 5.9 | • **An error in the analysis (NPI>3.4) means the assumed impact of Endopredict and Prosigna on treatment decisions is incorrect and substantially over-estimated.**<br>• **The cost-effectiveness conclusions for these tests are invalid.**<br>• **These tests should not be recommended for use in NHS clinical practice without a more robust evidence-based assessment being carried out.**<br>• It is incorrectly assumed that the proportion of patients receiving chemotherapy pre-testing is the same (43%) for each test risk group. This cannot be justified as multiple decision-impact studies cited in the DAR, show that far fewer (up to 49% fewer) | Thank you for your comment which the committee considered.<br><br>The EAG noted that this is not an error, but an intended assumption. The baseline chemotherapy use (without the tests) for the NPI>3.4 group was taken from the Genomic Health access scheme dataset as this was also the source of the post-test probabilities. This baseline level was similar to that in the NCRAS dataset and in the Bloomfield study. The studies by Wuestlein, Martin and Penault-Llorca are not UK-based and may |

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| | | | patients with a low-risk score by these tests would receive chemotherapy pre-testing, and vice versa for patients with high-risk scores.<br>• (Wuerstlein 2016: 9% chemotherapy for low-risk patients vs. 58% chemotherapy for high-risk patients; Martin 2015: 16% vs. 58%; Bloomfield 2017: 39% vs. 43%; Penault-Llorca 2016: 39% vs. 66 %) | have very different levels of baseline chemotherapy use. |
| 82 | Genomic Health | DAR, 1.1, 5.9 | [comment 3c continued]<br>• This means the EAG's analysis substantially over-estimates chemotherapy decision changes based on the EndoPredict and Prosigna tests for both low and high-risk test scores. E.g. Low-risk: Martin 2015 reported -12.9% change vs. -42% in EAG analysis (>3-fold difference). High-risk: Martin 2015 reported +27.3% vs. +46% in EAG analysis (>1.5-fold difference).<br>• The cost-effectiveness of these tests is artificially driven, in particular, by the exaggerated proportion of high-risk patients assumed to have a decision-change to add chemotherapy, from which all patients are assumed in the analysis to derive substantial benefit. In reality, an unknown but possibly substantial number of these patients would already receive chemotherapy based on current practice. | Thank you for your comment which the committee considered. |
| 83 | Genomic Health | DAR, 1.1, 5.9 | • Further to the error described above, the decision-impact assumed for Prosigna is not based on any data for this test at all, but rather on data for the Oncotype DX Breast Recurrence Score test. | Thank you for your comment which the committee considered. |

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| | | | • One would not expect this kind of arbitrary extrapolation of evidence from one product to another in NICE assessments of pharmaceuticals and equally should not be done for gene expression profiling tests that guide the use of pharmaceuticals<br>• The analysis is not sufficiently robust or reliable to recommend Prosigna for use in clinical practice | The assumption that the Genomic Health access scheme dataset could apply to other 3-level tests was supported by a clinical advisor to the EAG. The committee concluded that the assumptions and inputs used in the model were reasonable, but they were associated with considerable uncertainty (section 5.15 of the diagnostic guidance). |
| 84 | Peony Breast Care Unit | 3.4 DCD | The process of RNA extraction from paraffin blocks is complex and requires careful quality control. Myriad need to provide evidence of reproducibility when used by NHS laboratories before making the claim of a 2 day turn around. To quote Kronwenwett et al https://doi.org/10.1186/1471-2407-12-456 "it is important to know that the pathological laboratories involved in this technical verification study as well in the proficiency testing of EndoPredict were highly experienced in molecular work. Therefore, the results might be different in laboratories with less molecular diagnostic experience and ongoing quality control by periodical round robin tests might be reasonable." Also, "it is important to know that the pathological laboratories involved in this technical verification study as well in the proficiency testing of EndoPredict were highly experienced in molecular work. Therefore, the results might be different in laboratories with less molecular diagnostic experience | Thank you for your comment which the committee considered.<br>The committee noted that EndoPredict compared with current practice had ICERs between £20,000 and £30,000 per QALY gained, and varied depending on whether the testing was done at a local or a centralised laboratory. It also noted that localised testing was more cost effective than centralised testing, and that testing became more cost effective as test throughput increased (section 5.19 of the diagnostics guidance). |

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| | | | and ongoing quality control by periodical round robin tests might be reasonable."<br><br>The impression that this test can be done in local laboratories is incorrect and unlikely to be economically viable given the level of training required by the staff involved. Almost all the tests will need to be sent to Germany or an equivalent centre in the UK incurring significantly longer delays and the claim that the results will be available in 2 days is disingenuous. | |
| 85 | Peony Breast Care Unit | 3.5 DCD | There are two problems evident with prognostic data derived from pathological information. 1. Its subjectivity and limited reproducibility. 2. The artificial cut off points in the data evidenced by the big step in risk between a tumour 2 cm in diameter and 2.1 cm. This is most unlikely to represent a sudden change in tumour biology which we know is generally very stable in early breast cancer. To start adding these factors (tumour size and node status) back into a gene expression algorithm to make it prognostic suggests the combination of genes chosen in the first place is not ideal. | Thank you for your comment which the committee considered. The committee heard from the EAG that it was reasonable to include clinicopathological factors in a prognostic test. |
| 86 | Peony Breast Care Unit | 3.6 DCD | The EPClin cut off of 3.3 is arbitrary and leaves clinicians with less latitude in recommending chemotherapy or not depending on other all-important factors such as risk of complications depending on co-morbidities and the patient's view of what benefit they are looking for from such treatment. | Thank you for your comment which the committee considered.<br><br>An EPclin score of less than 3.3 indicates low risk (less than 10%) of metastases in |

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| | | | | the next 10 years (section 3.6 of the diagnostics guidance). |
| 87 | Peony Breast Care Unit | 3.2 DCD | The ABCSG 06 and 08 trials used to validate EP were both in postmenopausal patients. There must be some doubt that the test is equally valid in premenopausal patients. | Thank you for your comment which the committee considered.<br>A clinical expert explained that the biology of a cancer and its molecular subtype is more influential in determining the risk of distant recurrence than menopausal status. The committee concluded that the model results apply to premenopausal and postmenopausal populations (section 5.24 of the diagnostics guidance). |
| 88 | Peony Breast Care Unit | 3.18 DCD | Prosigna is for postmenopausal patients only and is not suitable as a general test for use in early breast cancer in the NHS where about half the cases are pre- or peri-menopausal. | Thank you for your comment which the committee considered. |
| 89 | Peony Breast Care Unit | 3.19 DCD | PAM50 was not developed as a prognostic tool but to understand the diversity of breast cancer gene expression. The subtype does not in itself give a prognosis and the Prosigna test makes no prediction of chemotherapy benefit. I have similar concerns for Prosigna as for EPClin (see comment 3 above) in that unreliable pathological data needs to be added to the algorithm to make it prognostic. | Thank you for your comment which the committee considered.<br>Prosigna had statistically significant prognostic accuracy for 10-year distant recurrence-free survival and interval in all unadjusted analyses of patients with LN-negative and LN-positive disease. In analyses adjusted for clinical and |

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| | | | | pathological variables or tools, Prosigna had prognostic accuracy for 10-year distant metastasis-free survival and distant recurrence-free survival (section 4.14 and 4.15 of the diagnostics guidance). |
| 90 | Peony Breast Care Unit | 4.28 DCD | It is noted that there is no clinical utility data available for EP and Prosigna. This significantly weakens NICE's decision to include them as recommended for use in the UK. | Thank you for your comment which the committee considered.<br>The committee noted that since the publication of TAILORx (Sparano et al. 2018) evidence on clinical utility was strongest for Oncotype DX (section 5.21 of the diagnostics guidance). |
| 91 | Peony Breast Care Unit | 4.35 DCD | It is not surprising that the test allocated different patients to different categories since on average 95% of the patients with early breast cancer will not benefit from chemotherapy. Each of the tests finds 50% or less low risk and able to avoid treatment. 45% are being falsely allocated into the high-risk group and each test is likely to be finding a different set of patients. 8% positive by all tests is reassuring since it is nearer the actual figure of 5%. For obvious reasons it is not practical to perform all three tests. It is critical that NICE await the results of TAILORX as this may allow the cut off RS to be moved up to 25 in which case less than 15% of patients will fall into the high-risk category allowing a very significantly greater number of patients to avoid chemotherapy. | Thank you for your comment which the committee considered.<br>The committee noted that most tests were estimated to increase chemotherapy use at least in some subgroups. It concluded that there was much more uncertainty around chemotherapy decision-making for the 2-level tests, and for the subgroups who were not included in the original NICE recommendation on tumour profiling tests (LN-negative disease and a NPI of 3.4 or |

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| | | | | less, and LN-positive disease) (section 5.11 of the diagnostics guidance). |
| 92 | Peony Breast Care Unit | 4.36 DCD | My understanding is that the decision impact studies for EP and Prosigna were mostly retrospective and thus subject to significant observer bias. | Thank you for your comment which the committee considered.<br>The EAG noted that most of these studies are prospective. |
| 93 | Peony Breast Care Unit | 4.64 Table 4 DCD | *"…shows Prosigna & EP are expected to increase CT use to at least the level when no genomic test was used*." There remains significant uncertainty about the clinical use of EP and Prosigna which if used would appear to return chemotherapy use to its historically high (and unnecessary) level. Not only would these two tests further fuel the argument that screening and early diagnosis is leading to significant over treatment but there is doubt that the average oncology unit could manage the increased demand on its services at a time of skills and cash crisis. | Thank you for your comment which the committee considered.<br>The EAG model suggests that whilst EndoPredict and Prosigna increase chemotherapy use in the LN-negative NPI>3.4 group, this increase is small. |
| 94 | Peony Breast Care Unit | Table 121 DAR | It would appear that the estimate made of the decision impact of EPClin and Prosigna is based on the OXD access scheme data and therefore likely to represent a significant overestimate which fundamentally changes the outcome of the cost-effectiveness assessments. | Thank you for your comment which the committee considered.<br>The EAG noted that post-test chemotherapy use for EndoPredict was based on the Bloomfield study. For Prosigna, an assumption was made that each of the 3-level tests would be interpreted by clinicians in the same way. |

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| 95 | Peony Breast Care Unit | General | Endorsing EPClin, Prosigna and OncotypeDX gives the false impression that all three tests are equivalent and there is a risk that commissioners will simply impose the cheapest of the three tests on clinicians. Whilst I understand that there is value in competition in the market, it is very clear that these tests are not the same. Prosigna is only suitable for postmenopausal patients and both EPclin and Prosigna are only prognostic and their use was rejected in the previous recommendations.<br><br>It is unclear why they are now included when the main justification for the change in recommendations seems to be a recognition that OncotypeDX is a predictor of chemotherapy benefit. | Thank you for your comment which the committee considered.<br><br>The committee considered how EndoPredict, Oncotype DX and Prosigna compare with each other, and heard from the EAG that because of limitations in the clinical evidence tests were not compared incrementally against one another. The committee noted that since the publication of TAILORx (Sparano et al. 2018) evidence on clinical utility was strongest for Oncotype DX. It also noted that it was not possible to determine which test was the most cost-effective use of NHS resources, and that it may not be the test with the lowest acquisition price. (section 5.21 of the diagnostics guidance). |

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**THEME: MammaPrint**

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| 96 | Agendia N.V. | Addendum: EAG responses to key themes within the Comments on the Diagnostics Consultation Document,version 19th April 2018<br><br>Section 8.1, p26)<br><br>(p538 in DAP 37 Evaluation report 12042018 [no ACIC].pdf) | *EAG response to themes with the comments on DCD: p26 section **8.1. "Re-analysis of MammaPrint by Agendia within the EAG model"***<br><br>Given the EAGs response in section 8.1 (on the interpretation of lack of additional benefit of chemotherapy) we would also like present a brief overview of the application of MammaPrint in clinical practice. This is to illustrate how physicians interpret the non-significant benefit of chemotherapy on DMFS in discordant groups.<br><br>In **Error! Reference source not found.** we include a slide from a presentation by Dr. Martine Piccart (head of EORTC working group and PI of MINDACT) at the European Breast Cancer Conference 2018. This outlines how she applies MammaPrint testing in her clinical practice.<br><br>For a hormone receptor positive patient, firstly, the clinical and pathological factors are assessed to define "clinical risk". If the patient is classified as "clinical low risk" they are treated according to the (inter)-national guidelines. If the patient is classified as "clinical high-risk" the physician discusses with the patient whether they would value a less than <2% possible gain in DMFS when treated with chemotherapy (i.e. the 1.5% non-statistically significant difference in chemo vs no chemo in MINDACT). If the patient says yes, then they receive chemotherapy. However, if the patient does not see the value in such a small and uncertain benefit in treatment with chemotherapy and would rather avoid such treatment, the physician orders MammaPrint. | Thank you for your comment which the committee considered.<br><br>The EAG noted that the economic analysis of MammaPrint by the EAG considered the MINDACT ITT population, and separately considered the mAOL high-risk and mAOL low-risk subgroups (plus some other subgroups). This followed the same general approach as Agendia's original cost-effectiveness paper. |

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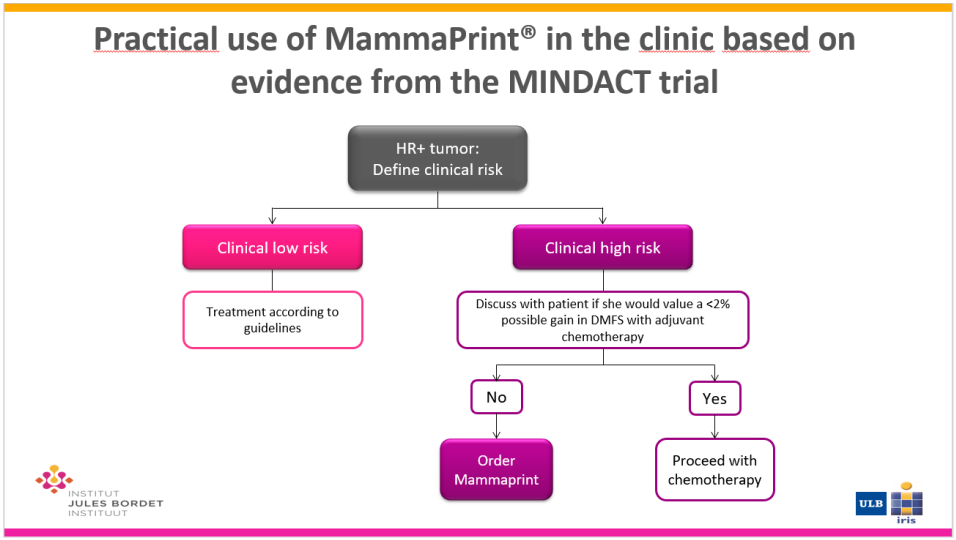
| | | | *Figure 1 - Slide depicting MammaPrint use in clinical practice (reproduced with courtesy of M. Piccart)*<br>  <br><br>As shown in MINDACT, ~46% of these clinical high-risk patients turn out to be genomic "low-risk" and could therefore be spared chemotherapy. After consulting both the combined clinico-pathological risk and genomic risk results the patient and physician are able to make a more informed final decision on whether to proceed or omit chemotherapy from the treatment regimen. | |

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| 97 | Agendia N.V. | PREDICT tool | MammaPrint genomic risk results have recently been correlated with risk assessment results obtained by modified Adjuvant Online (mAOL) and PREDICT (Groenendijk et al., 2018). This study involved a retrospective analysis of patients with MammaPrint results from the Dutch pathology registry. A sub-analysis was performed on 1893 patients with ER+ tumors from this registry. For mAOL, patients were classified as low-risk or high-risk according to criteria used in the MINDACT study (Adjuvant! Online version 8.0 with HER2, found in Suppl. table S13 of Cardoso et al., 2016). For PREDICT, predicted overall survival benefit with adjuvant chemotherapy (ACT) was assessed using PREDICT V2.0. As can be drawn from Suppl Table S3a (Groenendijk et al., 2018), as well as Table 6A and 6B below, the number of patients that are classified as either low or high risk are very similar between mAOL and MammaPrint. 64% of patients are low risk according to mAOL and 65% are Low Risk according to MammaPrint. However, the level of concordance is 70.7% for Low risk and 45.5% for high risk classification (see Table S3a and b). Indicating that both stratifiers do not fully overlap in identifing the same patients to be either low or high risk of recurrence.<br><br>Table S3b shows risk classification using the PREDICT tool. Unlike mAOL, PREDICT identifies many more patients to be low risk (<3% chemotherapy benefit), with 82.8% of the patients being low risk (939 of the 1134 patients that could retrospectively be assessed by PREDICT). Finding such a high percentage of low risk patients could potentially lead to a great number of patients to be subject to undertreatment, as thus far no data is available from prospective randomized trials using PREDICT risk assessment. Combining the MammaPrint genomic risk assessment and the knowledge derived from as the MINDACT trial could lead to more informed physician and patient discussions | Thank you for your comment which the committee considered.<br><br>The EAG noted that concordance data between AOL and PREDICT does not include long term outcomes. Therefore it is not possible to conclude which test is assigning the right patients to the right groups.<br><br>The EAG also noted that from OPTIMA prelim, all tests have fairly poor concordance with each other. |

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
and avoid overtreatment as well as undertreatment as we know that in MINDACT, overall, MammaPrint Low Risk patients had a 5year DMFI of 97.2% without chemotherapy and a 93.4% DMFI at 5years for MammaPrint High Risk patients that were treated with chemotherapy.
<br>Table 6A – Correlation between Adjuvant! Online and MammaPrint
<table>
<tr><td colspan="3"></td><td colspan="2">GENOMIC RISK (MAMMAPRINT)</td></tr>
<tr><td colspan="3"></td><td>MP low risk (%)</td><td>MP high risk (%)</td></tr>
<tr><td>ADJUVANT! ONLINE</td><td>Low risk</td><td>714 (64%)</td><td>505 (70.7%)</td><td>209 (29.3%)</td></tr>
<tr><td>CLINICAL RISK</td><td>High risk</td><td>411 (36%)</td><td>224 (54.5%)</td><td>187 (45.5%)</td></tr>
<tr><td>TOTAL</td><td colspan="2">1125</td><td>729 (65%)</td><td>396 (35%)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Table 6B – Correlation between PREDICT and MammaPrint
<table>
<tr><td colspan="3"></td><td colspan="2">GENOMIC RISK (MAMMAPRINT)</td></tr>
<tr><td colspan="3"></td><td>MP low risk (%)</td><td>MP high risk (%)</td></tr>
<tr><td>PREDICT</td><td>Low risk</td><td>939 (82.8%)</td><td>655 (69.8%)</td><td>284 (30.2%)</td></tr>
<tr><td>CLINICAL RISK</td><td>High risk</td><td>195 (17.2)</td><td>78 (40%)</td><td>117 (60%)</td></tr>
</table>
</td><td></td></tr>
</table>

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| | | | **TOTAL** | 1134 | 733 **(64.6%)** | 401 **(36.4%)** | | |

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**Supplementary Table S3a.** Correlation between MammaPrint genomic risk assessment in ER-positive tumors and clinical risk assessment according to modified Adjuvant! Online criteria*.

| | | ER+ tumors N=1893 | Genomic risk | |
|---|---|---|---|---|
| | | | Low risk N=1201 (63.4%) | High risk N=692 (36.6%) |
| Adjuvant! Online Clinical risk | Low risk | 714 | 505 70.7% | 209 29.3% |
| | High risk | 411 | 224 54.5% | 187 45.5% |
| | N/A | 768 | 472 61.5% | 296 38.5% |

* based on ER status, HER2 status, tumor grade, nodal status and tumor size.

**Supplementary Table S3b.** Correlation between MammaPrint genomic risk assessment in ER-positive tumors and overall survival benefit from 3rd generation (taxane-containing) adjuvant chemotherapy according to PREDICT V2.0*.

| | | ER+ tumors N=1893 | Genomic risk | |
|---|---|---|---|---|
| | | | Low risk N=1201 (63.4%) | High risk N=692 (36.6%) |
| PREDICT V2.0 Overall survival benefit adjuvant chemotherapy | <3% | 939 | 655 69.8% | 284 30.2% |
| | ≥3% | 195 | 78 40.0% | 117 60.0% |
| | N/A | 759 | 468 61.7% | 291 38.3% |
| | | | | |
| | *- ≤1%* | *74* | *64 86.5%* | *10 13.5%* |
| | *- 1.1-2.0%* | *589* | *415 70.4%* | *174 29.5%* |
| | *- 2.1-3.0%* | *296* | *185 62.5%* | *111 37.5%* |
| | *- 3.1-4.0%* | *103* | *44 42.7%* | *59 57.3%* |
| | *- 4.1-5.0%* | *48* | *15 31.3%* | *33 68.8%* |
| | *- >5%* | *24* | *10 41.7%* | *14 58.3%* |

* based on age, tumor size, tumor grade, number of positive nodes, ER status and HER2 status.

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| 98 | Agendia N.V. | Addendum: EAG responses to key themes within the Comments on the Diagnostics Consultation Document<br><br>(section 3.4)<br><br>(theme: ODx chemotherapy benefit)<br><br>(Evaluation report 12042018 [no ACIC].pdf, p525) | *Section 3.4 "d) Clinical relevance of chemotherapy benefit is unclear for the Oncotype DX intermediate-risk group: Hazard ratios for chemotherapy benefit are available for this group, but* ***it is unclear how they should be interpreted in clinical practice, i.e., would patients be treated, not treated, or would other clinicopathological variables be taken into consideration when making a decision?****"*<br><br>The medical community has also stressed that it is unclear how Oncotype DX (ODx) intermediate patients should be treated in clinical practice as well, and Agendia encounters this question frequently. Between 38-67% of women tested in different studies using ODx are classified as having an intermediate/ indeterminate Recurrence Score (RS 11/18-30) (Lo et al. 2011, Sulayman et al. 2012, Stemmer et al. 2013, Sparano et al. 2015). We feel this is an important issue to have been highlighted by the EAG as this large 'grey area' indeed brings to question the clinical usefulness of the test.<br><br>Agendia recognises this as an un-met need for physicians and would like to present briefly the evidence from the PROMIS trial. Results from PROMIS (Prospective study Of MammaPrint in breast cancer patients with an Intermediate recurrence Score) show that MammaPrint can provide risk stratification and treatment guidance on whether a patient should receive adjuvant chemotherapy (ACT) for ODx intermediate-risk group patients (Tsai et al. JAMA Oncol. 2017) see also comment 19 in previous consultation comments by Agendia (page 24).<br><br>PROMIS evaluated 840 ER-positive, women across 58 US institutions who had previously received an intermediate/indeterminate risk ODx score. Patient samples were re-tested using MammaPrint to re-stratify the risk classification | Thank you for your comment which the committee considered.<br><br>The EAG noted that the PROMIS trial was not included in the assessment as it did not meet the inclusion criteria for the review.<br><br>The EAG noted that MammaPrint may be able to reclassify some patients who are Oncotype DX RS intermediate as low or high risk, and equally, Oncotype DX applied to high risk MammaPrint patients, may reassign some patients as low risk. However, only long-term data would show whether these |

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| | | | and provide additional treatment guidance. While we appreciate that this is not a European study we believe that the results are highly relevant to the EAG's specific critic and also applicable to the UK given the shared genetic ancestry of a large proportion of the UK and US population.<br><br>Of the 840 intermediate risk patients, MammaPrint reclassified 55% (466) of these patients as MammaPrint High Risk and 45% (374) as Low Risk. As can be seen from Figure 15 , 50% of MammaPrint High Risk results were found between an ODx risk score of 18 and 25 highlighting a lack of correlation between the two tests and a potential risk of under-treatment of these patients when guided by ODx test results. | reassignments were appropriate. |

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| | | | | |
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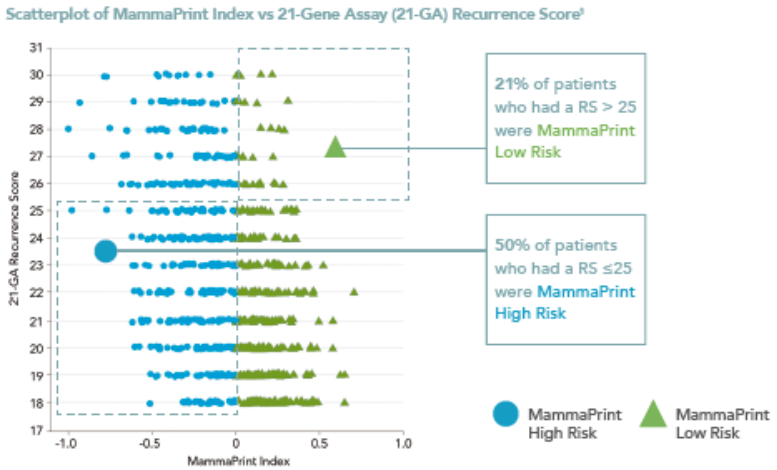
| | | | *Figure 15 - Scatterplot of MammaPrint Index versus Oncotype Dx Recurrence score*<br>  <br><br>Based on the outcome of the MammaPrint test, 89% of physicians adhered to the treatment decisions based on the definitive MammaPrint results, and 79% of physicians reported that they had greater confidence in their treatment recommendations with MammaPrint. In fact, 37% (171) of the high-risk patients had ACT added to their treatment recommendation and 29% (108) of the low risk patients had ACT removed from their treatment recommendation. Of the MammaPrint Low Risk patients who were previously indicated to receive ACT based on the ODx intermediate-risk results, 76% of patients decided to forego ACT, preventing unnecessary overtreatment in this group. Of the intermediate | |

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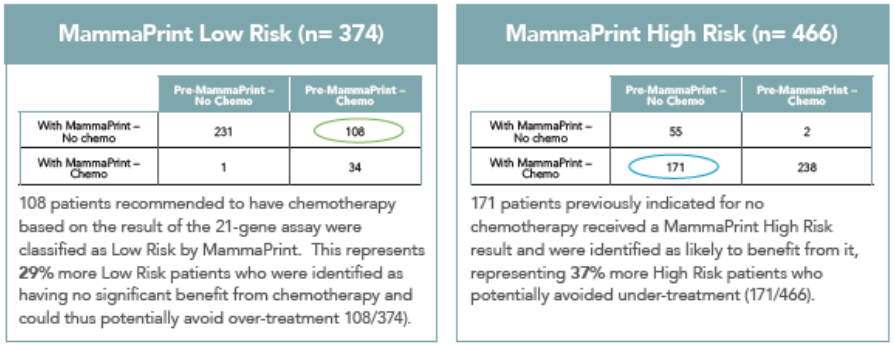
| | | | patients reclassified as High Risk by MammaPrint, 73% had an ODx Recurrence Score ≤25 and were not recommended for ACT by St. Gallen Guidelines (Goldhirsch, Winer et al. 2013), risking up to a 73% chance of undertreatment.<br><br>*Figure 16 – Summary of chemotherapy recommendations for patients with OncotypeDx intermediate results pre and post-MammaPrint testing (representing overtreatment or undertreatment in this patient group)*<br><br>  <br><br><br>The purpose of a prognostic test is to provide physicians and patients with definitive and actionable information in combination with other factors for accurate risk assessment. MammaPrint provides clinically actionable information regarding patients classified as intermediate risk by ODx and was associated with a change in treatment decision in 33.6% of these patients preventing both under and over treatment. | |

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**THEME: PREDICT tool**

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| 99 | Genomic Health | 1.1 | • We would encourage the NICE committee to recommend Oncotype DX for patients in whom there is uncertainty regarding the chemotherapy treatment decision, but not to set upper and lower thresholds based on the PREDICT or NPI tools, to try to define 'intermediate risk'. We suggest clinicians are best placed to make this clinical judgement based on multiple factors<br>• These tools have inherent limitations as they are based on population trends that are not reliable for the individual patient<br>• Furthermore, they rely on extrapolating 'possible' chemotherapy benefit based on both population-trends-based prognostic estimates and population-average relative chemotherapy effect; they do not identify the sub-set of patients 'likely' to benefit.<br>• Patients with a PREDICT score of >5% absolute benefit will not necessarily derive any benefit from chemotherapy and patients with a PREDICT score <3% cannot necessarily be safely spared chemotherapy.<br>• Setting these thresholds risks patients being over- or under-treated and missing out on having access to important information to help guide their treatment decisions. | Thank you for your comment which the committee considered.<br>The committee noted that compared with current practice, the ICERs for Oncotype DX in the group with LN-negative disease and a NPI of 3.4 or less were higher than those normally considered to be a cost-effective use of NHS resources (section 5.20 of the diagnostics guidance). |
| 100 | Myriad Genetics | General comment | Myriad respectfully requests clarification regarding the PREDICT model. In both versions that are currently available to consultants – v1.2 and v2.0 there is a question regarding second or third generation chemotherapy. In this case, would the calculation of intermediate risk be relevant for second or third generation chemotherapy regimens.<br>http://www.predict.nhs.uk/predict_v2.0.html | Thank you for your comment which the committee considered. The committee heard from clinical experts that 3rd generation regimens were the most commonly used in the NHS. |

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| 101 | Peony Breast Care Unit | 2.8 DCD | Although some laboratories test for Ki67 by IHC, evidence shows that this assessment has very poor reproducibility between pathologists and laboratories. Cut-offs are not standardised. Most authorities consider it unreliable and the guidance should make it clear that it is not suitable for use in this context. Therefore, by implication, PREDICT which incorporates this test must be used with caution. | Thank you for your comment which the committee considered.<br>The committee noted that PREDICT can be used without Ki67. |

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**THEME: Chemotherapy benefit and disutility**

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| 102 | NHS Professional | General | The latest DCD analysis assumes that all breast cancer patients derive the same 24% benefit of reduction of recurrence from chemotherapy, which is blatantly nonsense and a false assumption. The Oxford EBCTCG overview stated only 10% of patients benefit from chemotherapy, the other 90% obtain the toxicity of treatment without benefit.<br><br>The NSABP lead statistician wrote to NICE following the original DCD thatâ€□ the multivariate results from the B-20 study where HER2 positive disease is excluded, even more strongly support that the Recurrence Score is predictive of chemotherapy benefit in NSABP B-20â€□ â€œThe results of the published NSABP b-20 and SWOG 8814 studies indicate that the RS is predictive of chemotherapy benefit, with a much greater relative risk reduction for High Recurrence Score disease than for low Recurrence Score diseaseâ€□. In short within the DCD, an analysis assuming Low RS patients do not benefit from chemotherapy was required by NICE but not carried out.<br><br>The prediction of the RS Oncotype DX assay chemotherapy is accepted by Oncologists in most international guidelines, such as the St Gallen, the NCCN and ESMO guidelines. The concept means that there are a group of patients who have no benefit from chemotherapy and another group of patients who have a substantial benefit from chemotherapy and the genomic test can detect which they are. The assumption that all patients benefit from chemotherapy used again in the DCD is completely inappropriate | Thank you for your comment which the committee considered.<br><br>The EAG noted that a relative risk of distant recurrence for chemotherapy compared with no chemotherapy of 0.76 was used in the base case, and that this value had been varied between 0.6 and 0.9 in sensitivity analyses. The committee acknowledged that the ICERs are sensitive to this assumption, increasing as the relative risk moves from 0.6 to 0.9, but concluded that although the true treatment effect is unknown it is unlikely to be a relative risk of 0.9 (section 5.12 in the diagnostics guidance).<br><br>Following the Sparano et al. 2018 publication on TAILORx the EAG incorporated an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category, based on results from TAILORx. It noted that this analysis is based on the strong |

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| | | | and wrong. â€œThere is none so blind as will not see and no one so blind as will not hearâ€ !<br><br>Neoadjuvant chemotherapy data<br><br>Gianni L et al in the JCO 2005 paper [3] analysed Oncotype DX scores before neoadjuvant score chemotherapy analysis to predict chemotherapy benefit. No patients had a pathological complete response (accepted evidence of chemo sensitivity) with an Oncotype DX score less than 28 and a high recurrence score (absolute value) was positively correlated with a likelihood of pathological complete response.<br><br>Other neoadjuvant chemotherapy studies have found similar findings and the reverse that for those with a low recurrence score there is a very high 90% response rate to endocrine therapy in the low recurrence score but a very low response rate (20% in the high recurrence score) have been published.<br><br>It does not take randomised control trials to prove a point. 60,000 SEER data patients who were followed-up for 5 years. In patients with a low recurrence score ( only 7% who were given chemotherapy) , there was a survival in excess of 98% at 5 years which indicates the test identifies patients with a low recurrence score who do not benefit from chemotherapy. Neoadjuvant chemotherapy data<br><br>References | assumption that Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but will not respond to chemotherapy (section 5.13 of the diagnostics guidance).<br><br>Neoadjuvant chemotherapy data were not within the scope of the assessment. |

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|---|---|---|---|---|
| | | | 1) Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, McGale P, Pan HC, Taylor C, Wang YC, Dowsett M, Ingle J, Peto R. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011. 378:9793:771-784<br><br>2) Dowsett M, Cuzick J, Wale C, Forbes J, Mallon EA, Salter J, Quinn E, Dunbier A, Baum M, Buzdar A, Howell A, Bugarini R, Baehner FL, Shak S. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J Clin Oncol. 2010 Apr 10;28(11):1829-34. doi: 10.1200/JCO.2009.24.4798. Epub 2010 Mar 8.<br>3) Gianni L, Zambetti M, Clark K, Baker J, Cronin M, Wu J, Mariani G, Rodriguez J, Carcangiu M, Watson D, Valagussa P, Rouzier R, Symmans WF, Ross JS, Hortobagyi GN, Pusztai L, Shak S. Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. J Clin Oncol. 2005 Oct 10;23(29):7265-77. Epub 2005 Sep 6.<br><br>4) Ueno T, Masuda N, Yamanaka T, Saji S, Kuroi K, Sato N, Takei H, Yamamoto Y, Ohno S, Yamashita H, Hisamatsu K, Aogi K, Iwata H, Sasano H, Toi M. Evaluating the 21-gene assay Recurrence ScoreÂ® as a predictor of clinical response to 24 weeks of | |

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| | | | neoadjuvant exemestane in estrogen receptor-positive breast cancer. Int J Clin Oncol. 2014 Aug;19(4):607-13. doi: 10.1007/s10147-013-0614-x. Epub 2013 Oct 8.<br><br>5) Akashi-Tanaka S, Shimizu C, Ando M, Shibata T, Katsumata N, Kouno T, Terada K, Shien T, Yoshida M, Hojo T, Kinoshita T, Fujiwara Y, Yoshimura K. 21-Gene expression profile assay on core needle biopsies predicts responses to neoadjuvant endocrine therapy in breast cancer patients. Breast. 2009 Jun;18(3):171-4. doi: 10.1016/j.breast.2009.03.005. Epub 2009 May 2. | |
| 103 | NHS Professional | General | I do not feel that the document puts enough importance on the issue of chemotherapy avoidance. Chemotherapy is a very unpleasant treatment with potential long term as well as short term consequences. Infertility, cardiomyopathy and leukaemia can occur as late toxicities. In addition, there is the short term burden of chemotherapy in terms of social and financial hardship. Clearly it is essential that women who need chemotherapy should get it but it is equally important that those who do not can avoid it. I feel more note should be made of the role of these tests (in particular oncotype DX which has a predictive as well as a prognostic benefit) in allowing some women to avoid chemotherapy. | Thank you for your comment which the committee considered.<br><br>The committee decided to add extra detail to section 5.2 of the diagnostics guidance to emphasise the adverse effects associated with chemotherapy. |
| 104 | NHS Professional | General | NICEâ€™s analysis incorrectly supports increases in chemotherapy in low and intermediate risk patients (diagnostic assessment report addendum pg 1 table 1). | Thank you for your comment which the committee considered.<br><br>The committee decided to add extra detail to section 5.2 of the diagnostics |

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| | | | Subjective and collective experience within our unit and widely reveals the often great anxiety patients have regarding receiving chemotherapy. But more than this the potential for a significant side effect profile which can profoundly effect the quality of life and also working life of patients receiving this treatment. The physical, emotional and financial impact to an individual who receives chemotherapy without significant benefit in this intermediate risk cohort should not be underestimated.<br><br>I reiterate the point that actually sparing pateints chemotherapy without adversely effecting their prognosis in this cohort of patients would represent a real win for patients due to the many adverse effects physically, psychologically and financially to an individual which do not appear to have been considered. | guidance to emphasise the adverse effects associated with chemotherapy. |
| 105 | NHS Professional | General | The key clinical driver of this consultation is to guide chemotherapy decision-making.<br><br>The current model makes estimates of chemotherapy benefit based on indirect comparisons from historical NSABP studies (B14 and B20) and TransATAC. At inception none of these studies were intended to be used for this purpose, and the model appears to assume that all patients derive substantial benefit from chemotherapy. This is biologically implausible: because we know from numerous sources (including the neoadjuvant setting) that patients with a low RS, or low proliferative rate, lower grade, ER strongly positive breast cancers derive little benefit from | Thank you for your comment which the committee considered.<br><br>Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category, based on results from TAILORx. It noted that this analysis is based on the strong assumption that |

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| | | | chemotherapy compared with her grade/higher RS tumours. Moreover the populations treated and therapies utilised are very different today. Surgical and radiotherapy techniques have changed, aromatase inhibitors have supplanted tamoxifen in post menopausal women and CMF is rarely if ever used. | Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but will not respond to chemotherapy (section 5.13 of the diagnostics guidance). |
| 106 | NHS Professional | General | 1) The guidance still assumes the same relative benefit for chemotherapy for all risk groups, suggesting that sensitivity to chemotherapy is independent of other prognostic factors. There is spite of strong evidence that patients with low risk tumours not only have a low risk of recurrence, but that their risk would not be reduced if chemotherapy is given. | Thank you for your comment which the committee considered.<br>Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category, based on results from TAILORx. It noted that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but will not respond to chemotherapy (section 5.13 of the diagnostics guidance). |

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| 107 | NHS Professional | General | The assumption of a benefit from chemotherapy for the low recurrence score group in Oncotype DX in table 129 page 365 of diagnostics assessment report seems flawed when the predictive aspect suggests that it is zero. I don't comprehend the use of this benefit when recurrence score gives clear guidance on predictive benefit which is evidence-based.<br><br>Furthermore in DAR2 page 1 'Table 1 presents estimated hazard ratios for chemotherapy versus no chemotherapy based on naÃ¯ve indirect comparisons of Study B20, Study B14 and TransATAC' which is a type of direct comparison we would not support between studies as a clinical scientific community. It also seems to imply an even greater relative benefit for the low recurrence score group compared to table 129 referred to in my previous paragraph.<br><br>There is a lack of emphasis on the benefit of 'not receiving chemotherapy'. For the patients this is massive with the absence of morbidity and the mortality (albeit small for adjuvant patients). Further patient groups should be consulted, such as Independent Cancer Patients' Voice. | Thank you for your comment which the committee considered.<br><br>Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category, based on results from TAILORx. It noted that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but will not respond to chemotherapy (section 5.13 of the diagnostics guidance).<br><br>The committee decided to add extra detail to section 5.2 of the diagnostics guidance to emphasise the adverse effects associated with chemotherapy. |
| 108 | NHS Professional | General | A. The NICE draft guidelines still make the assumption that all patients have the same potential benefit from adjuvant chemotherapy. This is a highly controversial viewpoint, and | Thank you for your comment which the committee considered. |

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| | | | evidence from other settings (such as neoadjuvant chemotherapy use) suggest that this is simply incorrect. This has the effect of making analyses of survival benefit (or not), for all the assays, problematic. | Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category. It noted that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but will not respond to chemotherapy (section 5.13 of the diagnostics guidance). |
| 109 | Agendia N.V. | Addendum: EAG responses to key themes within the Comments on the Diagnostics Consultation Document (section 3) | *"Considering the limitations discussed above, the EAG considers that there remains uncertainty surrounding whether Oncotype DX is associated with a predictive benefit of chemotherapy (**i.e. a difference in relative effect by genomic risk group**), and if so, that there is uncertainty in the likely magnitude of this predictive effect within the clinical subgroups considered in this appraisal."*<br><br>We commend the EAG on their thorough examination of the studies assessing the predictive performance of the ODx for chemotherapy benefit. As explained in the Addendum, Section 3 in points a-d, there is not sufficient evidence of a high enough quality to make the case ODx is predictive of chemotherapy benefit. Based on the | Thank you for your comment which the committee considered.<br><br>The committee concluded that the evidence on the extent to which tumour profiling tests are able to predict relative treatment effects for chemotherapy is highly uncertain, but there may be some differences between Oncotype DX risk groups. The committee noted that no data were available to assess a difference in |

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| | | (version 19th April 2018)<br>(theme: ODx chemotherapy benefit)<br>(Evaluation report 12042018 [no ACIC].pdf p526) | EAG's evaluation of the data, we urge the NICE committee to report that ODx RS score, while prognostic, is not seen as being predictive of chemotherapy benefit. We believe the cost-effectiveness analysis relating to ODx chemo predictiveness is based on very uncertain data and therefore should not be weighted heavily in NICE's consideration to recommend the ODx test.<br>We believe it is has been made clear by multiple stakeholders including Agendia that the B20 study is very flawed, and overestimates chemotherapy benefit. We wish to ask, as it now has become clear that Genomic Health will present its TAILORx data for the intermediate risk group at ASCO in June 2018, whether the NICE committee will be taking these data into account for their cost-effectiveness assessment as this would then provide the best data available on ODx for the EAG to base their analysis on? | relative treatment effects for chemotherapy for EndoPredict, IHC4+C and Prosigna risk groups, and that data on MammaPrint suggest no difference in relative treatment effects for chemotherapy (section 5.5 of the diagnostics guidance).<br>Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category. It noted that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but will not respond to chemotherapy (section 5.13 of the diagnostics guidance). |
| 110 | Agendia N.V. | DAP37_comments_form2 | To address the magnitude of exaggeration of chemotherapy benefit in the B-20 dataset the NSABP statistician has developed Figure 14 . The figure depicts the 10-year risks of distant recurrence (solid line) and the associated 95% confidence intervals (dashed lines) for | Thank you for your comment which the committee considered. |

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| | | (version 19th April 2018)<br>Response to comments by NSABP-B20 Lead biostatistician<br>Comment number 148 regarding Section number 4.3.3, pages 97-112 | the B-20 tamoxifen alone arm, and the blue lines depict the 10-year risks of distant recurrence (solid line) and the associated 95% CI (dashed lines) for the B-14 tamoxifen alone arm. Depicted on the x-axis is the Recurrence Score (RS) which runs from zero to 50. | The committee concluded that the evidence on the extent to which tumour profiling tests are able to predict relative treatment effects for chemotherapy is highly uncertain, but there may be some differences between Oncotype DX risk groups. The committee noted that no data were available to assess a difference in relative treatment effects for chemotherapy for EndoPredict, IHC4+C and Prosigna risk groups, and that data on MammaPrint suggest no difference in relative treatment effects for chemotherapy (section 5.5 of the diagnostics guidance).<br>The EAG noted that their model tests different assumptions. 1) No prediction of relative treatment effect; 2) prediction of relative treatment effect purely based on B20 (LN-negative) or SWOG 8814 (LN-positive); and 3) prediction of relative treatment effect but with a lesser magnitude than in B20 (as B20 may overestimate this due to being the |

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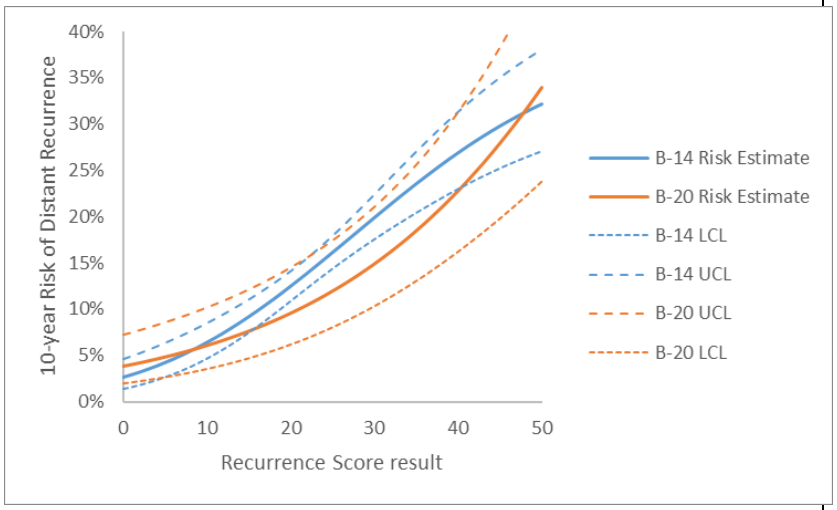
| | | | *Figure 14 – Ten-Year Risk of Distant Recurrence in Tamoxifen alone treated patients: Comparison of NSABP B-20 and NSABP B-14 (Submitted by NSABP-B20 Lead biostatistician 30JAN18)*<br>  <br><br>The statistician argues that the range of these distant recurrence risk estimates are very similar between NSABP B-20 and B-14. We want to make EAG aware that this figure actually shows the opposite, that the curves are very different.<br>Firstly, we want to draw the attention to the x-axis of Figure 14, which depicts the RS running from zero to 50. Oncotype Dx (ODx), as commercially marketed, has a RS that runs from zero to 100, | derivation set), using indirect comparison between B20 and B14 or TransATAC.<br>Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category, based on results from TAILORx. It noted that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but will not respond to chemotherapy (section 5.13 of the diagnostics guidance). |

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| | | | and the analysis of the commercial test is also based on the observations for RS > 50. However, many published analyses for ODx are based on a RS "per 50 units".<br><br>The Oncotype RS ranges from zero to 100, but as depicted on their patient test result form and in most publications the figures do not show Recurrence Scores over 50. In order to understand how reporting results based on binning of test results in 50-point differences is clinically meaningless, one should know how often patients have score exceeding a RS of 50.<br><br>With the ODX RS spanning from zero to 100, binning of RS every 50 units divides the test into two categories. When the RS is dichotomized into two bins (0-50 and 50-100) it is equivalent to comparing non-existing outliers to (almost) all the patients of the dataset (as outliers with ODx RS >50 hardly ever occur). The bin of 0-50 would contain the entire range of RS: low/moderate and high profile. So if the RS is included in an analysis "per 50 units" (See tables 2-4) this will always (per definition) give a significant result between groups.<br><br>What is observed in Figure 14 is that both datasets are fit with a quadratic/cubic curve, but each with a different pattern. The confidence intervals are very wide and are likely to be even wider for the range of RS not depicted (50-100). We find it questionable that the x-axis does not reflect the full range of RS scores from 0 to 100 (as in the commercial ODx test); we therefore would request | |

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that the statistician provide the EAG and all stakeholders with a graph with the full RS scores from 0-100.<br><br>
When depicting the 10 year risk of recurrence for low-risk patients for Intermediate, and for high-risk patients for both studies, then it becomes clear (see Table 7 below, and Table 6 in section 3 of “Addendum: EAG responses to key themes within the Comments on the Diagnostics Consultation Document, p12) that the recurrence risk for the low RS risk group in the B20 tamoxifen arm is 3.2%, much lower than the 6.8% recurrence risk in the B14 low Recurrence Score risk group. Whereas the risk of recurrence in the high RS risk group is much higher in the development series, 39.5% compared with 30.5% in the B14 validation series.<br><br>
So this explains how the curves can have the same tendency (low->higher->top) but the increases happen at a different point. It also becomes clear that patients in the low Recurrence Score risk group may actually have some benefit of chemotherapy, since the risk for recurrence decreases from 6.8% to 4.4%.<br><br>
Table 7. Comparison of Oncotype recurrence risk in B14 and B20
<table>
<tr><td rowspan="2">Oncotype Dx<br><br>RS score</td><td>NSABP-B14</td><td colspan="2">NSABP-B20</td></tr>
<tr><td>Tamoxifen treated</td><td>Tamoxifen treated</td><td>Tamo<br>+chemothera</td></tr>
</table>
</td><td></td></tr>
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<tr><td></td><td></td><td></td><td>
<table>
<tr><th></th><th>Recurrence Risk</th><th>Percentage of TAM treated patients in total study population (n)</th><th>Recurrence Risk</th><th>Percentage of TAM treated patients in total study population (n)</th><th>Recurrence Risk</th><th>Percentage of TAM+CT treated patients in total study population</th></tr>
<tr><td>Low RS</td><td>6.8%</td><td>51% (388)</td><td>3.2%</td><td>60% (135)</td><td>4.4%</td><td>51% (218)</td></tr>
<tr><td>Intermediate RS</td><td>14.3 %</td><td>22% (149)</td><td>9.1%</td><td>20% (45)</td><td>10.9%</td><td>21% (89)</td></tr>
<tr><td>High RS</td><td>30.5</td><td>27% (181)</td><td>39.5%</td><td>21% (47)</td><td>11.9%</td><td>28% (117)</td></tr>
</table>
The results in Table 7 are not mirrored in Figure 14, where B20 low RS patients have a higher risk than the B14 patients (is reversed in Figure 14), and B20 High Risk patients have a lower risk of distant recurrence than B14 patients High Risk (also the opposite of the curves in Figure 14).<br><br>In the SWOG8814 study by Alban et al. the only statistical significant result for the RS is a 50-point difference in RS which we have just argued above is clinically meaningless, since hardly any (close to zero) patients exist with a RS over 50. **No clinically relevant data exists today that Oncotype Dx is predictive for**</td><td></td></tr>
</table>

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| | | | **chemotherapy benefit.** NSABP-B20 is flawed because of the re-use of the development arm, and SWOG-8814 only shows a significant result when the RS is analyzed with a 50-point increment. The study should show the results for the Low Risk RS versus the intermediate/High RS patients.<br><br>In conclusion, we believe the cost-effectiveness analysis relating to ODx chemo predictiveness is based on very uncertain data. Figure 14 (submitted by the NSABP statistician) illustrates this uncertainty and is not supportive of the summary of the NSABP-B20 and B14 results in Table 7. We therefore believe that Figure 14 should not be weighted heavily in NICE's consideration to report that the ODx test is predictive for the benefit of chemotherapy. | |
| 111 | Association of Breast Surgery | Whole document | NICE continue to use an assumption that all patients benefit equally from chemotherapy, but this is not necessarily true, For example, Oncotype Dx seems to be identifying a group of patients who do not benefit from chemotherapy ie it is a predictive marker, not just a prognostic marker. If this is the case those with a low oncotype Dx score should not have chemotherapy even if they are in a poor prognostic group. Women may wish to know this information when they are involved in shared decision making with their oncologists. | Thank you for your comment which the committee considered.<br><br>Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category. It noted that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also |

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| | | | | identifies patients who will relapse but will not respond to chemotherapy (section 5.13 of the diagnostics guidance). |
| 112 | Association of Breast Surgery | Whole document | ABS believes one of the strongest cases in favour of tumour profiling is the saving of chemotherapy induced morbidity and mortality in those women who would otherwise potentially be prescribed this treatment. If assessment of the clinical utility of tumour profiling tests is limited to breast cancer survival only then the overwhelming benefit of avoiding chemotherapy induced morbidity will be missed. | Thank you for your comment which the committee considered.<br>The EAG model includes both chemotherapy harms and survival estimates. |
| 113 | CM-PATH | Diagnostic Assessment Report, p365, Table 129<br>Diagnostics Assessment Report, p351 | The document assumes equal benefit from chemotherapy across all patients. The practice in the UK shows that the majority of patients with a RS of less than 18 are spared chemotherapy. | Thank you for your comment which the committee considered.<br>When considering the results of TAILORx, the committee noted that in UK practice patients with recurrence scores of 11-25 may not receive chemotherapy routinely (section 5.6 of the diagnostics guidance). |
| 114 | Genomic Health | 1.1, DAR | • We welcome NICE's engagement with the NSABP regarding the additional analyses that they were able to provide since the first DCD, which reinforces the strength of evidence from the NSABP | Thank you for your comment which the committee considered. |

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| | | | B-20 trial of the ability of Oncotype DX to predict relative chemotherapy effect. | |
| 115 | Peony Breast Care Unit | 3.15 DCD | My colleagues and I remain very concerned that NICE still seems uncertain about the ability of OncotypeDX to predict chemotherapy benefit in spite of multiple trials and registry data* supporting this view. Several leading bio-statisticians including the lead from the NSABP B20 trial have confirmed their views to NICE, "*In summary, my colleagues and I at NSABP (currently part of the NRG Oncology) remain even more confident today than in 2006 that all the conclusions in the Paik NSABP B-20 publication in 2006 are strongly supported by evidence from all the studies."* (Comments 145-161 DAR responses). The only dissenter is Agendia whose view may be subject to commercial bias.<br><br>*NSABP b-14, NSABP B20, TransATAC, SWOG8814, ECOG 2197, NSABP-B28, PACS-01, PlanB, and the SEER and Clalit registry data. | Thank you for your comment which the committee considered.<br><br>The committee concluded that the evidence on the extent to which tumour profiling tests are able to predict relative treatment effects for chemotherapy is highly uncertain, but there may be some differences between Oncotype DX risk groups (section 5.5 of the diagnostics guidance). |
| 116 | Peony Breast Care Unit | Table 129 DAR | It appears that by using the proportionate benefit of chemotherapy as demonstrated in the Oxford overview of outdated information (mostly derived at a time when pathology was less well quality controlled,) rather than the modern view that chemotherapy sensitivity or resistance is dependent on tumour biology, the model used by NICE is rewarding the over use of chemotherapy to the detriment of many patients. It also gives an artificial advantage to the tests placing the greatest number of patients in the high risk | Thank you for your comment which the committee considered.<br><br>The EAG noted that their model tests different assumptions. 1) No prediction of relative treatment effect; 2) prediction of relative treatment effect purely based on B20 (LN-negative) or SWOG 8814 (LN-positive); and 3) prediction of relative |

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| | | | group. EBCTCG have themselves stressed that TailorX may well provide information on differential response rates which is another reason for awaiting the imminent reporting of this trial. | treatment effect but with a lesser magnitude than in B20 (as B20 may overestimate this due to being the derivation set), using indirect comparison between B20 and B14 or TransATAC. The committee concluded that although these analyses were associated with considerable uncertainty, they gave an indication of Oncotype DX's likely cost effectiveness if the relative treatment effects for chemotherapy did differ between Oncotype DX risk groups, but not to the extent reported in the Paik et al. (2006) study (section 5.13 of the diagnostics guidance).<br><br>Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category. It noted that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but |

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| | | | | will not respond to chemotherapy (section 5.13 of the diagnostics guidance). |
| 117 | Peony Breast Care Unit | General | Researchers are beginning to recognise that prognosis and chemotherapy benefit are not two side of the same coin but independent features of tumour biology. Prognosis reflects the point at which the diagnosis is made, the ability of the tumour to metastasis and tumour doubling time. Chemotherapy sensitivity reflects specifically disordered cellular control and a plasticity to develop resistance. HER2 positive disease is responsive to trastuzumab whatever the prognosis or stage at presentation. There is no reason to think chemotherapy response in ER positive breast cancer is not similar and an inherent property of the tumour at development (particularly since it is relatively biologically stable). Chemotherapy sensitivity is likely to be the same, independent of size, node status and metastatic status. This explains why clinic-pathological predictors are such poor predictors.<br><br>The EBCTCG meta-analyses of long-term outcome among 100,000 women in 123 randomised trials (Peto et al, Lancet 2012). Clinico-pathological features are simply a reflection of the time point at which the diagnosis is established (as with HER2 positive disease where response is independent of stage at presentation).<br><br>In the light of this understanding and the possibility that the TailorX will show no benefit to chemotherapy with an RS below 26, NICE | Thank you for your comment which the committee considered.<br><br>The committee concluded that the evidence on the extent to which tumour profiling tests are able to predict relative treatment effects for chemotherapy is highly uncertain, but there may be some differences between Oncotype DX risk groups (section 5.5 of the diagnostics guidance).<br><br>Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category. It noted that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also |

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| | | | could take the bold step of looking at OncotypeDX as a companion diagnostic for chemotherapy benefit versus endocrine therapy alone in breast cancer generally (including node positive and metastatic at presentation). This approach has the added benefit of identifying the small percentage (c 7%) of women who appear to be in the low risk category but who will (most importantly) avoid recurrence with early adjuvant chemotherapy. The cost analysis will be very different and almost certainly dominate current practice as well as substantially refining breast cancer care to the huge benefit of patients and the hard-pressed clinicians in the NHS. | identifies patients who will relapse but will not respond to chemotherapy (section 5.13 of the diagnostics guidance).<br><br>In people who are in the low clinical risk category (LN-negative disease and a NPI of 3.4 or less), the ICERs for EndoPredict and Prosigna compared with current practice were higher than those normally considered to be a cost-effective use of NHS resources (section 5.19 of the diagnostics guidance). |
| 118 | Royal College of Pathologists | | A comment made on the previous consultation however has still not been taken into account. The NICE document assumes that all patients have the same potential benefit from chemotherapy. This is not true (or at least controversial). The risk v/s benefit from chemotherapy use mus be taken into account | Thank you for your comment which the committee considered.<br><br>The committee concluded that the evidence on the extent to which tumour profiling tests are able to predict relative treatment effects for chemotherapy is highly uncertain, but there may be some differences between Oncotype DX risk groups (section 5.5 of the diagnostics guidance). |

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| | | | | The EAG noted that their model tests different assumptions. 1) No prediction of relative treatment effect; 2) prediction of relative treatment effect purely based on B20 (LN-negative) or SWOG 8814 (LN-positive); and 3) prediction of relative treatment effect but with a lesser magnitude than in B20 (as B20 may overestimate this due to being the derivation set), using indirect comparison between B20 and B14 or TransATAC.<br><br>Following the Sparano et al. 2018 publication on TAILORx the EAG repeated the analysis incorporating an additional assumption of zero chemotherapy benefit for patients in the Oncotype DX low recurrence score category. It noted that this analysis is based on the strong assumption that Oncotype DX not only identifies patients who will not relapse, but also identifies patients who will relapse but will not respond to chemotherapy |

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| | | | | (section 5.13 of the diagnostics guidance). |

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**THEME: EAG economic model**

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| 119 | Agendia N.V. | Addendum: EAG responses to key themes within the Comments on the Diagnostics Consultation Document,version April 2018<br><br>Section 8.1, p26)<br><br>(p538 in DAP 37 Evaluation report 12042018 [no ACIC].pdf) | *EAG response to themes with the comments on DCD: p26 section **8.1. "Re-analysis of MammaPrint by Agendia within the EAG model***<br><br>*Agendia have undertaken a re-analysis of the cost-effectiveness of MammaPrint using the EAG model "with corrected usage of available MammaPrint data in those instances where we [Agendia] strongly disagree with the chosen inputs in the current model." With respect to this analysis, the company claims that on the basis of altered model inputs, the ICER for MammaPrint is now less than £30,000 per QALY gained. However, the EAG notes that within the company's re-analysis, chemotherapy is assumed to be associated with no additional benefit in terms of DRFS for any patient population (including those with clinical-high MammaPrint-high risk). If this was the case, genomic testing would have no value as clinicians would never give chemotherapy to any patient. The EAG considers Agendia's re-analysis of the EAG model to be inappropriate and believes that the results are not meaningful."*<br><br>With all due respect to the EAG health economic team, we would like to clarify, in the Cardoso et al., 2016 publication the authors find that there is a non-significant benefit of chemotherapy in the **discordant groups only** in terms of DMFS. However, contrary to what is stated above, **adjuvant chemotherapy does in fact provide benefit** in terms of DRFS/DMFS in patients that are concordant in their tumor's high-risk classification, i.e. **clinical-high risk as well as MammaPrint high-risk.** This can also be observed in the data presented by Knauer et al., 2010. In this study, MammaPrint high risk patients had a distant disease-free survival (DDFS - defined as time from surgery to any distant metastasis) of 76% with endocrine therapy only versus 88% in patients that received both endocrine as well as chemotherapy (HR of 0.35 (95% CI 0.17–0.71; P<0.01)), **indicating significant survival benefit by adding CT in the MammaPrint high risk** | Thank you for your comment which the committee considered. |

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**THEME: EAG economic model**

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| | | | **group**. This value is very similar to the 76.6% DMFS estimated by the EAG for the clinical -high MammaPrint-high-risk no chemotherapy group. | |
| 120 | Agendia N.V. | **Section 5.3 Independent economic evaluation (**EAG model) in DAR2 (version 19th April 2018)<br>(theme: EAG model, general comment) | In the previous consultation (Jan-April 2018) we reasoned that MammaPrint was not cost-effective in the EAG model for the mAOL high-risk subgroup was because the EAG did not model the uncertainty surrounding the non-significant chemotherapy benefit in the mAOL high-risk/MammaPrint low-risk group for chemotherapy versus no chemotherapy. However, since the previous consultation period we believe we have found a programming error resulting in incorrect patient classification probabilities. We note that correction of this error results in MammaPrint being cost-effective; please read comment [121] and follow by reading comment [122] for further details.<br>However we wish the EAG to note that we still believe that the uncertainty of the non-significant chemotherapy benefit in the discordant risk groups (mAOL high-risk/MammaPrint low-risk, and mAOL low-risk/MammaPrint high-risk) should also be taken into account in the probabilistic model. | Thank you for your comment which the committee considered.<br>The EAG noted that the change made by the company introduces an error which makes the results invalid. |
| 121 | Agendia N.V. | **DAR2 Section 5.3** EAG model (version 19th April 2018) | We would like to address what we believe is a simple programming error in the original EAG model, which results in input of incorrect patient numbers from the MINDACT trial.<br>When we correct the programming error, MammaPrint is shown to be cost-effective in the ITT MINDACT population and dominating current practice in the mAOL high-risk analysis. We would like the EAG to note that this corrected EAG model does take into account the additional non-significant chemotherapy benefit seen in the different patient | Thank you for your comment which the committee considered. |

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| | | (theme: Deterministic analysis) | subgroups where a discordant risk classification was observed between clinical and genomic risk assessment. More specifically, the 1.5 % non-significant difference in the chemotherapy treated clinical high-risk/MammaPrint low risk group, and the non-significant 0.8% benefit in terms of DMFS in the chemotherapy treated clinical-low/MammaPrint high-risk group. Please find below a detailed explanation plus correction of this error:<br><br>We believe the EAG model does not input the correct classification probabilities (i.e. numbers of patients and proportion of patients) that fall into the genomic and clinical risk groups properly and this profoundly affects the outcome of the cost-effectiveness analysis. This classification error is found in the deterministic model as well as the probabilistic model. Correction of this results in MammaPrint being cost-effective (see comment [121] and comment [122]). Please find attached an updated version of the EAG model with the corrected values.<br><br>File name: **DAP37EAGModel_Agendia10MAY18.xlsx**<br><br>**Deterministic model**<br><br>The EAG model examines the cost-effectiveness of MammaPrint (genomic risk classification) versus the comparator modified Adjuvant! Online (mAOL) (clinical risk classification). The Parameters worksheet informs the deterministic analysis of MammaPrint and uses linked cells to pull data from the Premodel worksheet. In the Parameters worksheet the cells displaying the numbers of patients in each clinical and genomic risk category are located in cells B15:I35.<br><br>**Mislabelling of classification probabilities** | The EAG noted that the change made by the company introduces an error which makes the results invalid.<br><br>The change results in different numbers of patients within each genomic risk classification subgroup between the test and no test groups. This means that the model is no longer |

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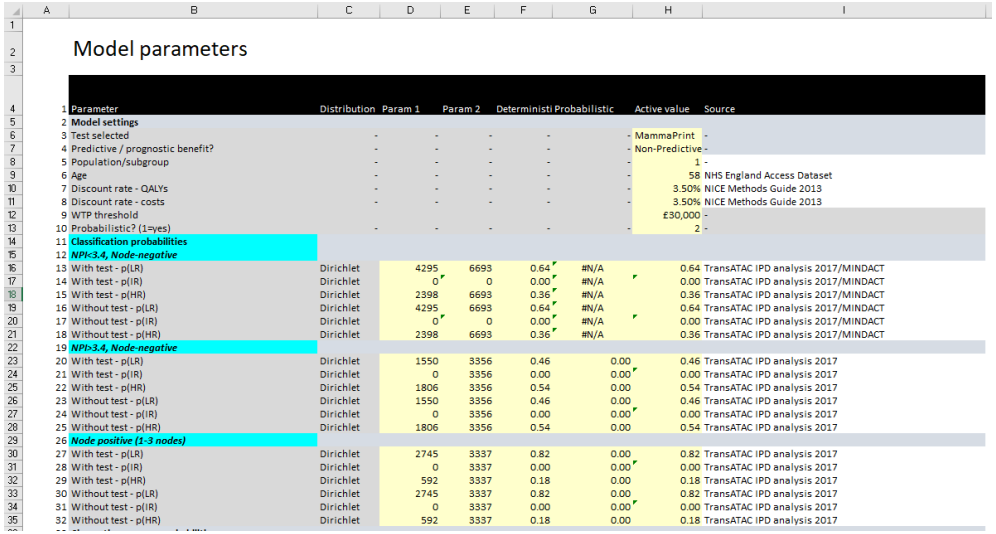
| | | | Firstly, the titles for the three classification probabilities are mislabelled. Looking from the Parameters worksheet back through the linked cells to the Premodel worksheet we were able to trace back how they should be labelled. In Figure we have highlighted the mislabelled cells in blue.<br>*Figure 2: Mislabelled cells in EAG model Parameters worksheet*<br>  <br>Model parameters<br>Parameter / Distribution / Param 1 / Param 2 / Deterministi / Probabilistic / Active value / Source<br>Model settings<br>Test selected - - - - - MammaPrint -<br>Predictive / prognostic benefit? - - - - - Non-Predictive -<br>Population/subgroup - - - - - 1 -<br>Age - - - - - 58 NHS England Access Dataset<br>Discount rate - QALYs - - - - - 3.50% NICE Methods Guide 2013<br>Discount rate - costs - - - - - 3.50% NICE Methods Guide 2013<br>WTP threshold £30,000 -<br>Probabilistic? (1=yes) - - - - - 2 -<br>Classification probabilities<br>*NPI<3.4, Node-negative*<br>With test - p(LR) Dirichlet 4295 6693 0.64 #N/A 0.64 TransATAC IPD analysis 2017/MINDACT<br>With test - p(IR) Dirichlet 0 0 0.00 #N/A 0.00 TransATAC IPD analysis 2017/MINDACT<br>With test - p(HR) Dirichlet 2398 6693 0.36 #N/A 0.36 TransATAC IPD analysis 2017/MINDACT<br>Without test - p(LR) Dirichlet 4295 6693 0.64 #N/A 0.64 TransATAC IPD analysis 2017/MINDACT<br>Without test - p(IR) Dirichlet 0 0 0.00 #N/A 0.00 TransATAC IPD analysis 2017/MINDACT<br>Without test - p(HR) Dirichlet 2398 6693 0.36 #N/A 0.36 TransATAC IPD analysis 2017/MINDACT<br>*NPI>3.4, Node-negative*<br>With test - p(LR) Dirichlet 1550 3356 0.46 0.00 0.46 TransATAC IPD analysis 2017<br>With test - p(IR) Dirichlet 0 3356 0.00 0.00 0.00 TransATAC IPD analysis 2017<br>With test - p(HR) Dirichlet 1806 3356 0.54 0.00 0.54 TransATAC IPD analysis 2017<br>Without test - p(LR) Dirichlet 1550 3356 0.46 0.00 0.46 TransATAC IPD analysis 2017<br>Without test - p(IR) Dirichlet 0 3356 0.00 0.00 0.00 TransATAC IPD analysis 2017<br>Without test - p(HR) Dirichlet 1806 3356 0.54 0.00 0.54 TransATAC IPD analysis 2017<br>*Node positive (1-3 nodes)*<br>With test - p(LR) Dirichlet 2745 3337 0.82 0.00 0.82 TransATAC IPD analysis 2017<br>With test - p(IR) Dirichlet 0 3337 0.00 0.00 0.00 TransATAC IPD analysis 2017<br>With test - p(HR) Dirichlet 592 3337 0.18 0.00 0.18 TransATAC IPD analysis 2017<br>Without test - p(LR) Dirichlet 2745 3337 0.82 0.00 0.82 TransATAC IPD analysis 2017<br>Without test - p(IR) Dirichlet 0 3337 0.00 0.00 0.00 TransATAC IPD analysis 2017<br>Without test - p(HR) Dirichlet 592 3337 0.18 0.00 0.18 TransATAC IPD analysis 2017<br>As shown in Figure , in the Parameters worksheet cell B15 is titled “NPI<3.4, Node-negative” but this analysis actually corresponds to the “MINDACT ITT population” | comparing like-with-like and in this instance the bias works in favour of the MammaPrint test.<br>The EAG agrees that the labelling in the model could have been corrected. The results are however unaffected by this. |

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| | | | analysis. For cell B22 “NPI>3.4, Node-negative” corresponds to the “mAOL high-risk” analysis. For cell B29 “Node positive (1-3 nodes)” corresponds to the “mAOL low-risk” analysis.<br><br>For clarity, we have corrected the labelling in the EAG model using red text for the updated label, and black strikethrough formatting indicates the old label. As a minor point in the Parameters worksheet in cells I23-35, we believe the cell labels should also indicate that the data source is MINDACT, not TransATAC so we have also corrected this in red text.<br><br>For clarity we will refer to the corrected cell labels for the rest of the text below, and the updated cells are shown in Figure 3 in red. | |

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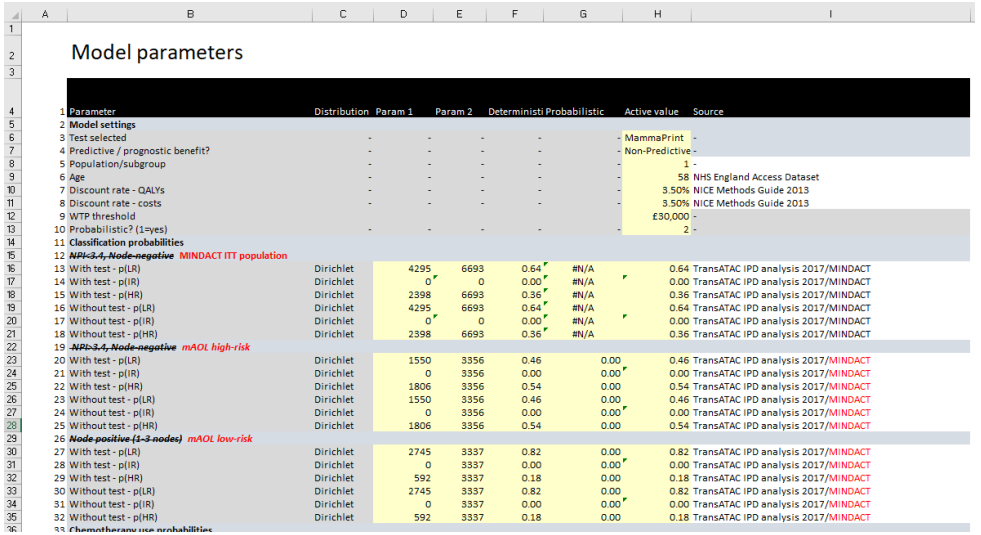
| | | | | |
|---|---|---|---|---|
| | | | *Figure 3 - Corrected cell labels for Parameters worksheet*<br>  <br>Model parameters<br>1 Parameter / Distribution / Param 1 / Param 2 / Deterministi / Probabilistic / Active value / Source<br>2 **Model settings**<br>3 Test selected - - - - - MammaPrint -<br>4 Predictive / prognostic benefit? - - - - - Non-Predictive -<br>5 Population/subgroup - - - - - 1 -<br>6 Age - - - - - 58 NHS England Access Dataset<br>7 Discount rate - QALYs - - - - - 3.50% NICE Methods Guide 2013<br>8 Discount rate - costs - - - - - 3.50% NICE Methods Guide 2013<br>9 WTP threshold £30,000 -<br>10 Probabilistic? (1=yes) - - - - - 2 -<br>11 **Classification probabilities**<br>12 ~~**NPI<3.4, Node-negative**~~ MINDACT ITT population<br>13 With test - p(LR) Dirichlet 4295 6693 0.64 #N/A 0.64 TransATAC IPD analysis 2017/MINDACT<br>14 With test - p(IR) Dirichlet 0 0 0.00 #N/A 0.00 TransATAC IPD analysis 2017/MINDACT<br>15 With test - p(HR) Dirichlet 2398 6693 0.36 #N/A 0.36 TransATAC IPD analysis 2017/MINDACT<br>16 Without test - p(LR) Dirichlet 4295 6693 0.64 #N/A 0.64 TransATAC IPD analysis 2017/MINDACT<br>17 Without test - p(IR) Dirichlet 0 0 0.00 #N/A 0.00 TransATAC IPD analysis 2017/MINDACT<br>18 Without test - p(HR) Dirichlet 2398 6693 0.36 #N/A 0.36 TransATAC IPD analysis 2017/MINDACT<br>19 ~~**NPI<3.4, Node-negative**~~ *mAOL high-risk*<br>20 With test - p(LR) Dirichlet 1550 3356 0.46 0.00 0.46 TransATAC IPD analysis 2017/MINDACT<br>21 With test - p(IR) Dirichlet 0 3356 0.00 0.00 0.00 TransATAC IPD analysis 2017/MINDACT<br>22 With test - p(HR) Dirichlet 1806 3356 0.54 0.00 0.54 TransATAC IPD analysis 2017/MINDACT<br>23 Without test - p(LR) Dirichlet 1550 3356 0.46 0.00 0.46 TransATAC IPD analysis 2017/MINDACT<br>24 Without test - p(IR) Dirichlet 0 3356 0.00 0.00 0.00 TransATAC IPD analysis 2017/MINDACT<br>25 Without test - p(HR) Dirichlet 1806 3356 0.54 0.00 0.54 TransATAC IPD analysis 2017/MINDACT<br>26 ~~**Node positive (1-3 nodes)**~~ *mAOL low-risk*<br>27 With test - p(LR) Dirichlet 2745 3337 0.82 0.00 0.82 TransATAC IPD analysis 2017/MINDACT<br>28 With test - p(IR) Dirichlet 0 3337 0.00 0.00 0.00 TransATAC IPD analysis 2017/MINDACT<br>29 With test - p(HR) Dirichlet 592 3337 0.18 0.00 0.18 TransATAC IPD analysis 2017/MINDACT<br>30 Without test - p(LR) Dirichlet 2745 3337 0.82 0.00 0.82 TransATAC IPD analysis 2017/MINDACT<br>31 Without test - p(IR) Dirichlet 0 3337 0.00 0.00 0.00 TransATAC IPD analysis 2017/MINDACT<br>32 Without test - p(HR) Dirichlet 592 3337 0.18 0.00 0.18 TransATAC IPD analysis 2017/MINDACT<br>33 Chemotherapy use probabilities<br>**Classification probabilities: Patient number inputs and risk group proportions**<br>In the Cardoso et al., 2016 publication “Clinical risk” is used to refer to mAOL (i.e. “Without test”) while “Genomic risk” is used to refer to MammaPrint (i.e. “With test”). In the EAG model the following labelling is used to direct to either the high risk (p(HR)) or low-risk (p(LR)) classification probabilities. | |

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| | | | For MammaPrint there are 4 relevant inputs “With test - p(LR)”, “With test - p(HR)”, “Without test - p(LR)” and “Without test - p(HR)”. “With test” corresponds to the number as well as proportion of patients classified with MammaPrint as either High, or Low Risk, and “Without test” refers to the values for patients classified with the mAOL comparator as clinically high or low risk. Column D (labelled “Param 1”) refers to the number of patients in each risk group, while column F (Deterministic) and G (Probabilistic) refer to the proportion of patients in that risk group out of the total (shown in column E).<br><br>In the EAG model, in cells B15:I35 of the Parameters worksheet we can see errors in the patient number inputs. In Figure 4 , these cells are highlighted in blue. Incorrect patient numbers in column D are mirrored by incorrect patient number proportions in column F, and these cells are highlighted in green. | |

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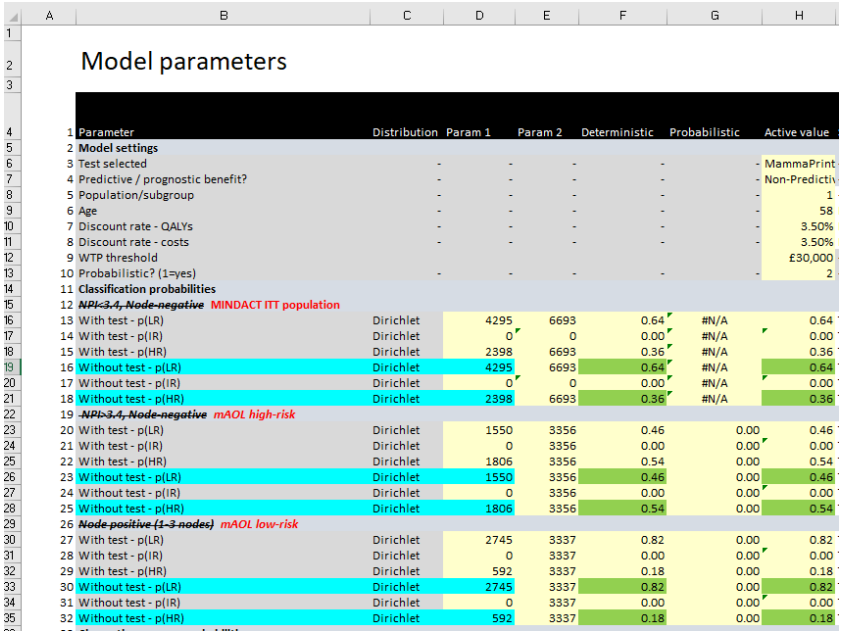
| | | | | |
|---|---|---|---|---|
| | | | *Figure 4 - Incorrect patient number inputs (blue) and incorrect proportions (green)*<br>  <br>As shown in Figure 4 , all the incorrect inputs correspond to the “Without-test” (mAOL/clinical risk only) risk classifications.<br>**Correct inputs for MammaPrint based on Cardoso et al., 2016** | |

Model parameters

| Parameter | Distribution | Param 1 | Param 2 | Deterministic | Probabilistic | Active value |
|---|---|---|---|---|---|---|
| **Model settings** | | | | | | |
| Test selected | - | - | - | - | - | MammaPrint |
| Predictive / prognostic benefit? | - | - | - | - | - | Non-Predicti |
| Population/subgroup | - | - | - | - | - | 1 |
| Age | - | - | - | - | - | 58 |
| Discount rate - QALYs | - | - | - | - | - | 3.50% |
| Discount rate - costs | - | - | - | - | - | 3.50% |
| WTP threshold | | | | | | £30,000 |
| Probabilistic? (1=yes) | - | - | - | - | - | 2 |
| **Classification probabilities** | | | | | | |
| ~~***NPI<3.4, Node-negative***~~ MINDACT ITT population | | | | | | |
| With test - p(LR) | Dirichlet | 4295 | 6693 | 0.64 | #N/A | 0.64 |
| With test - p(IR) | Dirichlet | 0 | 0 | 0.00 | #N/A | 0.00 |
| With test - p(HR) | Dirichlet | 2398 | 6693 | 0.36 | #N/A | 0.36 |
| Without test - p(LR) | Dirichlet | 4295 | 6693 | 0.64 | #N/A | 0.64 |
| Without test - p(IR) | Dirichlet | 0 | 0 | 0.00 | #N/A | 0.00 |
| Without test - p(HR) | Dirichlet | 2398 | 6693 | 0.36 | #N/A | 0.36 |
| ~~***NPI>3.4, Node-negative***~~ *mAOL high-risk* | | | | | | |
| With test - p(LR) | Dirichlet | 1550 | 3356 | 0.46 | 0.00 | 0.46 |
| With test - p(IR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 |
| With test - p(HR) | Dirichlet | 1806 | 3356 | 0.54 | 0.00 | 0.54 |
| Without test - p(LR) | Dirichlet | 1550 | 3356 | 0.46 | 0.00 | 0.46 |
| Without test - p(IR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 |
| Without test - p(HR) | Dirichlet | 1806 | 3356 | 0.54 | 0.00 | 0.54 |
| ~~***Node positive (1-3 nodes)***~~ *mAOL low-risk* | | | | | | |
| With test - p(LR) | Dirichlet | 2745 | 3337 | 0.82 | 0.00 | 0.82 |
| With test - p(IR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 |
| With test - p(HR) | Dirichlet | 592 | 3337 | 0.18 | 0.00 | 0.18 |
| Without test - p(LR) | Dirichlet | 2745 | 3337 | 0.82 | 0.00 | 0.82 |
| Without test - p(IR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 |
| Without test - p(HR) | Dirichlet | 592 | 3337 | 0.18 | 0.00 | 0.18 |

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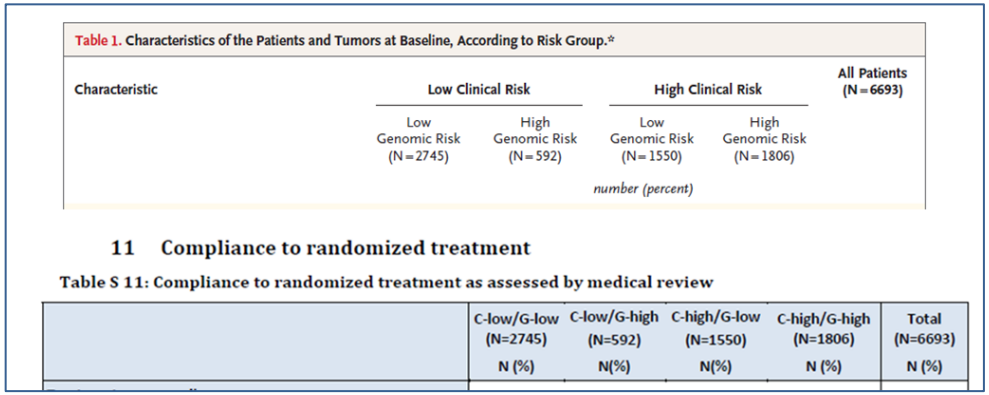
| | | | Table 1 of Cardoso et al., 2016 shows the number of patients in each clinical (mAOL) and genomic (MammaPrint) risk group. These numbers are the same as data shown in Table S11 (which the EAG uses to inform their model).<br><br>As shown in Figure 5 , the tables illustrate how within the Low Clinical Risk (mAOL low-risk) group there are 2745 low-genomic risk patients and 592 high-genomic risk patients. Therefore, the mAOL low-risk group contains a total of 3337 patients. Within the High Clinical Risk (mAOL high-risk) group there are 1550 low-genomic risk patients and 1806 high-genomic risk patients, and therefore the mAOL high-risk group contains total of 3356 patients. Please see the tables below:<br><br>*Figure 5 - MINDACT patient numbers per clinical and genomic risk classification (Cardoso et al., 2016)*<br><br>  <br>Table 1. Characteristics of the Patients and Tumors at Baseline, According to Risk Group.*<br>Characteristic \| Low Clinical Risk: Low Genomic Risk (N=2745), High Genomic Risk (N=592) \| High Clinical Risk: Low Genomic Risk (N=1550), High Genomic Risk (N=1806) \| All Patients (N=6693)<br>number (percent)<br><br>11 Compliance to randomized treatment<br>Table S 11: Compliance to randomized treatment as assessed by medical review<br>C-low/G-low (N=2745) N (%) \| C-low/G-high (N=592) N(%) \| C-high/G-low (N=1550) N(%) \| C-high/G-high (N=1806) N (%) \| Total (N=6693) N (%) | |

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
To summarise this clearly, we have included this data in Table 2 below, indicating that the Without-test low-risk group contains 3337 patients, and the Without-test high-risk group contains 3356 patients.<br><br>
Table 2 – Summary of mAOL risk group patient numbers
<table>
<tr><td>”Without-test” group</td><td>N in group</td><td>Percent of total patients (N=6693) in MINDACT</td></tr>
<tr><td>mAOL low-risk / Without-test low-risk</td><td>C-low/G-low + C-low/G-high<br>(2745+592) = 3337</td><td>49.9%</td></tr>
<tr><td>mAOL high-risk / Without-test high-risk</td><td>C-high/G-high + C-high/G-low<br>(1806+1550) = 3356</td><td>50.1%</td></tr>
</table>
It is important to note that the mAOL low-risk / Without-test low-risk group cannot contain any mAOL high-risk patients as all patients in this group are mAOL low-risk.(i.e. for mAOL low-risk Without test p(HR) = 0). Similarly, the mAOL high-risk/ Without-test high risk group contains zero mAOL low-risk patients as by definition it is the mAOL high-risk group.<br><br>
Referring back to the Parameters sheet in the EAG model it is therefore clear that the patient numbers highlighted in blue and green in Figure 4 do not reflect the MINDACT data and should be corrected to correctly represent the risk classification in the “Without-test” situation.<br><br>
Correct inputs for MammaPrint in the EAG model
</td><td></td></tr>
</table>

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
To correct the error in the patient numbers for the comparator/mAOL/“Without-test” patient risk groups, we have updated these cells for the “MINDACT ITT population”, “mAOL high-risk” and “mAOL low-risk” analyses in the Parameters worksheet. The corrected patient input values for the Parameters worksheet are summarised in Table 3. The updated values are also shown (in red) in the Parameters worksheet in Figure 6 below.
<br><br>
Table 3 – Correct patient number inputs for MammaPrint in EAG model Parameters worksheet
<table>
<tr><td></td><td>Column B</td><td>Column D</td><td>Column E</td><td>Column F</td><td>Column H</td></tr>
<tr><td></td><td>Classification probabilities</td><td>Parameter 1</td><td>Parameter 2</td><td>Deterministic</td><td>Active value<br>(for deterministic analysis)</td></tr>
<tr><td>Row 15</td><td colspan="5">MINDACT ITT population</td></tr>
<tr><td>Row 16</td><td>With test – p(LR)</td><td>4295</td><td>6693</td><td>0.64</td><td>0.64</td></tr>
<tr><td>Row 18</td><td>With test – p(HR)</td><td>2398</td><td>6693</td><td>0.36</td><td>0.36</td></tr>
<tr><td>Row 19</td><td>Without test – p(LR)</td><td>3337</td><td>6693</td><td>0.50</td><td>0.50</td></tr>
<tr><td>Row 21</td><td>Without test – p(HR)</td><td>3356</td><td>6693</td><td>0.50</td><td>0.50</td></tr>
<tr><td>Row 22</td><td colspan="5">mAOL high-risk</td></tr>
<tr><td>Row 23</td><td>With test – p(LR)</td><td>1150</td><td>3356</td><td>0.46</td><td>0.46</td></tr>
<tr><td>Row 25</td><td>With test – p(HR)</td><td>1806</td><td>3356</td><td>0.54</td><td>0.54</td></tr>
</table>
</td><td></td></tr>
</table>

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|---|---|---|---|---|---|---|---|---|---|
| | | | Row 26 | Without test – p(LR) | **0** | 3356 | **0.00** | **0.00** | |
| | | | Row 28 | Without test – p(HR) | **3356** | 3356 | **1.00** | **1.00** | |
| | | | Row 29 | **mAOL low-risk** | | | | | |
| | | | Row 30 | With test – p(LR) | 2745 | 3337 | 0.82 | 0.82 | |
| | | | Row 32 | With test – p(HR) | 592 | 3337 | 0.18 | 0.18 | |
| | | | Row 33 | Without test – p(LR) | **3337** | 3337 | **1.00** | **1.00** | |
| | | | Row 35 | Without test – p(HR) | **0** | 3337 | **0.00** | **0.00** | |

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*Figure 6 - Corrected classification probability inputs*

Model parameters

| Parameter | Distribution | Param 1 | Param 2 | Deterministic | Probabilistic | Active value | Source |
|---|---|---|---|---|---|---|---|
| **Model settings** | | | | | | | |
| Test selected | - | - | - | - | - | MammaPrint | - |
| Predictive / prognostic benefit? | - | - | - | - | - | Non-Predictive | - |
| Population/subgroup | - | - | - | - | - | 1 | - |
| Age | - | - | - | - | - | 58 | NHS England Access Dataset |
| Discount rate - QALYs | - | - | - | - | - | 3.50% | NICE Methods Guide 2013 |
| Discount rate - costs | - | - | - | - | - | 3.50% | NICE Methods Guide 2013 |
| WTP threshold | | | | | | £30,000 | - |
| Probabilistic? (1=yes) | - | - | - | - | - | 2 | - |
| **Classification probabilities** | | | | | | | |
| ~~*NPI<3.4, Node-negative*~~ *MINDACT ITT population* | | | | | | | |
| With test - p(LR) | Dirichlet | 4295 | 6693 | 0.64 | #N/A | 0.64 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(IR) | Dirichlet | 0 | 0 | 0.00 | #N/A | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(HR) | Dirichlet | 2398 | 6693 | 0.36 | #N/A | 0.36 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(LR) | Dirichlet | 3337 | 6693 | 0.50 | #N/A | 0.50 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(IR) | Dirichlet | 0 | 0 | 0.00 | #N/A | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(HR) | Dirichlet | 3356 | 6693 | 0.50 | #N/A | 0.50 | TransATAC IPD analysis 2017/MINDACT |
| ~~*NPI>3.4, Node-negative*~~ *mAOL high-risk* | | | | | | | |
| With test - p(LR) | Dirichlet | 1550 | 3356 | 0.46 | 0.00 | 0.46 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(IR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(HR) | Dirichlet | 1806 | 3356 | 0.54 | 0.00 | 0.54 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(LR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(IR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(HR) | Dirichlet | 3356 | 3356 | 1.00 | 0.00 | 1.00 | TransATAC IPD analysis 2017/MINDACT |
| ~~*Node positive (1-3 nodes)*~~ *mAOL low-risk* | | | | | | | |
| With test - p(LR) | Dirichlet | 2745 | 3337 | 0.82 | 0.00 | 0.82 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(IR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(HR) | Dirichlet | 592 | 3337 | 0.18 | 0.00 | 0.18 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(LR) | Dirichlet | 3337 | 3337 | 1.00 | 0.00 | 1.00 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(IR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(HR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |

**Deterministic Results – MammaPrint is now cost-effective**

When the patient numbers and proportions are corrected as shown in above Table 3 and Figure 6, we now find that MammaPrint is cost-effective below a QALY threshold of £20,000. As shown in Figure 7, MammaPrint is dominating over mAOL/current practice in the mAOL high-risk analysis and is cost-effective with an ICER of ~£17,500 in the

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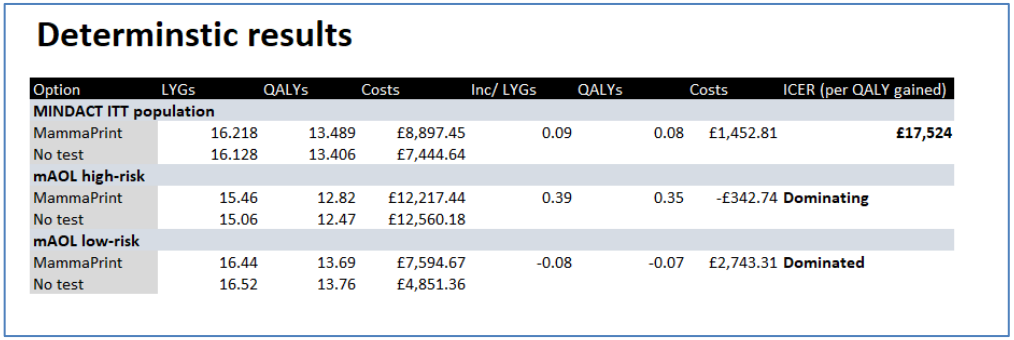
| | | | MINDACT ITT population. In the mAOL low-risk analysis MammaPrint is dominated by current practice.<br>*Figure 7 - Corrected deterministic results*<br>  | |

**Determinstic results**

| Option | LYGs | QALYs | Costs | Inc/ LYGs | QALYs | Costs | ICER (per QALY gained) |
|---|---|---|---|---|---|---|---|
| **MINDACT ITT population** | | | | | | | |
| MammaPrint | 16.218 | 13.489 | £8,897.45 | 0.09 | 0.08 | £1,452.81 | **£17,524** |
| No test | 16.128 | 13.406 | £7,444.64 | | | | |
| **mAOL high-risk** | | | | | | | |
| MammaPrint | 15.46 | 12.82 | £12,217.44 | 0.39 | 0.35 | -£342.74 | **Dominating** |
| No test | 15.06 | 12.47 | £12,560.18 | | | | |
| **mAOL low-risk** | | | | | | | |
| MammaPrint | 16.44 | 13.69 | £7,594.67 | -0.08 | -0.07 | £2,743.31 | **Dominated** |
| No test | 16.52 | 13.76 | £4,851.36 | | | | |

**Deterministic sensitivity analyses**

When we now perform the deterministic sensitivity analyses as shown in Figure 8 below, correction of the patient number parameter inputs in the EAG model results in MammaPrint dominating current practice in 18 out of 22 sensitivity analysis scenarios and being cost effective with ICERs <£1000 in the remaining 4 out of 22 analyses.

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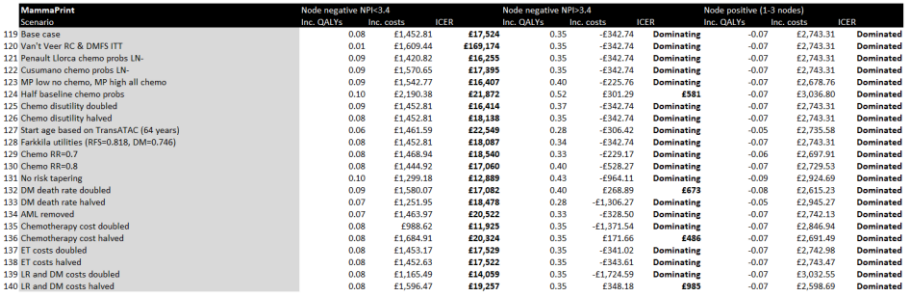
| | | | *Figure 8- Corrected Deterministic sensitivity analysis results*<br>  <br>**Conclusion**<br>Correction of the patient input numbers and proportions in the EAG model results in MammaPrint dominating current practice in the mAOL high-risk and being cost-effective (below £20K threshold) in the MINDACT ITT population respectively. MammaPrint is also cost-effective in all deterministic sensitivity analysis scenarios (and dominating in 18 out of 22 scenarios) We hope the EAG agrees with these corrections as suggested by us and will report the corrected results in the final guidance report. | |
| 122 | Agendia N.V. | DAR2 (version 19th April 2018)<br><br>Section 5.3 - EAG model | **EAG Probabilistic model**<br>As detailed in comment [121] we discovered an error in the classification probabilities (patient numbers and proportions) for the "Without-test" risk groups. Patient input numbers were corrected previously, so for the probabilistic model the remaining errors are located in column G of the Parameters worksheet as shown in Figure 9 (highlighted | Thank you for your comment which the committee considered. |

| MammaPrint | Node negative NPI<3.4 | | | Node negative NPI>3.4 | | | Node positive (1-3 nodes) | | |
|---|---|---|---|---|---|---|---|---|---|
| Scenario | Inc. QALYs | Inc. costs | ICER | Inc. QALYs | Inc. costs | ICER | Inc. QALYs | Inc. costs | ICER |
| 119 Base case | 0.08 | £1,452.81 | **£17,524** | 0.35 | -£342.74 | Dominating | -0.07 | £2,743.31 | Dominated |
| 120 Van't Veer RC & DMFS ITT | 0.01 | £1,609.44 | **£169,174** | 0.35 | -£342.74 | Dominating | -0.07 | £2,743.31 | Dominated |
| 121 Penault Llorca chemo probs LN- | 0.09 | £1,420.82 | **£16,255** | 0.35 | -£342.74 | Dominating | -0.07 | £2,743.31 | Dominated |
| 122 Cusumano chemo probs LN- | 0.09 | £1,570.65 | **£17,395** | 0.35 | -£342.74 | Dominating | -0.07 | £2,743.31 | Dominated |
| 123 MP low no chemo, MP high all chemo | 0.09 | £1,542.77 | **£16,407** | 0.40 | -£225.76 | Dominating | -0.07 | £2,678.76 | Dominated |
| 124 Half baseline chemo probs | 0.10 | £2,190.38 | **£21,872** | 0.52 | £301.29 | **£581** | -0.07 | £3,036.80 | Dominated |
| 125 Chemo disutility doubled | 0.09 | £1,452.81 | **£16,414** | 0.37 | -£342.74 | Dominating | -0.07 | £2,743.31 | Dominated |
| 126 Chemo disutility halved | 0.08 | £1,452.81 | **£18,188** | 0.35 | -£342.74 | Dominating | -0.07 | £2,743.31 | Dominated |
| 127 Start age based on TransATAC (64 years) | 0.06 | £1,461.59 | **£22,549** | 0.28 | -£306.42 | Dominating | -0.05 | £2,735.58 | Dominated |
| 128 Farkkila utilities (RFS=0.818, DM=0.746) | 0.08 | £1,452.81 | **£18,087** | 0.34 | -£342.74 | Dominating | -0.07 | £2,743.31 | Dominated |
| 129 Chemo RR=0.7 | 0.08 | £1,468.94 | **£18,540** | 0.33 | -£229.17 | Dominating | -0.06 | £2,697.91 | Dominated |
| 130 Chemo RR=0.8 | 0.08 | £1,444.92 | **£17,060** | 0.40 | -£528.27 | Dominating | -0.07 | £2,729.53 | Dominated |
| 131 No risk tapering | 0.10 | £1,299.18 | **£12,889** | 0.43 | -£964.11 | Dominating | -0.09 | £2,924.69 | Dominated |
| 132 DM death rate doubled | 0.09 | £1,580.07 | **£17,082** | 0.40 | £268.89 | **£673** | -0.08 | £2,615.23 | Dominated |
| 133 DM death rate halved | 0.07 | £1,251.95 | **£18,478** | 0.28 | -£1,306.27 | Dominating | -0.05 | £2,945.27 | Dominated |
| 134 AML removed | 0.07 | £1,463.97 | **£20,522** | 0.33 | -£328.50 | Dominating | -0.07 | £2,742.13 | Dominated |
| 135 Chemotherapy cost doubled | 0.08 | £988.62 | **£11,925** | 0.35 | -£1,371.54 | Dominating | -0.07 | £2,846.94 | Dominated |
| 136 Chemotherapy cost halved | 0.08 | £1,684.91 | **£20,324** | 0.35 | £171.66 | **£486** | -0.07 | £2,691.49 | Dominated |
| 137 ET costs doubled | 0.08 | £1,453.17 | **£17,529** | 0.35 | -£341.02 | Dominating | -0.07 | £2,742.98 | Dominated |
| 138 ET costs halved | 0.08 | £1,452.63 | **£17,522** | 0.35 | -£343.61 | Dominating | -0.07 | £2,743.47 | Dominated |
| 139 LR and DM costs doubled | 0.08 | £1,165.49 | **£14,059** | 0.35 | -£1,724.59 | Dominating | -0.07 | £3,032.55 | Dominated |
| 140 LR and DM costs halved | 0.08 | £1,596.47 | **£19,257** | 0.35 | £348.18 | **£985** | -0.07 | £2,598.69 | Dominated |

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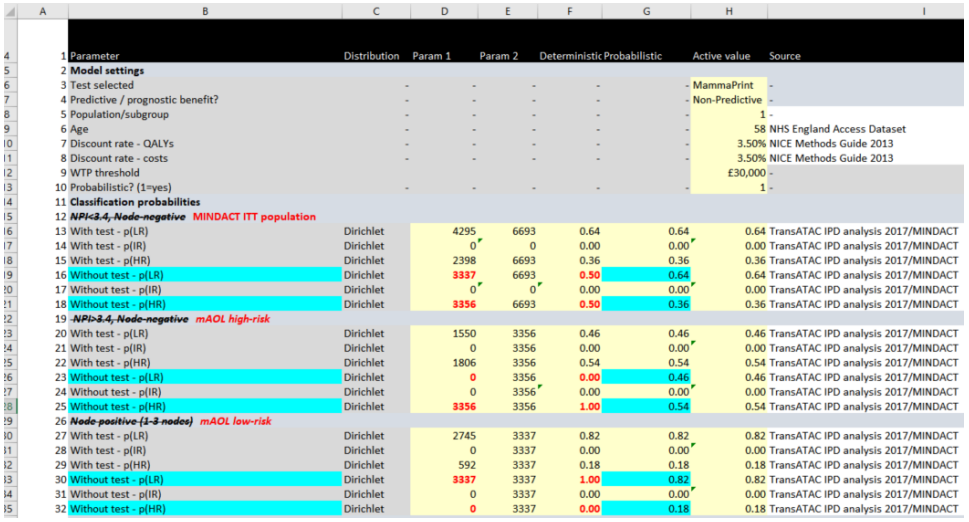
| | | (theme: Probabilistic analysis) | in blue). The text and values in red correspond to the corrections made previously for the deterministic model (please see comment [155] for more details).<br><br>*Figure 9- Incorrect patient proportions in Without-test classification in Parameters sheet – Probabilistic model (blue)*<br><br>  <br><br>As detailed in comment 6 we believe that the classification probabilities for "Without-test" should reflect the patient numbers and proportions of patients classified using mAOL alone. As an example, in the mAOL high-risk analysis: Without test – p(HR) should | The EAG noted that the change made by the company introduces an error which makes the results invalid.<br><br>The change results in different numbers of patients within each genomic risk classification subgroup between the test and no test groups. This means that the model is no longer |

| Parameter | Distribution | Param 1 | Param 2 | Deterministic | Probabilistic | Active value | Source |
|---|---|---|---|---|---|---|---|
| **Model settings** | | | | | | | |
| Test selected | | - | - | - | - | MammaPrint | - |
| Predictive / prognostic benefit? | | - | - | - | - | Non-Predictive | - |
| Population/subgroup | | - | - | - | - | 1 | - |
| Age | | - | - | - | - | 58 | NHS England Access Dataset |
| Discount rate - QALYs | | - | - | - | - | 3.50% | NICE Methods Guide 2013 |
| Discount rate - costs | | - | - | - | - | 3.50% | NICE Methods Guide 2013 |
| WTP threshold | | | | | | £30,000 | - |
| Probabilistic? (1=yes) | | - | - | - | - | 1 | - |
| **Classification probabilities** | | | | | | | |
| ~~**NPI<3.4, Node-negative**~~ MINDACT ITT population | | | | | | | |
| With test - p(LR) | Dirichlet | 4295 | 6693 | 0.64 | 0.64 | 0.64 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(IR) | Dirichlet | 0 | 0 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(HR) | Dirichlet | 2398 | 6693 | 0.36 | 0.36 | 0.36 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(LR) | Dirichlet | 3337 | 6693 | 0.50 | 0.64 | 0.64 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(IR) | Dirichlet | 0 | 0 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(HR) | Dirichlet | 3356 | 6693 | 0.50 | 0.36 | 0.36 | TransATAC IPD analysis 2017/MINDACT |
| ~~**NPI>3.4, Node-negative**~~ *mAOL high-risk* | | | | | | | |
| With test - p(LR) | Dirichlet | 1550 | 3356 | 0.46 | 0.46 | 0.46 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(IR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(HR) | Dirichlet | 1806 | 3356 | 0.54 | 0.54 | 0.54 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(LR) | Dirichlet | 0 | 3356 | 0.00 | 0.46 | 0.46 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(IR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(HR) | Dirichlet | 3356 | 3356 | 1.00 | 0.54 | 0.54 | TransATAC IPD analysis 2017/MINDACT |
| ~~**Node-positive (1-3 nodes)**~~ *mAOL low-risk* | | | | | | | |
| With test - p(LR) | Dirichlet | 2745 | 3337 | 0.82 | 0.82 | 0.82 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(IR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| With test - p(HR) | Dirichlet | 592 | 3337 | 0.18 | 0.18 | 0.18 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(LR) | Dirichlet | 3337 | 3337 | 1.00 | 0.82 | 0.82 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(IR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| Without test - p(HR) | Dirichlet | 0 | 3337 | 0.00 | 0.18 | 0.18 | TransATAC IPD analysis 2017/MINDACT |

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| | | | contain all patients classified as clinically high risk by mAOL and zero patients classified low risk by mAOL (see Table 2).<br>**Dirichlet Sampling**<br>The EAG probabilistic model is informed by the parameters generated in the Dirichlet worksheet with the same sampling used to generate values for the "With-test" and "Without-test" parameters (see Figure 10 below, blue highlighting). | comparing like-with-like and in this instance the bias works in favour of the MammaPrint test. |

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| | | | | |
|---|---|---|---|---|
| | | | *Figure 10 - Dirichlet sampling in EAG model (received January 2018 by Agendia)*<br>Dirichlet sampling<br>**Classification with or without test**<br>**Node negative NPI<3.4**<br>Prior distribution parameters: Low 0.01, Intermediate 0.01, High 0.01, Total 0.03<br>Observed data: Low 4295, Intermediate 0, High 2398, Total 6693<br>Posterior distribution parameters: Low 4295.01, Intermediate 0.01, High 2398.01, Total 6693.03<br>Posterior distribution probabilities: Low 0.64, Intermediate 0.00, High 0.36, Total 1.00<br>Random numbers: Low 0.60, Intermediate 0.78, High 0.67 -<br>Cumulative gamma/normal functions: Low 4312.37, Intermediate 0.00, High 2419.99, Total 6732.36<br>Random Dirichlet samples: Low 0.64, Intermediate 0.00, High 0.36, Total 1.00<br>**Node negative NPI>3.4**<br>Prior distribution parameters: Low 0.01, Intermediate 0.01, High 0.01, Total 0.03<br>Observed data: Low 1550, Intermediate 0, High 1806, Total 3356<br>Posterior distribution parameters: Low 1550.01, Intermediate 0.01, High 1806.01, Total 3356.03<br>Posterior distribution probabilities: Low 0.00, Intermediate 0.00, High 0.00, Total 0.00<br>Random numbers: Low 0.69, Intermediate 0.03, High 0.22 -<br>Cumulative gamma/normal functions: Low 0.00, Intermediate 0.00, High 0.00, Total 0.00<br>Random Dirichlet samples: Low 0.00, Intermediate 0.00, High 0.00, Total 0.00<br>**Node positive**<br>Prior distribution parameters: Low 0.01, Intermediate 0.01, High 0.01, Total 0.03<br>Observed data: Low 2745, Intermediate 0, High 592, Total 3337<br>Posterior distribution parameters: Low 2745.01, Intermediate 0.01, High 592.01, Total 3337.03<br>Posterior distribution probabilities: Low 0.00, Intermediate 0.00, High 0.00, Total 0.00<br>Random numbers: Low 0.17, Intermediate 0.93, High 0.37 -<br>Cumulative gamma/normal functions: Low 0.00, Intermediate 0.00, High 0.00, Total 0.00<br>Random Dirichlet samples: Low 0.00, Intermediate 0.00, High 0.00, Total 0.00<br>However, as detailed in comment [121] the “Observed data” (patient numbers) for the with-test and without-test situation are not identical. To correct this the Dirichlet worksheet was duplicated and 1 worksheet used for the with-test situation and the other for the without-test values. The “Dirichlet_Without_test” worksheet is used to calculate the correct parameters for “Without-test”, and “Dirichlet” worksheet calculates the values | |

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| | | | for the "With test" parameters. Please see Figure 11A and 11B for the corrected worksheets.<br><br>"Dirichlet_Without_test" worksheet<br><br>As shown in comment [121] and Table 2 correcting the classification probabilities means that in the Without test situation all patients should be classified as per mAOL as this represents the clinical-pathological evaluation of the patient's tumor. In the mAOL high risk subgroup 3356 are classified as high risk and zero patients classified low risk by mAOL. In the mAOL low risk subgroup 3337 are classified as low risk and 0 patients as high risk by mAOL. As the probabilistic sensitivity analysis cannot be run with values = 0, an uninformative prior was applied to the "Observed data" inputs in the "Dirichlet_Without_test" worksheet for the mAOL high-risk and mAOL low-risk analyses (See cell C17, E17, C26 and E26 respectively); One patient was added to the observed data for the low-risk and high-risk parameters (i.e. 0=1; 3356 = 3357, 3337 = 3338) (please see Figure 11A ). | |

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*Figure 11A Corrected sampling in EAG model for "Without-test" parameters (located in "Dirichlet_Without_test" worksheet)*

Dirichlet sampling

**Classification WITHOUT test**

| ~~NPI<3.4, Node-negative~~ MINDACT ITT population | Low | Intermediate | High | Total |
|---|---|---|---|---|
| Prior distribution parameters | 0.01 | 0.01 | 0.01 | 0.03 |
| Observed data | 3337 | 0 | 3356 | 6693 |
| Posterior distribution parameters | 3337.01 | 0.01 | 3356.01 | 6693.03 |
| Posterior distribution probabilities | 0.50 | 0.00 | 0.50 | 1.00 |
| Random numbers | 0.26 | 0.07 | 0.70 | - |
| Cumulative gamma/normal functions | 3300.73 | 0.00 | 3386.27 | 6686.99 |
| Random Dirichlet samples | 0.49 | 0.00 | 0.51 | 1.00 |

| ~~NPI>3.4, Node-negative~~ mAOL high-risk | Low | Intermediate | High | Total |
|---|---|---|---|---|
| Prior distribution parameters | 0.01 | 0.01 | 0.01 | 0.03 |
| Observed data | 1 | 0 | 3357 | 3358 |
| Posterior distribution parameters | 1.01 | 0.01 | 3357.01 | 3358.03 |
| Posterior distribution probabilities | 0.000301 | 0.00 | 1.00 | 0.00 |
| Random numbers | 0.38 | 0.31 | 0.53 | - |
| Cumulative gamma/normal functions | 0.49 | 0.00 | 3361.18 | 3361.67 |
| Random Dirichlet samples | 0.00 | 0.00 | 1.00 | 1.00 |

| ~~Node positive (1-3 nodes)~~ mAOL low-risk | Low | Intermediate | High | Total |
|---|---|---|---|---|
| Prior distribution parameters | 0.01 | 0.01 | 0.01 | 0.03 |
| Observed data | 3338 | 0 | 1 | 3339 |
| Posterior distribution parameters | 3338.01 | 0.01 | 1.01 | 3339.03 |
| Posterior distribution probabilities | 1.00 | 0.00 | 0.000302 | 0.00 |
| Random numbers | 0.92 | 0.52 | 0.80 | - |
| Cumulative gamma/normal functions | 3418.49 | 0.00 | 1.63 | 3420.12 |
| Random Dirichlet samples | 1.00 | 0.00 | 0.00 | 1.00 |

*Figure 11B - Corrected sampling in EAG model for "With-test" parameters (located in "Dirichlet" worksheet)*

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Dirichlet sampling

Classification WITH test

| ~~NPI<3.4, Node-negative~~ MINDACT ITT population | Low | Intermediate | High | Total |
|---|---|---|---|---|
| Prior distribution parameters | 0.01 | 0.01 | 0.01 | 0.03 |
| Observed data | 4295 | 0 | 2398 | 6693 |
| Posterior distribution parameters | 4295.01 | 0.01 | 2398.01 | 6693.03 |
| Posterior distribution probabilities | 0.64 | 0.00 | 0.36 | 1.00 |
| Random numbers | 0.26 | 0.07 | 0.70 | - |
| Cumulative gamma/normal functions | 4253.85 | 0.00 | 2423.59 | 6677.43 |
| Random Dirichlet samples | 0.64 | 0.00 | 0.36 | 1.00 |

| ~~NPI>3.4, Node-negative~~ mAOL high-risk | Low | Intermediate | High | Total |
|---|---|---|---|---|
| Prior distribution parameters | 0.01 | 0.01 | 0.01 | 0.03 |
| Observed data | 1550 | 0 | 1806 | 3356 |
| Posterior distribution parameters | 1550.01 | 0.01 | 1806.01 | 3356.03 |
| Posterior distribution probabilities | 0.46 | 0.00 | 0.54 | 0.00 |
| Random numbers | 0.38 | 0.31 | 0.53 | - |
| Cumulative gamma/normal functions | 1538.30 | 0.00 | 1809.07 | 3347.37 |
| Random Dirichlet samples | 0.46 | 0.00 | 0.54 | 1.00 |

| ~~Node positive (1-3 nodes)~~ mAOL low-risk | Low | Intermediate | High | Total |
|---|---|---|---|---|
| Prior distribution parameters | 0.01 | 0.01 | 0.01 | 0.03 |
| Observed data | 2745 | 0 | 592 | 3337 |
| Posterior distribution parameters | 2745.01 | 0.01 | 592.01 | 3337.03 |
| Posterior distribution probabilities | 0.82 | 0.00 | 0.18 | 0.00 |
| Random numbers | 0.92 | 0.52 | 0.80 | - |
| Cumulative gamma/normal functions | 2817.99 | 0.00 | 612.54 | 3430.53 |
| Random Dirichlet samples | 0.82 | 0.00 | 0.18 | 1.00 |

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**Parameters sheet**

The relevant formulas were updated in the Parameters worksheet once the Dirichlet sampling was corrected. In Table 4 we have summarized what we believe the values should be after correcting the Dirichlet sampling. Figure 12 shows the updated worksheet. Please also refer to the updated version of the EAG model with the corrected values. File name: **DAP37EAGModel_Agendia10MAY18.xlsx**

*Table 4 – Probabilistic model - Correct patient number and proportion inputs for MammaPrint in EAG model Parameters worksheet*

| | Column B | Column D | Column E | Column G | Column H |
|---|---|---|---|---|---|
| | **Classification probabilities** | **Parameter 1** | **Parameter 2** | **Probabilistic** | **Active value** (for probabilistic analysis) |
| Row 15 | **MINDACT ITT population** | | | | |
| Row 16 | With test – p(LR) | 4295 | 6693 | 0.64 | 0.64 |
| Row 18 | With test – p(HR) | 2398 | 6693 | 0.36 | 0.36 |
| Row 19 | Without test – p(LR) | **3337** | 6693 | **0.49** | **0.49** |
| Row 21 | Without test – p(HR) | **3356** | 6693 | **0.51** | **0.51** |
| Row 22 | **mAOL high-risk** | | | | |
| Row 23 | With test – p(LR) | 1150 | 3356 | 0.46 | 0.46 |
| Row 25 | With test – p(HR) | 1806 | 3356 | 0.54 | 0.54 |

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|---|---|---|---|---|---|---|---|---|---|
| | | | Row 26 | Without test – p(LR) | **0** | 3356 | **0.00** | **0.00** | |
| | | | Row 28 | Without test – p(HR) | **3356** | 3356 | **1.00** | **1.00** | |
| | | | Row 29 | **mAOL low-risk** | | | | | |
| | | | Row 30 | With test – p(LR) | 2745 | 3337 | 0.82 | 0.82 | |
| | | | Row 32 | With test – p(HR) | 592 | 3337 | 0.18 | 0.18 | |
| | | | Row 33 | Without test – p(LR) | **3337** | 3337 | **1.00** | **1.00** | |
| | | | Row 35 | Without test – p(HR) | **0** | 3337 | **0.00** | **0.00** | |

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*Figure 12 - Corrected Parameters worksheet for EAG Probabilistic model*

Model parameters

| | Parameter | Distribution | Param 1 | Param 2 | Deterministi | Probabilistic | Active value | Source |
|---|---|---|---|---|---|---|---|---|
| 2 | **Model settings** | | | | | | | |
| 3 | Test selected | - | - | - | - | - | MammaPrint | - |
| 4 | Predictive / prognostic benefit? | - | - | - | - | - | Non-Predictive | - |
| 5 | Population/subgroup | - | - | - | - | - | 1 | - |
| 6 | Age | - | - | - | - | - | 58 | NHS England Access Dataset |
| 7 | Discount rate - QALYs | - | - | - | - | - | 3.50% | NICE Methods Guide 2013 |
| 8 | Discount rate - costs | - | - | - | - | - | 3.50% | NICE Methods Guide 2013 |
| 9 | WTP threshold | | | | | | £30,000 | - |
| 10 | Probabilistic? (1=yes) | - | - | - | - | - | 1 | - |
| 11 | **Classification probabilities** | | | | | | | |
| 12 | ~~***NPI>3.4, Node-negative***~~ MINDACT ITT population | | | | | | | |
| 13 | With test - p(LR) | Dirichlet | 4295 | 6693 | 0.64 | 0.64 | 0.64 | TransATAC IPD analysis 2017/MINDACT |
| 14 | With test - p(IR) | Dirichlet | 0 | 0 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| 15 | With test - p(HR) | Dirichlet | 2398 | 6693 | 0.36 | 0.36 | 0.36 | TransATAC IPD analysis 2017/MINDACT |
| 16 | Without test - p(LR) | Dirichlet | 3337 | 6693 | 0.50 | 0.49 | 0.49 | TransATAC IPD analysis 2017/MINDACT |
| 17 | Without test - p(IR) | Dirichlet | 0 | 0 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| 18 | Without test - p(HR) | Dirichlet | 3356 | 6693 | 0.50 | 0.51 | 0.51 | TransATAC IPD analysis 2017/MINDACT |
| 19 | ~~***NPI>3.4, Node-negative***~~ *mAOL high-risk* | | | | | | | |
| 20 | With test - p(LR) | Dirichlet | 1550 | 3356 | 0.46 | 0.46 | 0.46 | TransATAC IPD analysis 2017/MINDACT |
| 21 | With test - p(IR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| 22 | With test - p(HR) | Dirichlet | 1806 | 3356 | 0.54 | 0.54 | 0.54 | TransATAC IPD analysis 2017/MINDACT |
| 23 | Without test - p(LR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| 24 | Without test - p(IR) | Dirichlet | 0 | 3356 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| 25 | Without test - p(HR) | Dirichlet | 3356 | 3356 | 1.00 | 1.00 | 1.00 | TransATAC IPD analysis 2017/MINDACT |
| 26 | ~~***Node positive (1-3 nodes)***~~ *mAOL low-risk* | | | | | | | |
| 27 | With test - p(LR) | Dirichlet | 2745 | 3337 | 0.82 | 0.82 | 0.82 | TransATAC IPD analysis 2017/MINDACT |
| 28 | With test - p(IR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| 29 | With test - p(HR) | Dirichlet | 592 | 3337 | 0.18 | 0.18 | 0.18 | TransATAC IPD analysis 2017/MINDACT |
| 30 | Without test - p(LR) | Dirichlet | 3337 | 3337 | 1.00 | 1.00 | 1.00 | TransATAC IPD analysis 2017/MINDACT |
| 31 | Without test - p(IR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |
| 32 | Without test - p(HR) | Dirichlet | 0 | 3337 | 0.00 | 0.00 | 0.00 | TransATAC IPD analysis 2017/MINDACT |

**Probabilistic Results – MammaPrint is now cost-effective**

When the classification probabilities are corrected as shown in above in Table 4 and Figures 11A and 11B, we now find that MammaPrint is cost-effective below a QALY threshold of £20,000. As shown in Figure 13, MammaPrint is dominating over mAOL/current practice in the mAOL high-risk analysis and is cost-effective with an ICER

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
of £17,546 in the MINDACT ITT population. In the mAOL low-risk analysis MammaPrint is dominated by current practice.<br><br>
Figure 13 - Corrected Probabilistic model results<br><br>
Probabilistic sensitivity analysis<br><br>
PSA_index 10000<br>
Max PSA iterations 10001<br>
Threshold £0<br>
Max lambda £100,000<br><br>
Probabilistic ICERs<br><br>
<table>
<tr><th>Option</th><th>QALYs</th><th>Costs</th><th>QALYs</th><th>Costs</th><th>ICER (per QALY gained)</th></tr>
<tr><td>MINDACT ITT population</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>MammaPrint</td><td>13.51</td><td>£9,151</td><td>0.08</td><td>£1,428</td><td>£17,546</td></tr>
<tr><td>No test</td><td>13.43</td><td>£7,723</td><td>-</td><td>-</td><td></td></tr>
<tr><td>mAOL high-risk</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>MammaPrint</td><td>12.86</td><td>£12,726</td><td>0.35</td><td>-£470</td><td>Dominating</td></tr>
<tr><td>No test</td><td>12.51</td><td>£13,197</td><td>-</td><td>-</td><td></td></tr>
<tr><td>mAOL low-risk</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>MammaPrint</td><td>13.70</td><td>£7,777</td><td>-0.07</td><td>£2,769</td><td>Dominated</td></tr>
<tr><td>No test</td><td>13.77</td><td>£5,008</td><td>-</td><td>-</td><td></td></tr>
</table>
<br>
<table>
<tr><th></th><th>LN-, NPI<3.4</th><th>LN-, NPI>3.4</th><th>LN+</th></tr>
<tr><td>P(optimal) λ=£20,000</td><td>0.62</td><td>0.98</td><td>0.00</td></tr>
<tr><td>P(optimal) λ=£30,000</td><td>0.89</td><td>0.98</td><td>0.00</td></tr>
</table>
<br>
As shown in Figure 13 and Table 5 , the probabilistic sensitivity analysis indicates that within the overall MINDACT population the probability that MammaPrint produces more net benefit than current practice at willingness to pay (WTP) thresholds of £20,000 and £30,000 per QALY gained is 0.62 and 0.89, respectively. Within the clinical high risk subgroup this increases to 0.98 for both WTP thresholds. In the clinical low-risk subgroup this probability is approximately zero.<br><br>
Table 5 - Probability of optimality – MammaPrint versus current practice (mAOL)<br><br>
<table>
<tr><td>Subgroup</td><td>Probability (λ=£20,000 per QALY gained)</td><td>Probability (λ=£30,000 per QALY gained)</td></tr>
</table>
</td><td></td></tr>
</table>

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th></th><th>MammaPrint</th><th>Current practice</th><th>MammaPrint</th><th>Current practice</th></tr>
<tr><td>MINDACT ITT population</td><td>0.62</td><td>0.38</td><td>0.89</td><td>0.11</td></tr>
<tr><td>mAOL high-risk subgroup</td><td>0.89</td><td>0.02</td><td>0.98</td><td>0.02</td></tr>
<tr><td>mAOL low-risk subgroup</td><td>0</td><td>1.0</td><td>0</td><td>1.0</td></tr>
</table>
Conclusion<br>
Correction of the patient input numbers and proportions in the EAG probabilistic model results in MammaPrint dominating current practice in the mAOL high-risk and being cost-effective (below £20K threshold) in the MINDACT ITT population respectively. We hope the EAG agrees with these corrections as suggested by us and will report the corrected results in the final guidance report.
</td><td></td></tr>
</table>

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|---|---|---|---|---|
| 123 | Agendia N.V. | Updated Agendia cost effectiveness model | **Correction of errors within the Agendia model**<br>Given that the EAG found correctable errors within the Agendia model we have revised our model for resubmission. File name: **VRetelModel_Agendia11MAY18.xls**<br>We agree there were some errors in the model presented and have adjusted the model accordingly. In the comments below (16 to 28) we present each correction made and the corresponding results. | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |
| 124 | Agendia N.V. | Page 323 DAP 37 evaluation report, Nov 2017<br><br>(theme: updated Agendia cost effectiveness model) | *The EAG noted that the time horizon of the Agendia model was short (5 years).*<br>We extended the time horizon to 10 years using a Weibull extrapolation approach: Time-to- DMFS and time-to-death were derived from a Weibull exponential distribution. The time between events was modelled by randomly sampling values from parametric survival distributions. The results for the Weibull extrapolation can be found in the sheet “extrapolation ITT”, and are shown in Figure 21 and 22: | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |

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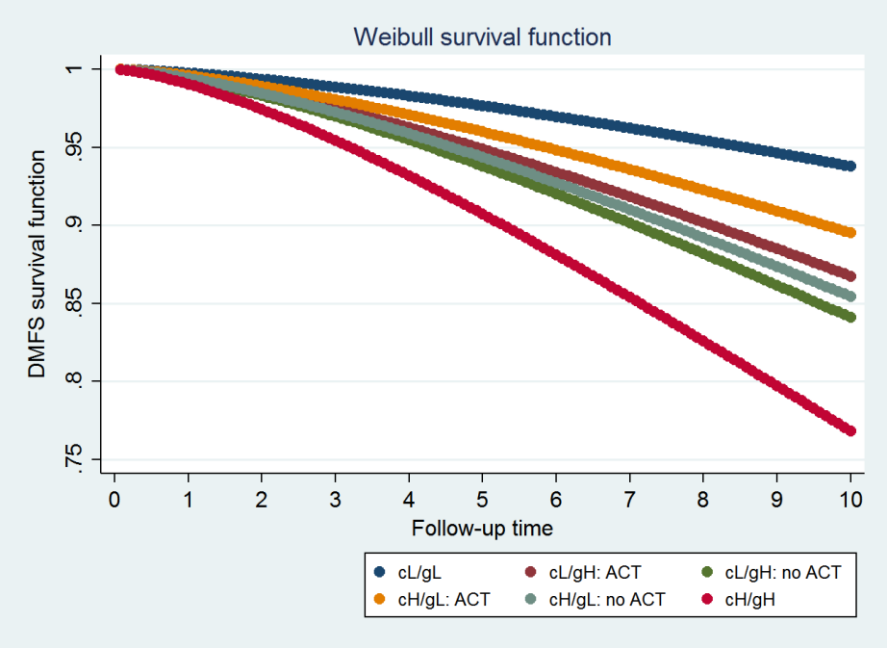
| | | | | |
|---|---|---|---|---|
| | | | *Figure 22 - Weibull extrapolation for all risk and treatment subgroups: DMFS 0-10 yrs*<br>  <br> | |

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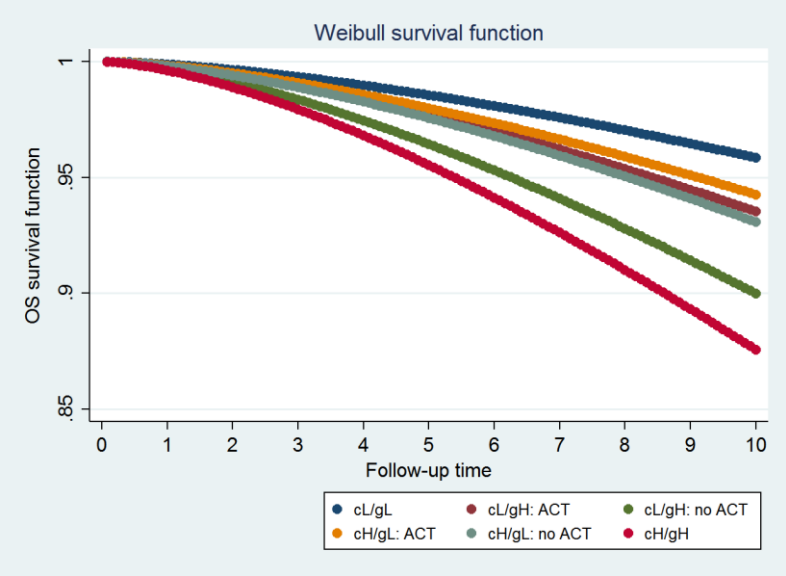
|---|---|---|---|---|
| | | | *Figure 23 - Weibull extrapolation for all risk and treatment subgroups: OS 0-10 yrs*<br>  <br> | |
| 125 | Agendia N.V. | Addendum: EAG responses to key themes within the | **Patient survival data for 10 year Weibull extrapolation**<br><br>The EAG found that the Agendia model contained programming errors resulting in incorrect extrapolation of survival data for patients from 6-10 years. We thank the EAG team for pointing this out and have corrected these errors. Please find below the model trace of survival data for the total MINDACT population and the clinical | Thank you for your comment which the committee considered. |

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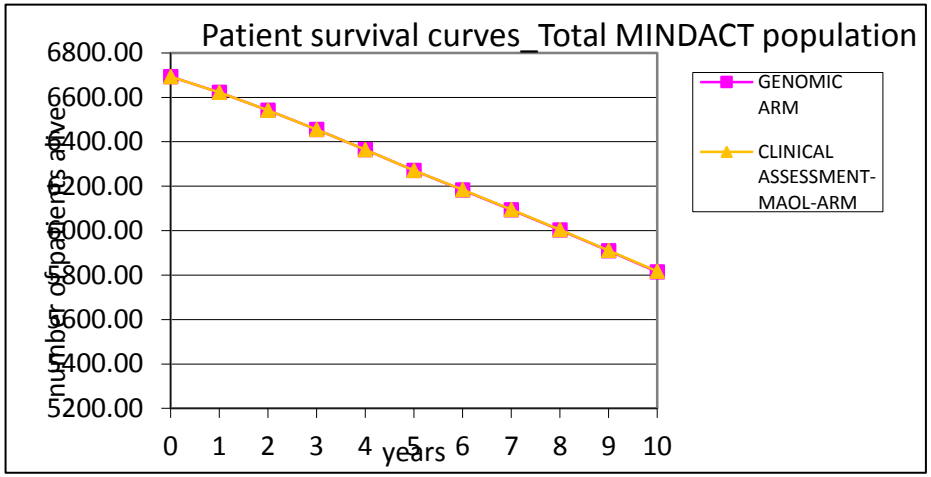
| | | Comments on the Diagnostics Consultation Document<br><br>(section 9. New model submitted by Agendia, p28-29 of 31)<br><br>(theme: updated Agendia cost effectiveness model) | high-risk population. For ease of reference these graphs are also displayed in the MODEL worksheet of the corrected Agendia model.<br><br>*Figure 17 - Number of patients alive, genomic and clinical assessment arm (mAOL) corrected Agendia model for total MINDACT population*<br><br>  <br> | The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |

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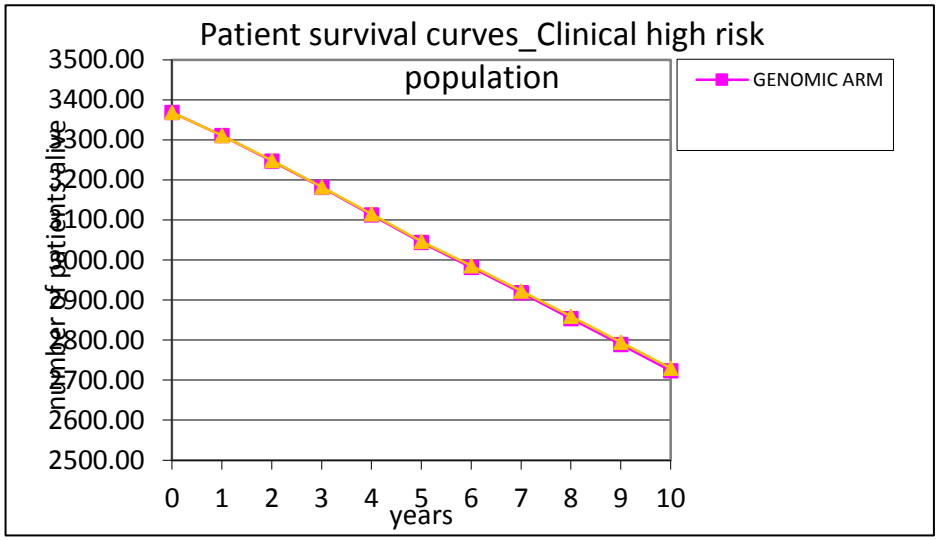
| | | | | |
|---|---|---|---|---|
| | | | *Figure 18 - Number of patients alive, genomic and clinical assessment arm (mAOL) corrected Agendia model for total MINDACT population*<br>  <br><br>In addition, we compared the Weibull extrapolation data to the original survival data from the EORTC MINDACT database. In figure 19 we show an example of the overlap of the EORTC database survival data with the Weibull extrapolation data. The extrapolation overlays well with the original survival data.<br>*Figure 19 - Overlap of original trial survival data (EORTC MINDACT database) with 0-10yr Weibull extrapolation data: DMFS in Clinical high-risk/Genomic high-risk subgroup* | |

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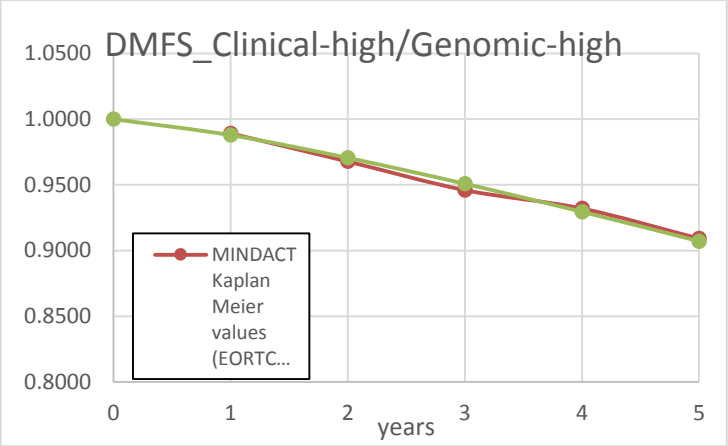
|---|---|---|---|---|
| | | |  | |
| 126 | Agendia N.V. | Updated Agendia model- fundamental change in structure | Before we go into detail on the adaptations that were made in the Agendia model based on the EAG suggestions, we would like to explain a fundamental change in the structure of the model:<br>The cost-effectiveness was calculated based on the MINDACT findings that for the clinical high-risk /genomic low-risk patients, chemotherapy can be safely omitted, as it does not provide clinically significant benefit. Based on this finding, ASCO amongst others, have recently updated their guideline recommendations for MammaPrint. The Agendia model examines the cost-effectiveness of MammaPrint (MP) when used in accordance with these guidelines. | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to |

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| | | | The Agendia analysis models 2 scenarios in clinical practice, namely, "MP for Clinical high risk only" and "MP for all patients" against the comparator arm "No MP" (see Figure 20 for the decision tree). "No MP" models patients treated according to clinical risk only (classification according to modified Adjuvant Online (mAOL)). As shown in Figure 20 "MP for all patients" models a scenario where patients are categorized in 4 risk groups according to the MINDACT trial; C-low/G-low, C-low/G-high, C-high/G-low and C-high/G-high.<br><br>"MP for Clinical high risk only" models the use of MammaPrint only in clinical high-risk patients (as defined by modified Adjuvant Online in MINDACT). This scenario in the decision tree was also used for a third analysis set: the ER+/Her2- subgroup (only in the clinical high-risk population), because this group represents the scope of the evaluation best. | comments on DCD2 (5 June 2018). |

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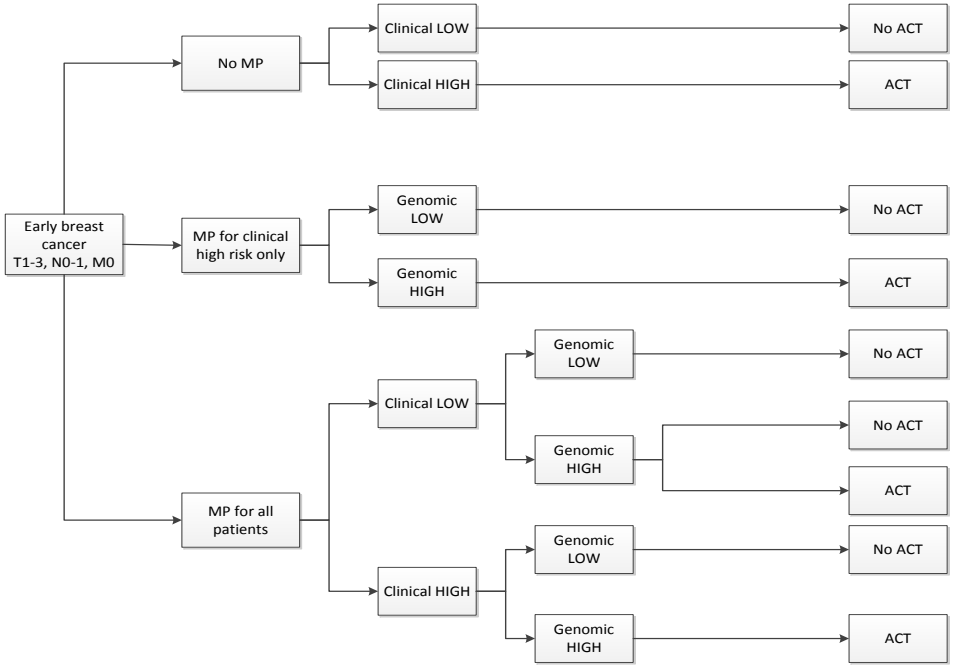
| | | | | |
|---|---|---|---|---|
| | | | *Figure 20 – Updated Agendia model decision tree*<br>  <br><br>The results below are the results of the base case analysis, (keeping (non-)compliance to MammaPrint recommendation into account based on Bloomfield et al., 2017.), which shows that MammaPrint is dominating mAOL in the clinical high-risk group and in the clinical high risk, ER+/Her2- group. | |

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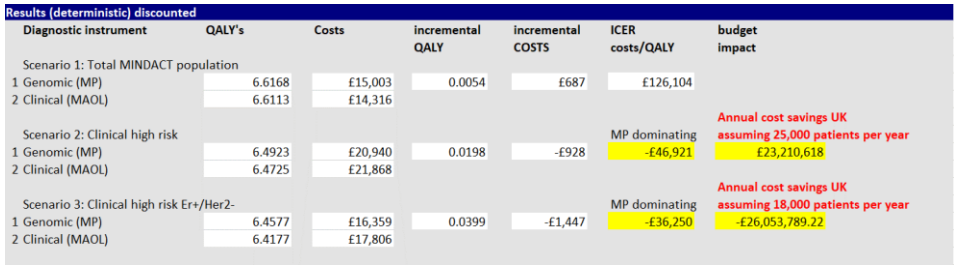
| | | | In addition to the cost-effectiveness analysis we have also included a budget impact analysis. For the budget impact, the total costs for using MammaPrint were multiplied by the current numbers of patients in the targeted group per year in the UK. For the clinical high risk group, this was estimated on 25,000 patients per year. For the clinical high risk ER+/Her2- group, this was estimated on 20,000 clinical high risk patients per year in the UK (source: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer).<br>  <br>Results (deterministic) discounted<br>Diagnostic instrument / QALY's / Costs / incremental QALY / incremental COSTS / ICER costs/QALY / budget impact<br>Scenario 1: Total MINDACT population<br>1 Genomic (MP) 6.6168 £15,003 0.0054 £687 £126,104<br>2 Clinical (MAOL) 6.6113 £14,316<br>Scenario 2: Clinical high risk — MP dominating — Annual cost savings UK assuming 25,000 patients per year<br>1 Genomic (MP) 6.4923 £20,940 0.0198 -£928 -£46,921 £23,210,618<br>2 Clinical (MAOL) 6.4725 £21,868<br>Scenario 3: Clinical high risk Er+/Her2- — MP dominating — Annual cost savings UK assuming 18,000 patients per year<br>1 Genomic (MP) 6.4577 £16,359 0.0399 -£1,447 -£36,250 -£26,053,789.22<br>2 Clinical (MAOL) 6.4177 £17,806 | |
| 127 | Agendia N.V. | Page 323 DAP 37 evaluation report, Nov 2017<br>(theme: updated Agendia cost | The EAG noted that the calculation of transition probabilities for all analyses was incorrect.<br>We corrected the calculation as follows:<br>We have submitted an updated version of the Agendia cost-effectiveness model where we applied the calculation as pointed out by EAG. The unadjusted survival rates can be found in the "Parameter" sheet of the Agendia model, cells I12-I143. The formula applied to calculate the conditional survival can be found in the cells D12-D143 of the same sheet. (document name: **VRetelModel_Agendia11MAY18.xls**) | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to |

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| | | effectiveness model) | | responses to comments on DCD2 (5 June 2018). |
| 128 | Agendia N.V. | Page 323 DAP 37 evaluation report, Nov 2017<br><br>(theme: updated Agendia cost effectiveness model) | The EAG noted that the Agendia model used a "*Questionable assumption that risk exclusively determines whether patients receive adjuvant chemotherapy".*<br><br>To clarify, the model submitted by Agendia does *not* assume that risk is the sole determinant of whether patients receive adjuvant chemotherapy.<br><br>In the updated Agendia model we have incorporated the post-test chemotherapy use probabilities for the MammaPrint from Bloomfield et al., 2017 in the base case scenario, and Cusumano et al., 2014 data in a sensitivity analysis. Post-test chemotherapy use probabilities for the clinical assessment was based on the expert opinion of Dr.Rob Stein, as used in the current NICE DAP 37.<br><br>This data can be found in the "model" sheet of the Agendia model (document name: **VRetelModel_Agendia11MAY18.xls)**, range A1-K12. The results from the sensitivity analysis can be found in the sheet "sensitivity analyses" range A89-S110. The addition of these specified chemotherapy use probabilities did not change the overall conclusion of the analysis that MammaPrint is dominating mAOL in the clinical high-risk group and in the clinical high risk, ER+/Her2- group, as shown in the figures below.<br><br>Base case (using Bloomfield and Stein adherence): | Thank you for your comment which the committee considered.<br><br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |

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Results (deterministic) discounted<br>
<table>
<tr><th>Diagnostic instrument</th><th>QALY's</th><th>Costs</th><th>incremental QALY</th><th>incremental COSTS</th><th>ICER costs/QALY</th><th>budget impact</th></tr>
<tr><td>Scenario 1: Total MINDACT population</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 Genomic (MP)</td><td>6.6168</td><td>£15,003</td><td>0.0054</td><td>£687</td><td>£126,104</td><td></td></tr>
<tr><td>2 Clinical (MAOL)</td><td>6.6113</td><td>£14,316</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Scenario 2: Clinical high risk</td><td></td><td></td><td></td><td></td><td>MP dominating</td><td>Annual cost savings UK assuming 25,000 patients per year</td></tr>
<tr><td>1 Genomic (MP)</td><td>6.4923</td><td>£20,940</td><td>0.0198</td><td>-£928</td><td>-£46,921</td><td>£23,210,618</td></tr>
<tr><td>2 Clinical (MAOL)</td><td>6.4725</td><td>£21,868</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Scenario 3: Clinical high risk Er+/Her2-</td><td></td><td></td><td></td><td></td><td>MP dominating</td><td>Annual cost savings UK assuming 18,000 patients per year</td></tr>
<tr><td>1 Genomic (MP)</td><td>6.4577</td><td>£16,359</td><td>0.0399</td><td>-£1,447</td><td>-£36,250</td><td>-£26,053,789.22</td></tr>
<tr><td>2 Clinical (MAOL)</td><td>6.4177</td><td>£17,806</td><td></td><td></td><td></td><td></td></tr>
</table>
Sensitivity Analysis (using Cusumano and Stein adherence):<br>
Results (deterministic) discounted<br>
<table>
<tr><th>Diagnostic instrument</th><th>QALY's</th><th>Costs</th><th>incremental QALY</th><th>incremental COSTS</th><th>ICER costs/QALY</th><th>budget impact</th></tr>
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<tr><td>2 Clinical (MAOL)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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<tr><td>2 Clinical (MAOL)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td><td></td></tr>
<tr><td>129</td><td>Agendia N.V.</td><td>Page 323 DAP 37 evaluation report, Nov 2017</td><td>The EAG noted the use of potentially outdated cost estimates in the Agendia model.<br><br>The corrected model now includes the cost estimates from as the EAG model (2015/2016adjusted costs) (see Sheet “parameters”, Cells range D490-D505, and sheet “cost countries”, range D1-D19.</td><td>Thank you for your comment which the committee considered.<br><br>The EAG identified a number of errors in</td></tr>
</table>

**DIAGNOSTICS ASSESSMENT PROGRAMME**

**Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer**

**Diagnostics Consultation Document – Comments**

**Diagnostics Advisory Committee date: 13 June 2018**

**THEME: Agendia economic model**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| | | | | the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |
| 130 | Agendia N.V. | 5.2.1 (Page 325 DAP 37 evaluation report, Nov 2017 | *(5) Potential bias in the redefinition of clinical risk by NPI*<br>The redefinition of the NPI was based on the "I= 0.2 x size + stage + grade" formula [Todd JH, BJC, 1987], where size is in cm, stages A, B and C are coded 1-3 and grade is also coded 1-3. The index was computed for each patient, who was then assigned to one of two prognostic groups: Good (1≤3.4), and Poor (1> 3.4). The values for size, stage and grade were determined on the raw data (individual patient characteristics) of the MINDACT trial. After consideration of the EAG comments on potential bias of these analyses, we have removed these analyses from the Agendia model. | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |
| 131 | Agendia N.V. | Page 323 DAP 37 evaluation report, Nov 2017 | The EAG noted that the disutility associated with chemotherapy was applied for 2 years in the Agendia model, which they assessed as being too long. In the updated Agendia model, the disutility for chemotherapy has now been applied for 1 year, the same as in the updated EAG model. See e.g. Cell AX81 in the "MODEL" sheet. | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in |

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**THEME: Agendia economic model**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| | | | | the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |
| 132 | Agendia N.V. | Updated Agendia model - Sensitivity analysis: using MINDACT utilities | In the former comment round, we suggested EAG to use the "test" utilities for the first cycle, based on EQ-5D values measured in the first 800 women of the MINDACT trial. Quality of life (Qol) in the Agendia model was modelled by assigning utilities to the different health states. Utilities regarding clinical and MammaPrint assessment results were measured by means of the EQ-5D-3L amongst the first 800 enrolled patients in the MINDACT trial, of which a total of n=347 were included in a QoL study (Retèl et al., 2013). This is a small sample, however, no other data on QoL by means of the EQ5D is available in literature. EQ-5D health states, defined by the EQ-5D descriptive system, were converted into a single summary index by applying a formula that essentially attaches values to each of the levels in each dimension. Subsequently, the general population-based value set of the Netherlands was used (because it concerned Dutch patients). We believe that Dutch patients are not very different to the UK patients (Dolan et al., 1997) and therefore the EQ5D data was applied in the updated Agendia model. For distant metastasis and patients who received adjuvant chemotherapy, a disutility was incorporated during 1,5 cycle, according to Campbell and colleagues (Campbell et al., 2011), who suggest that the negative impact of chemotherapy on underlying HRQoL persists for at least a year following completion of treatment. We once again suggest using these values (these values are located in the updated Agendia model, "parameters" worksheet, Cells D472-D477). | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |

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| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| 133 | Agendia N.V. | Page 323 DAP 37 evaluation report, Nov 2017 | *The EAG noted that there is uncertainty surrounding UK clinical high risk analysis.*<br>We agree with this and have removed this analysis (referred to as Analysis 8 in the DAR version January 2018) from the updated Agendia model. | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |
| 134 | Agendia N.V. | Page 323 DAP 37 evaluation report, Nov 2017 | *The EAG mentioned that a minor error in the Agendia model is that half-cycle correction has not been applied.*<br>Half-cycle correction has been applied in the corrected Agendia model in Sheet "MODEL", Rows 31 and 52 (this was incorporated in the base case analysis). The addition of the half cycle correction did not change the main conclusion of the model that MammaPrint is cost effective. | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |

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**THEME: Agendia economic model**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| 135 | Agendia N.V. | Updated Agendia model: Additional sensitivity analysis (SA5) | **Sensitivity analyses – Adherence to MammaPrint results**<br>As there are no UK specific decision impact studies for MammaPrint, the updated Agendia model includes 3 sensitivity analyses ("sensitivity analyses" worksheet) examining the effect of physician/patient adherence to test results (and resulting treatment). The first analysis assumes 100% adherence to MammaPrint test results (as a best-case scenario). When applying the first sensitivity analysis, MammaPrint is even more cost-effective compared to mAOL in the clinical high risk and clinical high-risk ER+/Her2- subgroups. The second analysis applied MammaPrint test result adherence from Cusumano et al., 2014 rather than Bloomfield et al., 2017. When applying the Cusumano adherence (sensitivity analysis 2), the ICERs increased slightly for all scenarios, but the main conclusion remains unchanged. To model a "worst-case" situation (3rd sensitivity analysis) changing the adherence to 50-50% both for MammaPrint and the clinical assessment, MammaPrint remains cost-effective in the targeted clinical high-risk ER+/Her2- group but is not cost-effective in the other scenarios.<br>Sensitivity Analysis 1: leaving out the non-adherence: best case scenario | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |

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# DIAGNOSTICS ASSESSMENT PROGRAMME

## Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer

## Diagnostics Consultation Document – Comments

## Diagnostics Advisory Committee date: 13 June 2018

## THEME: Agendia economic model

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|

**Results (deterministic) discounted**

| Diagnostic instrument | QALY's | Costs | incremental QALY | incremental COSTS | ICER costs/QALY | budget impact |
|---|---|---|---|---|---|---|
| Scenario 1: Total MINDACT population | | | | | | |
| 1 Genomic (MP) | 6,6139 | £15.094 | 0,0059 | £411 | £70.045 | |
| 2 Clinical (MAOL) | 6,6080 | £14.683 | | | | |
| Scenario 2: Clinical high risk | | | | | MP dominating | annual cost savings UK assuming 20,000 patients per year |
| 1 Genomic (MP) | 6,4943 | £20.718 | 0,0283 | -£1.880 | -£66.517 | -£37.604.583 |
| 2 Clinical (MAOL) | 6,4660 | £22.598 | | | | |
| Scenario 3: Clinical high risk Er+/Her2- | | | | | MP dominating | annual cost savings UK assuming 20,000 patients per year |
| 1 Genomic (MP) | 6,4616 | £16.214 | 0,0570 | -£2.068 | -£36.250 | -£41.355.221 |
| 2 Clinical (MAOL) | 6,4046 | £18.282 | | | | |

Sensitivity Analysis 2: using Cusumano probabilities of receiving chemotherapy

**Results (deterministic) discounted**

| Diagnostic instrument | QALY's | Costs | incremental QALY | incremental COSTS | ICER costs/QALY | budget impact |
|---|---|---|---|---|---|---|
| Scenario 1: Total MINDACT population | | | | | | |
| 1 Genomic (MP) | 6,6136 | £15.171 | 0,0023 | £855 | £376.423 | |
| 2 Clinical (MAOL) | 6,6113 | £14.316 | | | | |
| Scenario 2: Clinical high risk | | | | | MP dominating | annual cost savings UK assuming 20,000 patients per year |
| 1 Genomic (MP) | 6,4923 | £20.940 | 0,0198 | -£928 | -£46.921 | -£18.568.494 |
| 2 Clinical (MAOL) | 6,4725 | £21.868 | | | | |
| Scenario 3: Clinical high risk Er+/Her2- | | | | | MP dominating | annual cost savings UK assuming 20,000 patients per year |
| 1 Genomic (MP) | 6,4577 | £16.359 | 0,0399 | -£1.447 | -£36.250 | -£28.948.655 |
| 2 Clinical (MAOL) | 6,4177 | £17.806 | | | | |

Sensitivity Analysis 3: Only 50% adherence to treatment recommendation based on MammaPrint result

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**THEME: Agendia economic model**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| | | | **Results (deterministic) discounted**<br>**Diagnostic instrument** / **QALY's** / **Costs** / **incremental QALY** / **incremental COSTS** / **ICER costs/QALY** / **budget impact**<br>Scenario 1: Total MINDACT population<br>1 Genomic (MP) 6,6151 £15.444 0,0001 £1.543 £13.139.043<br>2 Clinical (MAOL) 6,6150 £13.901<br>Scenario 2: Clinical high risk — MP dominating<br>1 Genomic (MP) 6,4804 £22.272 0,0006 £1.229 £2.173.906<br>2 Clinical (MAOL) 6,4798 £21.043<br>Scenario 3: Clinical high risk Er+/Her2- — MP dominating — annual cost savings UK assuming 20,000 patients per year<br>1 Genomic (MP) 6,4337 £17.227 0,0011 -£41 -£36.250 -£827.104<br>2 Clinical (MAOL) 6,4326 £17.269 | |
| 136 | Agendia N.V. | Summary of updated Agendia CE model | To summarise current updated Agendia model: Using Weibull extrapolation, Bloomfield and Stein chemotherapy use probabilities, half cycle correction, conditional survival, updated UK costs as a base case, our conclusion is: When using the MammaPrint test for the clinical high-risk population, MammaPrint is dominating compared to mAOL, and in the ER+/Her2- population, MammaPrint is also dominating compared to mAOL. | Thank you for your comment which the committee considered.<br>The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |

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**THEME: Alternative technologies**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| 137 | NHS Professional | General | I wondered if the committee had considered the much more cost effective approach of using a predictive nomogram to find out the likelihood of a low or high Oncotype score? In Cambridge we use a web calculator (https://gsm.utmck.edu/nomograms/) to estimate the chances of getting a definite high or low score. We cycle through the four estimates in this calculator, and if any value is >90% we do not send the tumour sample off for testing, and make clinical decisions on the predicted score. This web calculator has been developed and validated in 40,000 patients (four times the number used to develop PREDICT, which most centres use without question). In our MDM we send off an Oncotype only about once every six weeks. | Thank you for your comment which the committee considered.<br>The committee did not consider this nomogram because it was outside the scope for the assessment. |

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**THEME: Conflicts of interest**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| 138 | NHS Professional | General | The competing interest section of this comment form is inadequate and makes NICE seem rather unworldly about what is going on with these technologies which are being very actively marketed. Because it does not fall under ABPI, the marketing is much more lightly regulated than for drugs.<br><br>The form has a tick box and an "anything of relevance box" which I believe is insufficient. Many (I think all) of my consultant oncology and surgical consultants have been expensively wined and dined locally by these companies. A large number have been flown to conferences where they have been put up in luxury hotels. And some have been paid directly to give advertorial lectures at local meetings (often without declaring their interests). Some national opinion leaders have been given substantial consultancy fees to give "academic lectures", again without declaring their interests. Is all this activity being captured by this NICE comments form? I strongly suspect it isnt. You are leaving it up to the NICE website user to decide what is "relevant" and what isn't. In my experience, doctors are in such denial about the influence of marketing that they believe they are immune to corruption, and think the fact that they have received consultancy fees is not relevant. You should have a much more rigorous competing interest section, asking if they have been fed, flown, or been paid lecturing, advisory, consulting or honorarium fees, or had any payments at all from any company involved in this technology, and the amounts of these payments should also be asked for.<br><br>When the General Comments are published, can we see the competing interests? | Thank you for your comment which the committee considered.<br><br>The self-declared conflicts of interest for stakeholders and public commenting on the consultation documents are not published at present. This will be noted for future updates of the diagnostics assessment programme manual. |

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**THEME: TransATAC**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| 139 | Peony Breast Care Unit | 4.43 DCD | NICE needs to justify more fully its decision to use a bespoke analysis based on the ATAC data in spite of the further justifications set out in the response to the initial guidance. Using NICE's own criteria for excluding the results of the B20 and SWOG 8814 trials, these data should have been rejected also. The trial was not designed to answer this question, and this is a sub-analysis of a 20-year-old trial when treatments were very different. There is no evidence of an independent statistical analysis. There is no evidence to show that this subset is representative of the whole cohort. There is no confirmation of central histological review or a controlled re-analysis of the ER, PR and HER2 status up to today's standards. The Trans-ATAC trial included postmenopausal patients only. There are no supporting trials which confirm this conclusion, indeed there are many which contradict it and, therefore, it does not fulfil the Simon criteria of significance. If these outcomes are correct, then the data management committee of the TailorX trial would have stopped this trial in its early stages. The conclusions reached do not accord with wide clinical experience. | Thank you for your comment which the committee considered.<br><br>The EAG noted that this TransATAC was chosen as a data source because it included data on 4 of the 5 tests of interest and was specific to the population included in the scope. The alternative would be to use different data sources for each test, which would have introduced additional uncertainty and complexity. Also, the group with LN-negative disease could not have been split according to level of clinical risk. The committee concluded that the TransATAC analysis had some limitations, but was the best available data for use in the model (section 5.10 of the diagnostics guidance). |

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**THEME: General comments**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| 140 | NHS Professional | General | I am pleased that NICE listened to the UK Oncology community and acknowledged the ability of OncotypeDx RS assay to predict chemotherapy benefit. | Thank you for your comment which the committee considered. |
| 141 | NHS Professional | General | Dear Committee<br>We as an MDT were delighted to see that you reconsidered the decision to reverse the use of Genomic profiling to help decide on the use of chemotherapy in specific Breast cancer patients. We have been using Oncotype DX for several years and find its role in determining the benefit of chemotherapy invaluable. It has helped identify those who biologically benefit from the addition of chemotherapy to their endocrine treatment and those that don't. | Thank you for your comment which the committee considered. |
| 142 | NHS Professional | General | I hope NICE will reconsider its position on equivalence of the genomic assays recommended and on providing N1 patients access to oncotype DX with low and intermediate risk scores. | Thank you for your comment which the committee considered. |
| 143 | NHS Professional | General | As Oncologists treating breast cancer, we are pleased the new NICE guidelines will allow us to continue using Oncotype Dx testing for node negative patients with higher risk factors. It is extremely important to us that any treatment we give is likely to benefit our patients and that we avoid giving unnecessary and potentially harmful treatment to those who will not benefit, so we strongly support continuing NHS funding for tumour profile testing for node negative, grade 3 and large grade 2 tumours, | Thank you for your comment which the committee considered. |

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**THEME: General comments**

| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| | | | which we all believe has been an important advance in the management of our breast cancer patients.<br><br>We do, however, still have concerns about some of the clinical assumptions remaining in the guidance and also that some important information will not be taken into account. | |
| 144 | NHS Professional | General | I believe that withdrawing the genomic tests will represents a retrograde step, in particular, with respect to node negative patients, who have benefited from genomic testing for several years. Oncotype testing has meant that all those patients with low recurrence scores have been spared chemotherapy and all the toxicities related to the treatment. Furthermore, as genomic testing has been standard of care in some patient groups, there is a duty of candour to disclose the option of this testing to patients in the private sector, which will lead to patients having different treatment pathways based on their ability to self-fund a test. | Thank you for your comment which the committee considered. |
| 145 | NHS Professional | General | Given the weight of high quality evidence from TAILORx it is likely to necessitate a third period of consultation. this should carefully consider whether the evidence supports all three tests. in addition further consideration should be given to including the lower node positive group, particularly micromets only but also 1/2/3 involved nodes. | Thank you for your comment which the committee considered.<br><br>The committee decided to pause guidance development for a month to allow the EAG to do additional work based on the TAILORx publication (Sparano et al. 2018). The committee concluded that although TAILORx is an important piece of evidence |

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| | | | | |
|---|---|---|---|---|
| | | | | showing the effectiveness of gene profiling to guide adjuvant chemotherapy decisions in breast cancer in principle, it is uncertain how applicable it is to people with breast cancer in the UK who are considering adjuvant chemotherapy treatment (section 5.6 of the diagnostics guidance).<br><br>The committee considered evidence on micrometastatic disease presented by the EAG and added a new consideration to the guidance document (section 5.4). It noted that patients with micrometastases were likely to have been included in key studies as LN negative, and concluded that tumour profiling tests should be available as an option for people with micrometastatic disease.<br><br>The committee concluded that the evidence was weaker in the group with LN-positive disease than in the group with LN-negative disease (section 5.3 of the diagnostics guidance), and that further studies |

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| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| | | | | would be helpful to assess the clinical effectiveness of the tests in the group with LN-positive disease (section 5.17 of the diagnostics guidance). |
| 146 | NHS Professional | General | NICE's review of data and comments to allow the use of multiparametric tests to assist decision-making on the need for adjuvant chemotherapy in early breast cancer is welcome. This will continue to ensure chemotherapy is not over prescribed in the UK in those who will not benefit, and indeed will suffer toxicity. However: [see comments 63 and 121] | Thank you for your comment which the committee considered. |
| 147 | NHS Professional | General | I welcome the revised guidance to approve some of the genomic tests, especially to re-instate the previous approval for Oncotype DX. I am sorry, however, to see the we haven't used the opportunity of this review not to move forward the use on Oncotype DX from the 2013 position. | Thank you for your comment which the committee considered. |
| 147 | Agendia N.V. | General | Agendia would like to acknowledge the numerous physicians, breast cancer charities, and other stakeholders that contributed with their comments of support for gene expression diagnostic tests in the public consultation. As elegantly put by one commenter "*The focus of all international meetings in the last three years has been on personalising treatments and only giving patients treatments shown to be of benefit and NOT giving potentially harmful (in the short and long term) and unpleasant treatments just in case they are of benefit*." | Thank you for your comment which the committee considered.<br>The EAG noted that the change made by the company to the EAG model introduces an error which makes the results invalid.<br>The EAG also identified a number of errors in the new Agendia model. |

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|---|---|---|---|---|
| | | | In the assessment of the clinical utility of MammaPrint, the EAG and NICE committee reports that MINDACT provides the highest level of clinical evidence. Moreover, it is also acknowledged that the MammaPrint test identifies a substantial proportion of clinical high-risk patients that that could safely omit chemotherapy without adversely affecting outcome.<br><br>We understand that the lack of a recommendation for MammaPrint by NICE in the previous draft reports was due to MammaPrint not being found cost-effective in the EAG model. We believe we have found a simple programming error in the EAG model that explains why we were not cost-effective previously. In our comments below we present what we feel is the evidence that MammaPrint is cost-effective in the EAG model when this error is corrected. We also present evidence that MammaPrint is cost-effective in an updated Agendia model. | Please refer to the addendum to responses to comments on DCD2 (5 June 2018). |
| 149 | Association of Breast Surgery | Whole document | The Association of Breast Surgery (ABS) believes that NICE is correct to reconsider their original, conclusion regarding the use of tumour profiling tests to guide chemotherapy decisions.<br><br>NICE now recommend that Oncotype, Endopredict and Ensigna are tumour profiling tests that may be used for individualising treatment choices for women diagnosed with breast cancer and found by predict.nhs or the Nottingham Prognostic Index to be of intermediate risk of breast cancer recurrence.<br><br>ABS believes that this will reduce the risk of over treatment with chemotherapy for many women. ABS members will now be able to | Thank you for your comment which the committee considered. |

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| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| | | | continue to use the tumour profiling tests within the recommended parameters for the benefit of their patients. | |
| 150 | Breast Cancer Now | General comment | • *Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?*<br><br>We are very pleased that NICE has now updated their initial recommendation from January 2018 that provisionally rejected five tumour profiling tests for NHS use, including Oncotype DX, which had previously been recommended for NHS use in 2013. This would have represented a significant backwards step for patients, clinicians and breast cancer care across the NHS.<br><br>The updated draft guidance which now provisionally recommends EndoPredict, Oncotype DX and Prosigna as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (ER) positive, HER2 negative, and lymph node negative early breast cancer represents real progress for patients. Prognostic tests like these show great potential to personalise breast cancer treatment and enable some women to be safely spared the gruelling side-effects of chemotherapy. This can help to maintain patients' quality of life, while reducing the costs associated with chemotherapy.<br><br>We know that breast cancer patients are faced with a difficult choice when considering chemotherapy, and even the possibility of chemotherapy is often a major reason for people feeling anxious after a receiving a diagnosis. These tests which can help predict the risk of recurrence, can importantly equip patients with invaluable information to | Thank you for your comment which the committee considered**.** |

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| Comment number | Name and organisation | Section number | Comment | NICE response |
|---|---|---|---|---|
| | | | help them and their clinician make a decision about the best treatment for them. Therefore, we believe the updated draft recommendations now provide a much more sound and suitable basis for guidance to the NHS and hope this will shortly become final guidance. | |
| 151 | Department of Health and Social Care | | I wish to confirm that the Department of Health and Social Care has no substantive comments to make, regarding this consultation. | Thank you for your comment. |
| 152 | NHS England Breast Cancer Clinical Expert Group | General | The Breast Cancer Clinical Expert Group welcomes NICE's further review of data and comments to allow the use of OncoType Dx, Endopredict and Prosigna tests in a selected subset of patients, to assist decision-making on the need for adjuvant chemotherapy in early breast cancer. It is our belief that this will continue to reduce the chemotherapy overtreatment that exists with standard clinico-pathological methods alone. In addition to the obvious cost savings, this will save patients the severe short term toxicity of such treatment which can have prolonged adverse physical, psychological and social effects (which we note in passing seem inappropriately understated in the current NICE draft), as well as the long-term risks of cardiotoxicity and leukaemias which although rare are life-threatening.<br><br>We believe however that three further important issues need to be addressed before the recommendation is finalised, as outlined in the following comments. | Thank you for your comment which the committee considered. |

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**THEME: General comments**

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| 153 | Royal College of Pathologists | | The change from version 1 to version 2 (where multi-gene assays have been recommended) is very welcome | Thank you for your comment which the committee considered. |

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**THEME: Comments on factual accuracy, process and editorial points**

<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td>154</td><td>NHS Professional</td><td>2.1 (page 6)<br><br>3.28 (page 12)</td><td>"stage of disease" should be “stage & grade of disease" Same applies to 3.27"<br><br>Intermediate risk = >3.4 to =<5.4, NOT just >3.4 (the latter definition would include poor prognostic disease,).</td><td>Thank you for your comment. These changes have been made in the diagnostics guidance.</td></tr>
<tr><td>155</td><td>Agendia N.V.</td><td>Erratum (version 19th April 2018), Table 1, p13 of 16<br><br>(corresponds to Table 123, p355 in DAR)<br><br>(theme: incorrect risk classification probabilities)</td><td>Incorrect risk classification probabilities<br><br>The values displayed in Table 1 of the Erratum (p13 of 16) are incorrect and do not correspond to the values published in Cardoso et al., 2016, nor are they the values used in the EAG cost effectiveness model.<br><br>For easy reference the corrected values are displayed below in Table 1 in red text.<br><br>Table 1 – Corrected Risk classification probabilities using MammaPrint (MINDACT)
<table>
<tr><th>Population</th><th>Proportion of patients with risk classification</th><th></th></tr>
<tr><th></th><th>MammaPrint low-risk</th><th>MammaPrint high-risk</th></tr>
<tr><td>MINDACT ITT population (n=6,693)</td><td>0.64</td><td>0.36</td></tr>
<tr><td>MINDACT mAOL clinical high-risk subgroup (n=3,356)</td><td>0.46</td><td>0.54</td></tr>
<tr><td>MINDACT mAOL clinical low-risk subgroup (n=3,337)</td><td>0.82</td><td>0.18</td></tr>
</table></td><td>Thank you for your comment which the committee considered.<br><br>The EAG agreed that the values shown in the table of the erratum do not reflect the correct values for the model. The values in the table were calculated from the patient flow diagram presented in Figure 1 of the MINDACT paper reported by Cardoso et al. However, the model does not use these data. Instead, the model uses the corrected genomic risk data (see “Premodel” worksheet, table in cells B163:L171).</td></tr>
</table>

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| 156 | Agendia N.V. | DAR2 (version 19th April 2018)<br><br>Section 3.1.1.<br>p24 of 510.<br><br>Section 3.2.3<br>p32 of 510<br><br>(theme: Adjuvant! Online) | **Wording to describe Adjuvant! Online throughout current DAR**<br><br>We feel the text on Adjuvant! Online (AOL) does not make it clear to physicians that while the web-based version of AOL is unavailable, mAOL is available to them in an offline form in in the supplementary information (Table S13) of the MINDACT trial [Cardoso et al., NEJM 2016]. Agendia has experience of physicians using this table for this purpose. The modified Adjuvant! Online decision tree used in the MINDACT trial is the only clinical tool, unlike PREDICT and NPI, to have been validated in a prospective randomised control trial and therefore is supported by the highest level of evidence. We feel it is important to communicate to UK physicians in UK national guidelines that the modified offline version of Adjuvant! Online is available to them. We feel that NICE should remain neutral and not promote the PREDICT tool over other tools as has been mentioned in comments by other stakeholders.<br><br>In addition, there exists an online version of the modified Adjuvant! Online tool as used in the MINDACT trial at http://www.mymammaprint.com. This tool incorporates the clinical risk assessment table with clickable options to select the ER status, tumour size, tumour grade and nodal status. The tool then returns a clinical risk classification of “high-risk” or “low-risk” exactly as is used in the MINDACT trial.<br><br>*Section 3.1.1 p24: “Clinicians may use tools such as the Nottingham Prognostic Index (NPI),11 PREDICT or Adjuvant! Online (AOL) to predict disease course and treatment options, although it should be noted that AOL is in the process of being updated and is not currently available.”* | Thank you for your comment which the committee considered.<br><br>PREDICT is now recommended in the NICE guideline on early and locally advanced breast cancer. |

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| | | | Please re-phrase this sentence to: "Clinicians may use tools such as the Nottingham Prognostic Index (NPI),11 PREDICT or AOL to predict disease course and treatment options, although it should be noted that AOL is in the process of being updated and is not currently available in an online executable form."<br><br>*Section 3.2.3 p32 "At the time of writing this report (October 2017), AOL was in the process of being updated and was not accessible"*<br><br>Please re-phrase this section to include the following: 'At the time of writing this report (October 2017), AOL was in the process of being updated and was not accessible. However, the AOL clinical risk decision tree is publicly available and can be found in the supplementary information (Table S13) of the MINDACT trial [Cardoso et al., NEJM 2016]."<br><br>Please also see comment [122] for previous comments on this issue, as we feel it has not been addressed adequately in the DAR (version April 2018). | |
| 157 | Agendia N.V. | Diagnostics Assessment Report (DAR) – Comments, version 30th January 2018 (section: Comparator, | **Adjuvant! Online: Unaddressed previous comment**<br><br>Agendia comment: "*AOL is currently being updated and has been temporarily disabled*."<br><br>Please re-phrase this sentence to: 'Although AOL is currently being updated and has been temporarily disabled the decision tree is publicly available and allows for risk classification of clinical low and clinical high-risk patients and can be found in the supplementary information (Table | Thank you for your comment which the committee considered.<br><br>NICE does not think that an addendum or erratum to the DAR is required because the |

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| | | comment #90 p 96 of 212),<br><br>(DAP37 evaluation report 301117 [No ACIC].pdf, p699)<br><br>(theme: Adjuvant! Online, unaddressed previous comment) | S13) of the MINDACT trial [Cardoso et al., NEJM 2016].' Moreover, this table version of mAOL is as easily accessible or used as NPI e.g. and the offline status of AOL is thus not a reason not to use this tool in current clinical practice or be included in this assessment."<br><br>*EAG response in Diagnostics Assessment Report (DAR) – Comments (version 30th January 2018) p96 of 212 : "This sentence is accurate. Adjuvant online is currently offline because it is being updated with new risk information, meaning the previous version is not the best available tool. The developers of Adjuvant! Online currently (21st November 2017) direct users to PREDICT until Adjuvant becomes available (https://www.adjuvantonline.com/). The report has not been amended."*<br><br>The assumption that "the previous version is not the best available" discounts that Adjuvant! Online v8.0 was validated in a prospective randomized control which NPI and PREDICT have not. This argument can also not be used to discount the usefulness of the decision tree found in the supplementary information (Table S13) of the MINDACT trial [Cardoso et al., NEJM 2016]. We believe it is important that physicians are informed in the DAR report that this table is available to them to use as a tool in the same way that NPI is also available in the form of a publication. | statement does not contain a factual error.<br><br>PREDICT is now recommended in the NICE guideline on early and locally advanced breast cancer. |
| 158 | Agendia N.V. | DCD2 (version 19th April 2018) | *Section 2.11 p6 "Adjuvant! Online is not currently available to the NHS."*<br><br>Please see also see comment [121-122]. Adjuvant! Online is available to the NHS in the form of the supplementary table S13 in the Cardoso et al., 2016 publication. As mAOL is the only tool that has been validated in a randomised control trial, we believe the DAR should not omit this | Thank you for your comment which the committee considered.<br><br>Reference to the description of Adjuvant! Online has been |

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| | | Section 2.11 p6 of 58<br>(theme: Adjuvant! Online) | important information and should categorically provide the reference for this table in the final guidance report. | added to section 2.11 of the diagnostics guidance. |
| 159 | Agendia N.V. | Addendum: EAG responses to key themes within the Comments on the Diagnostics Consultation Document (section 2)<br>(theme: ODx chemotherapy benefit)<br>(Evaluation report 12042018 [no | **Other minor points**<br>Sections 2.1-2.5 in this document appear to be missing. This may be the result of mis-numbering yet please see p4 of the Addendum "EAG responses to key themes within the Comments on the Diagnostics Consultation Document". | Thank you for yor comment.<br>The EAG noted that this was a result of mis-numbering and no information was missing from the document. |

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| | | ACIC].pdf p526) | | |
| 160 | Breast Cancer Now | 3.7, 3.17, 3.22 | During the first consultation in January 2018, Breast Cancer Now along with other commentators were unable to see what evidence had overturned the previous NICE decision to approve Oncotype DX in the node negative group of patients. With this second consultation, it has now become apparent that a number of access proposals have since been put forward by companies and accepted by NICE which appear to have been crucial in influencing the change in the draft recommendation. While we welcome the impact of the access proposals on enabling NICE to provisionally recommend 3 of the tests, we would question whether this could have happened earlier in the process and whether this second consultation and extra committee meeting now required represent a good use of time and resources by NICE which is already stretched.<br><br>Meanwhile, the initial draft recommendation announced in January 2018 also caused significant anxiety among clinicians and patients about the future use of tumour profiling tests on the NHS. We understand that the interim addendum to the diagnostics assessment programme manual: access proposals only enables access proposals to be submitted during the first public consultation period on its draft guidance or at the beginning of the assessment if the price is transparent. It is unclear why this is the case and would suggest NICE considers updating along the same lines as technology appraisals. | Thank you for your comment which the committee considered.<br><br>As noted, the process for producing this piece of guidance has been run in accordance with the NICE diagnostics assessment programme manual and the interim addendum on access proposals.<br><br>Your comments have been noted for any future updates of the diagnostics assessment programme manual. |

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| | | | *Will NICE now review the diagnostics manual to see if any steps in the diagnostics process could be improved which could have led to this outcome in the first instance?* | |
| 161 | Peony Breast Care Unit | 4.48 DCD | Table 1 should have used the data from B20 alone and the RRR is assumed at 36% which is even higher than the 24% RRR used across all risk groups in the EP and Prosigna. B20 showed no benefit to the low risk group. NHSE data shows that 99% of patients in the low risk group are spared chemotherapy. TailorX when reported in 3 weeks time is likely to add significant information to this analysis. | Thank you for your comment.<br>Table 1 in the diagnostics guidance relates to the post-test probability of having chemotherapy, not the relative risk of distant recurrence. |