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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

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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 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: 31 January 2018

Second diagnostics advisory committee meeting: 8 February 2018

1 Draft recommendations

1.1 There is not enough evidence to recommend the routine adoption of EndoPredict, MammaPrint, Oncotype DX Breast Recurrence Score, Prosigna and IHC4+C to guide adjuvant chemotherapy decisions for people with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer with 0 to 3 positive lymph nodes. In particular, more evidence is needed to prove that these tests have a positive effect on patient outcomes. Their cost effectiveness compared with current practice is highly uncertain.

1.2 Further research is recommended on the effect of EndoPredict, MammaPrint, Oncotype DX Breast Recurrence Score and Prosigna

on long-term patient outcomes such as distant recurrence, and on pre- and post-test adjuvant chemotherapy decisions compared with the PREDICT tool (see sections 5.16 and 6.1).

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 the relative benefit of 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 that 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 benefit from improved 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 [PR] or both), human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (stages I or II) 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, lymph node-negative and HER2-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. 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.

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 women 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.

MammaPrint (Agendia)

3.7 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 women with stage I or II 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.

3.8 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.

3.9 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.

3.10 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)

3.11 Oncotype DX Breast Recurrence Score (hereafter referred to as Oncotype DX) is designed to quantify the 10-year risk of distant recurrence and predict the likelihood of chemotherapy benefit. The test also reports the underlying tumour biology: ER, progesterone receptor (PR) and HER2 status. The test is for pre- and postmenopausal women with stage I or II 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 done by Genomic Health.

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

3.13 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.

3.14 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 chemotherapy benefit. A score between 18 and 30 indicates intermediate risk of recurrence and claims to predict no substantial chemotherapy benefit. A score of 31 or more indicates high risk of recurrence and claims to predict a large benefit from chemotherapy.

3.15 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.

Prosigna (NanoString Technologies)

3.16 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 women with early breast cancer that is ER-positive, HER2-negative and LN-negative or LN-positive (up to 3 positive nodes).

3.17 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.

3.18 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.

3.19 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).

IHC4 and IHC4+C

3.20 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 women with early breast cancer that is ER-positive and LN-negative or LN-positive (up to 3 positive nodes).

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

3.22 The IHC4+C test is used in the Royal Marsden Breast Cancer Unit, but the test could be run in local NHS laboratories if appropriate training and quality assurance programmes for the individual assays are in place. At the Royal Marsden NHS foundation trust, the average turnaround time is 1 week.

3.23 The IHC4+C 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

3.24 The comparator is current decision-making for adjuvant chemotherapy prescribing, which is based on clinical and pathological features or the results of tools used to assess risk. 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.

4 Evidence

The diagnostics advisory committee (section 9) 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 chemotherapy benefit – 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 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 chemotherapy benefit were quality assessed using relevant criteria selected 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. However, the details were academic in confidence.

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 NPI in LN-negative, but not LN-positive, disease.

Prediction of chemotherapy benefit

4.22 Oncotype DX and MammaPrint claim to be able to identify patients who will benefit from chemotherapy. The external assessment group (EAG) reviewed evidence in support of this claim.

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 chemotherapy benefit.

4.24 The 2 reanalyses of RCTs suggest that Oncotype DX may predict chemotherapy benefit. Hazard ratios for disease-free survival for patients having chemotherapy compared with those having no chemotherapy suggested that the greatest relative benefit was for patients in the Oncotype DX high-risk category. Unadjusted interaction tests between Oncotype DX risk group and chemotherapy benefit were mainly statistically significant, but

adjusted interaction tests were not always statistically significant. Therefore the EAG concluded that the significant results could be because potentially important covariates were omitted from the statistical model.

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 chemotherapy benefit and RSPC risk group. This suggests that the interaction between treatment effect and recurrence score risk group may be confounded by clinical and pathological variables.

MammaPrint

4.27 Two studies reported the ability of MammaPrint to predict the benefit of 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 discordant risk scores 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 modified Adjuvant! Online high clinical risk, MammaPrint low-risk group, 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 modified Adjuvant! Online low clinical risk, MammaPrint high-risk group, 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 NPI, but not over the NHS PREDICT tool.

RASTER was judged to be at high risk of bias by the EAG 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 have methodological limitations. The comparability of test algorithms applied to microarray data with the commercial assays is unknown, so the generalisability of findings from microarray studies to the decision problem is uncertain. All the studies reported data on Oncotype DX and MammaPrint, and 2 also reported data on EndoPredict. The microarray studies generally support 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 the benefit of 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. 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. 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 dataset, 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 benefit of 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 a 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. The NHS England access scheme dataset is owned by Genomic Health and is a result of the research recommendation from NICE's original diagnostics guidance 10.

Table 1 Source for 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 dataset	0.07		
LN-negative, NPI>3.4	NHS England access scheme dataset	0.43		
LN-positive (1–3 nodes)	NCRAS dataset	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	NHS England access scheme dataset	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				

4.49 In the base-case analysis, the benefit of 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. Sensitivity analyses explored the relative risks of distant recurrence in the modified Adjuvant! Online low- and high-risk subgroups, which were estimated to be 0.84 and 0.74, respectively.

4.50 In sensitivity analyses, the effect of assuming that Oncotype DX could predict the benefit of chemotherapy was explored, based on the studies by Paik et al. (2006) and Albain et al. (2010). For the group with LN-negative disease, the 10-year relative risks of relapse 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.

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.

Costs

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

Table 2 Test costs

Test	Cost	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).
EndoPredict	£1,500	Tests carried out in Myriad's laboratory in Munich.
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 model

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 benefit of 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 the patient had previously developed distant metastases.
- A disutility associated with adjuvant chemotherapy was applied once during the first model cycle only (while the patient is receiving 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 an NPI of 3.4 or less, for tumour profiling tests compared with current practice, the probabilistic model gave incremental cost-effectiveness ratios (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 an NPI of more than 3.4, for tumour profiling tests 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)
- ICH4+C was dominant over current practice (that is, it was less expensive and more effective).

4.62 In the population with LN-positive disease, for tumour profiling tests 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
- ICH4+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.

Probabilistic sensitivity analyses

4.64 The cost-effectiveness planes from the probabilistic sensitivity analyses showed considerable variability in cost-effectiveness estimates.

4.65 In the subgroup with LN-negative disease and an 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.

4.66 In the subgroup with LN-negative disease and an 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.

4.67 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).

4.68 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

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

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

- Subgroup with LN-negative disease and an NPI of 3.4 or less: ICERs remained over £34,000 per QALY gained across all analyses.
- Subgroup with LN-negative disease and an 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 chemotherapy benefit. 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 chemotherapy benefit (it was dominant), and when the cost of chemotherapy was doubled (£3,700 saved per QALY lost).

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

- Subgroup with LN-negative disease and an 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 an 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.

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

- Subgroup with LN-negative disease and an NPI of 3.4 or less: ICERs were greater than £71,000 per QALY gained across all analyses.
- Subgroup with LN-negative disease and an 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.

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

- Subgroup with LN-negative disease and an NPI of 3.4 or less: ICERs remained greater than £91,000 per QALY gained across all analyses.
- Subgroup with LN-negative disease and an 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 conditional 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.

4.74 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 rather than Adjuvant! Online or the Nottingham Prognostic Index (NPI). 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, lymph node (LN)-negative and human epidermal growth factor receptor 2 (HER2)-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 that the tumour profiling tests may have for people with early breast cancer who are deciding whether to have adjuvant chemotherapy. It heard that there is potential benefit for cancers identified as being at low clinical risk, when test results suggest these have a high risk of distant recurrence. These cancers would therefore benefit from chemotherapy. It also heard that there is potential benefit for cancers categorised as high clinical risk, when test results suggest

a low risk of distant recurrence. The committee heard that some people with these cancers could decide not to have chemotherapy, therefore avoiding toxic side effects and effects on fertility. They could potentially resume normal daily activities earlier. Alternatively, others may wish to have chemotherapy regardless of the test result. Also, the clinical experts explained that the tests may mean that additional information can be provided to help people discuss further treatment options. 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 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 on prognostic ability were more variable but all tests except IHC4+C showed statistically 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 some patients who had hormone receptor-negative or HER2-positive disease. The committee concluded that despite the potential spectrum bias, evidence suggests that all the tumour profiling tests have the ability to predict the risk of distant recurrence in the population included in the assessment.

5.4 The committee considered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy. The committee heard from clinical experts that it is likely some patients could have a greater relative benefit from chemotherapy than others, for example, patients with hormone receptor-positive cancer that is insensitive to endocrine therapy, but that evidence is not available to support this. The EAG explained that the evidence on differential chemotherapy benefit according to tumour profiling test results is weak because it is at high risk of bias from potential confounding. The interaction tests (which show whether the tumour profiling test is able to predict a differential relative treatment effect by risk group) in the adjusted analysis in the Paik et al. (2006) study and the Albain et al. (2010) study were statistically significant, but did not adjust for all relevant clinical and pathological variables, in particular hormone receptor status. The committee heard from clinical experts that hormone receptor status may also predict chemotherapy benefit. The committee considered that if all known clinical and pathological variables were included in the analyses then it was likely that the interaction test would no longer be statistically significant, suggesting no differential chemotherapy benefit of the tumour profiling tests alone. The committee concluded that the evidence does not support the assumption that tumour profiling tests can predict chemotherapy benefit.

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 (RCTs) 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, which 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 5.16). 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 dataset provided in confidence to NICE by Genomic Health. The dataset 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 dataset 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 dataset was an important piece of real world evidence for use in the economic model, but that more complete data could potentially have been collected and reported.

5.7 The committee discussed the analytical validity of IHC4+C. The EAG explained that evidence has developed since diagnostics guidance 10 was published. The committee noted that the data showed good correlation between different centres on scoring and staining when 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 decreased substantially. The committee concluded that because of these issues with Ki67, the reproducibility of IHC4+C is poor. It also heard that different methods of assessing ER and PR receptors may be needed for the IHC4+C method compared with those already used routinely, which may introduce additional complexity. The committee concluded that if this test were to be developed further there would need to be substantial investments in staff training and a quality assurance scheme would need to be set up.

Cost effectiveness

5.8 The committee discussed the assumptions and inputs used in the model, and considered the stakeholder comments on the model and EAG responses to these comments. It noted that a bespoke analysis of the TransATAC data was used for risk classification probabilities and for distant recurrence rates conditional on test result for Oncotype DX, EndoPredict, Prosigna and IHC4+C. 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 are 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 committee agreed that the bespoke TransATAC analysis was the best available data for use in the model. The committee also noted their earlier conclusions that current evidence does not support the assumption that tumour

profiling tests can predict chemotherapy benefit (see section 5.4). It agreed that in the base case it was appropriate to assume the same relative risk of distant recurrence across all test risk categories (0.76). The committee considered other assumptions used in the model such as the cost of chemotherapy, the fixed benefit of chemotherapy, and the probability of having chemotherapy. 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.

5.9 The committee noted that the baseline probability of having adjuvant chemotherapy and the probability of having chemotherapy dependent on test result were key inputs driving the differences between the results of the original model for diagnostics guidance 10 and the results of the updated model for the intermediate clinical risk group in this assessment. It also noted that the data sources for these inputs in the original model were a published abstract with few details available about the methods (Holt et al. 2013) and data from the English Cancer Registry, and that the updated EAG model used data from Genomic Health's access scheme dataset. The committee concluded that this dataset is most likely to reflect chemotherapy use in NHS clinical practice and is therefore a more suitable data source for the model.

5.10 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 reflect current NHS clinical practice, which leads to uncaptured uncertainty in the model results. The committee concluded that future research on tumour profiling tests should include comparisons with PREDICT (see section 6.1).

5.11 The committee considered the incremental quality-adjusted life year (QALY) results from the model. It noted that the differences in the QALYs were small and that in the base-case analyses Oncotype DX and MammaPrint both had a QALY loss in some subgroups compared with current practice or modified Adjuvant! Online respectively. This led to these tests being dominated by the comparator. It also noted that in deterministic sensitivity analyses, Oncotype DX and MammaPrint sometimes had a QALY gain compared with the comparator. The committee concluded that the QALYs derived from the model are uncertain.

5.12 The committee considered the incremental cost-effectiveness ratios (ICERs) resulting from the model. It noted that the ICERs for EndoPredict in LN-positive disease, and for Prosigna in LN-negative intermediate-risk disease and LN-positive disease, fell between £20,000 and £30,000 per QALY gained. However, the committee considered these ICERs to be highly uncertain because of the available clinical data. It also noted that the ICERs for IHC4+C were low or dominating in all subgroups. But the committee noted its earlier conclusion on the analytical validity of IHC4+C (see section 5.7) and felt that the test cost had been underestimated because it did not include any costs for training or for setting up a quality assurance scheme. The committee concluded that the cost effectiveness of all tumour profiling tests was highly uncertain.

5.13 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. The committee heard from a clinical expert that the biology of a cancer and its molecular subtype, for example the 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.

5.14 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.

5.15 The committee considered its earlier conclusions that none of the tests had strong enough evidence of a positive effect on patient outcomes (see section 5.5) and that their cost effectiveness compared with current practice was uncertain (see sections 5.10 and 5.12). The committee concluded that none of the tumour profiling tests should be recommended for routine use in the NHS.

Research considerations

5.16 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 (see section 6).

6 Draft recommendations for further research

6.1 Further research is recommended comparing the tumour profiling tests (EndoPredict, Oncotype DX, MammaPrint and Prosigna) with the PREDICT tool. The results should record both pre- and post-test adjuvant chemotherapy decisions.

7 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 6 into its guidance research recommendations database (available on the NICE website) and highlight these recommendations to public research bodies.

8 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
January 2018

9 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:

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Diagnostics Advisory Committee date: 14 March 2018

THEME: General comments

Comment number	Name and organisation	Section number	Comment	NICE response
1	NHS Professional	General	Being able to request an Oncotype Dx test for my breast patients where there is uncertain benefit has revolutionised my practice. It is difficult to put a price on the relief that a patient has when told that they do not need to have chemotherapy which is unlikely to help them. The more we can personalise treatment, the less wastage we shall have and be able to focus treatments on those who are likely to benefit.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
2	NHS Professional	General	I am writing on behalf of the Breast Multidisciplinary Team at The Great Western Hospital, Swindon. We have several years of experience using the Oncotype DX test for patients at higher risk of breast metastases, who would normally receive adjuvant chemotherapy. Approximately 50% of patients with higher risk breast cancer (using on line risk calculators) will not benefit from chemotherapy - there is a good evidence base for this. Not only is the unnecessary chemotherapy costly to the Trust but there is significant morbidity for the patient for little survival benefit. The Oncotype DX assay can predict the likely benefit of chemotherapy, thereby having a positive effect on patient outcomes.	Thank you for your comment which the committee considered. The EAG noted that all available data from TAILORx were included in the diagnostics assessment report. It also noted that TAILORx uses RS<11 and RS>25 as the cut off points for low and high risk patients respectively, rather than RS<18 and RS>30 as defined in the scope for this assessment.

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			The TAILORx Trial data has not been incorporated into the document for consultation. We feel that individualized, tailored treatment for our breast cancer patients will be lost if we lose the ability to send patient's samples for genetic analysis. In an era where other common tumours such as lung and colon tumours undergo genetic evaluation, taking away that option for breast cancer patients means that women will have less access to personalized treatment. It is the view of the MDM that this would be a retrograde step and one which we do not agree with.	The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
3	NHS Professional	General	Despite involvement in several economic modelling studies and a workable knowledge of the field it is quite impossible to do justice to the complex 63 page ICER analysis in the hour or so a busy Clinical Oncologist can afford. In brief: Excluding decision utility papers from the review seems odd to say the least as this is the whole raison d'etre for predictive molecular tests being developed for adjuvant decisions many cancers. The aim is to reduce the NNT 30 year data from the original Milan studies show a sustained OS and DFS benefit particularly in the 4+ node group. Using the meta analysis data and assuming an equal chemo benefit is not realistic. I am not sure that a QUALY and ICER analysis is required for this question. The DFS and OS outcomes from chemo vs no chemo are a different issue and not the question. The question is can we save morbidity and mortality from over-treatment,	Thank you for your comment which the committee considered. The EAG noted that the cost-effectiveness of adjuvant chemotherapy is likely to be dependent on patient subgroup; it is not a foregone conclusion that adjuvant chemotherapy cannot be cost-effective in any population. It is reasonable to suggest that the cost-effectiveness of chemotherapy will depend on the baseline recurrence rate and the relative benefit of treatment. Please refer to EAG addendum point 8.

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			not the disease or adjuvant benefits, small or large. It is self evident that node negative chemotherapy given routinely for the last 20 years would never get NICE ICER based approval now as the costs per QUALY would be prohibitive. The question is which node negative patient groups should it be used in until OPTIMA reports. eg rather than the outdated NPI, the Magee equations or similar can be used to reduce overuse of Dx. Finally to include AML in the modelling seems odd as there are many much bigger late mortality and morbidity effects from adjuvant chemotherapy than AML which have not been mentioned. cardiac, metabolic syndrome etc etc	Further analyses on the differential benefit of chemotherapy, and on adverse effects of chemotherapy can be found in the third addendum to the diagnostics assessment report. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
4	NHS Professional	General	It is a significant concern both to myself and our MDT at Milton Keynes University Hospital that this proposal document seems to be taking a step back away from good patient care. We are very used to tailoring care to meet the individual patient and their cancer. With the small, early breast cancers, which are HER 2 -ve and 0 - 3 lymph nodes, we have a significant number of our patients. This group is a difficult group to treat as we know their cancers are not identical. Oncotype-DX and other assays allow us to discriminate the patients who will benefit from chemotherapy and those who won't. To go back to a one size fits all approach to cancer treatment is a backward step and will end up in some patients dying needlessly of cancer, due to under treatment or patients suffering the significant side effects of over treatment. It	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			is also seems financial mismanagement to treat patients with expensive medication they do not require for the price of an assay. I invite you to meet our patients who have benefitted from this treatment, and urge you to reconsider your decision to not drag breast cancer treatment backwards but go forward with excellent care.	1 in the second diagnostics consultation document.
5	NHS Professional	General	Agree with the draft guidance. There is lack of evidence to show that genomic tests add additional value to freely available tools such as PREDICT, Adjuvant online etc. to plan patient management. More importantly, there is no prospective randomised study showing the benefit of the genomic tests in improving patient outcomes.	Thank you for your comment which the committee considered.
6	NHS Professional	General	Our MDT has been using Oncotype for more than a year. I found it very useful in decisions on chemotherapy especially in the PREDICT 3-5% benefit group. Please consider the recent long term studies and the Taylor X study expected in June 2018 before making a final decision on the cost benefit of genomic testing. Overall I feel that it helps target chemotherapy better in breast cancer patients.	Thank you for your comment which the committee considered. The EAG noted that these studies were included in the diagnostics assessment report, but that TAILORx has not fully reported. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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				1 in the second diagnostics consultation document.
7	NHS Professional	General	*Without access to a tumour profile test patients may well receive unnecessary chemotherapy (over treatment) OR in a patient that would normally be considered to be low risk they will not be identified as high risk and will not receive the necessary chemotherapy treatment (undertreated).* *In both these scenarios patients will not be getting the best treatment for them and both options would incur additional costs. Withdrawal of these tools appears to be a short sighted view and a backward step for our patients with breast cancer.*	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
8	NHS Professional	General	*This would be a massive retrograde step for breast cancer patients. In the real world data and in the audit of oncotype Dx in NHS patients with a low score are spared chemotherapy - it would seem that the model doesn't adequately take into account the impact of avoiding chemotherapy.*	Thank you for your comment which the committee considered. The EAG did further analyses on the adverse effects of chemotherapy which can be found in the third addendum to the diagnostics assessment report. The committee considered the extensive comments on the draft

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				recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
9	NHS Professional	General	The proposed decision to block the use of gene profiling is perverse and unreasonable. It places no value on giving chemotherapy to the most appropriate patients, but instead concentrates narrowly on total cost. Pound-centred decision making, I expected more patient-centred consideration.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
10	NHS Professional	General	The high rate of uptake of Oncotype, plus the 99% rate of "no" chemotherapy in the low RS group: emphasise the faith the UK oncology community have in the Oncotype data.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the

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				companies, and decided to revise section 1 in the second diagnostics consultation document.
11	NHS Professional	General	My opinion is that this guidance represents a backward step in the care of patients with breast cancer in the UK and will leave us lagging behind the rest of the world. The potential outcomes from this guidance may be an increased number of patients receiving chemotherapy (perhaps unnecessarily) and experiencing potentially life-long and life-changing effects (the long term toxicity of chemotherapy does not appear to have been modelled in the cost effectiveness analyses). In addition, the increase in number of patients receiving chemotherapy will place additional burden on the already stretched chemotherapy units across the country (potentially leading to more delays in treatment and suboptimal outcomes) and acute emergency services managing the acute morbidity effects of chemotherapy (e.g. neutropenic sepsis). I strongly appeal to NICE to reverse this decision.	Thank you for your comment which the committee considered. The EAG did further analyses on the adverse effects of chemotherapy which can be found in the third addendum to the diagnostics assessment report. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
12	NHS Professional	1 (page 2)	1.NICE's recommendation 'There is not enough evidence to recommend the routine adoption of [ANY genomic or IHC test] to guide adjuvant chemotherapy decisions' Document 1 (DCD), Section 1, Page 2/48	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
			Comment: If this draft guidance stays as it is , more than 4 years of progress in the management of early breast cancer will be undone, as many more patients will inevitably receive unnecessary chemotherapy from my personal experience, leading many patients to endure unnecessary debilitating side-effects, and potential long-term harm without any substantial benefit. This will also place substantial increased demands on already stretched NHS resources including staff and chair time in the day units. Document 1 (DCD) Section 1 ˜Draft recommendationsâ€™, Page 2/48 “There is not enough evidence to recommend the routine adoption of the Oncotype DX test. In particular, more evidence is needed to prove that these tests have a positive effect on patient outcomes” COMPLETLEY AT ODDS FROM 2012 NICE RECOMENDATIONS	The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
13	NHS Professional	General	The Sandwell and West Birmingham Breast MDT represents a large proportion of the population of Birmingham and Sandwell. This MDT has a diverse socio-economic catchment area and includes some of the most deprived areas in the country. We have read with dismay the recent draft guidance regarding the withdrawal provision of genomic testing in adjuvant breast cancer patients with ER positive Her2 negative disease. We believe this 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 which is associated with	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			significant long and short term sequellae, for example permanent effects on fertility, cardiovascular system, peripheral nervous system in addition to short term effects such as infection (often requiring hospital admission), diarrhoea and lethargy. Many breast cancer patients are working and/or have caring responsibilities and thus chemotherapy can cause significant economic and social hardship. 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, this may lead to less well of patients having different treatment pathways based on their ability to self-fund a test. Thus, those unable fund their own genomic testing (which will represent most of our patients) will be routinely offered chemotherapy which may not be of clinical benefit. The data provided by genomic testing is far more discriminating than tools such as NHS Predict which our MDT already uses. We strongly urge you to reconsider your decision to withdraw genomic testing in this patient population in particular in those node negative patients who have previously been routinely tested. [redacted] - Consultant Oncologist [redacted] - Consultant Oncologist [redacted] - Consultant Surgeon [redacted] - Consultant Surgeon [redacted] - Consultant Surgeon	1 in the second diagnostics consultation document.

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			[redacted] Consultant Oncologist [redacted] - Consultant Surgeon [redacted] - Consultant Surgeon [redacted] - Consultant Oncologist [redacted] - Consultant Oncologist	
14	NHS Professional	General	I would like the NICE committee to reconsider the decision about the use of Oncotype Assay for node negative (ER positive, Her-2 negative) patients. The appropriate use of test has reduced the unnecessary use of chemotherapy for patients with low/intermediate RS and select the high risk patients who are most likely to derive the benefits of adjuvant chemotherapy. It reduce overall patient's treatment related morbidity from chemotherapy and potential save valuable NHS resources. The cost-effectiveness model takes patients risk of developing metastatic cancer and benefits of adjuvant chemotherapy as standard with no stratification of benefits based on prognostic features/RS.	Thank you for your comment which the committee considered. The EAG noted that the model is evaluated in terms of 3 risk groups: LN0 NPI≤3.4, LN+ NPI>3.4 and LN+ (1-3 nodes). Patients' prognosis differs considerably between these 3 groups. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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15	NHS Professional	General	The oncotype DX assay has been used at our NHS trust since Apr 2015 following NICE evaluation in September 2013 and inclusion in diagnostic guidance 10. Local audit of 2015/16 has shown full integration of this tool in our clinical practice with all NICE eligible patients tested. My concern in this regard with the withdrawal of the use of oncotype DX is that this may expose an inequality to breast cancer care. The test may then reside only with the affluent or privately insured patients creating a potential divergence in care pathways for these patient groups as clinicians will continue to value the test as I do based on my review of the clinical data. This clinical evidence base is also continuing to increase providing further evidence for clinicians to use to their use of the test in practice. Please see my comment part 2 [comment 16] for conclusion of my feedback and response.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
16	NHS Professional	General	The drive towards individualised and targeted treatments for patients has made very important and positive strides across all branches of medicine. The oncotype DX assay has been an important part of delivering more bespoke and tailored treatment options for our breast cancer patients. I see great further potential of this assay to provide further assistance to clinicians and patients in tailoring treatment for other potentially lower risk patients such as N1 (1-3 nodes) and in assisting the use of neoadjuvant chemotherapy discussions. I am obviously disappointed at the	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			NICE consultation document that may now see the removal of this valued test. I also believe this will set back the advances in genomic profiling being made that will provide the opportunity to provide that bespoke treatment plan for greater cohorts of breast cancer patients. I hope that NICE reconsiders the evidence and the feedback provided so that we may continue to offer Oncotype DX to aid the treatment of breast cancer patients.	1 in the second diagnostics consultation document.
17	NHS Professional	General	The availability of Oncotype DX has, in our practice, in the last 4 years resulted in a significant reduction in the proportion of women being recommended adjuvant chemotherapy in the group where clinicians had previously had uncertainty regarding the potential (often small) benefits from chemotherapy. This draft guidance would appear to suggest that other highly qualified, internationally recognised groups such as ASCO, NCCN, ESMO, St Gallen etc which have all endorsed these tests in one form or another, as being the best available evidence on which to support these decisions are wrong. The results generated for Oncotype DX using the EAG model appear to be flawed and misinterpret the evidence seen in the published literature. For clinicians having to return to the difficulties of decision making with only standard clinico-pathological variables, with their well recognised limitations is extremely disappointing and does not do justice to the breast cancer population either patients or clinicians. Further evidence in the form of prospective clinical trials	Thank you for your comment which the committee considered. Clinical guidelines do not always include an analysis of cost-effectiveness and as such different decisions are to be expected from time to time. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			(apart from those already ongoing) will prove difficult where the international world has moved on and already endorsed these tests leaving the UK even further behind.	
18	NHS Professional	General	I am submitting the comments in the capacity of a health care professional (consultant breast surgeon since 2001) and a clinical academic actively involved in breast cancer research, including clinical trials and translational research with a focus on endocrine therapy and breast cancer in older patients.	Thank you for your comment which the committee considered.
19	NHS Professional	General	The draft recommendation is INCONSISTENT with international guidelines/consensus e.g. American Society of Clinical Oncology and St Gallen Consensus: 1. American Society of Clinical Oncology (ASCO) - Use of Biomarkers to Guide Decisions on Systemic Therapy for Women With Metastatic Breast Cancer Guideline Status: Current Published online before print July 10, 2017, doi: 10.1200/JCO.2017.74.0472 'If a patient has hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population	Thank you for your comment which the committee considered. Clinical guidelines do not always include an analysis of cost-effectiveness and as such different decisions are to be expected from time to time.

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			with potentially limited chemotherapy benefit. Women in the low clinical risk category did not benefit from chemotherapy regardless of genomic MammaPrint risk group. Therefore, the MammaPrint assay does not have clinical utility in such patients. If a patient has hormone receptor-positive, HER2-negative, node-positive breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and a high clinical risk to inform decisions on withholding adjuvant systemic chemotherapy. However, such patients should be informed that a benefit from chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node. The clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy in patients with hormone receptor-positive, HER2-negative, node-positive breast cancer at low clinical risk, nor any patient with HER2-positive or triple-negative breast cancer, because of the lack of definitive data in these populations.' 2. St Gallen's Consensus - Breast Care (Basel). 2017 May;12(2):102-107. doi: 10.1159/000475698. Epub 2017 Apr 26. St. Gallen/Vienna 2017: A Brief Summary of the Consensus Discussion about Escalation and De-Escalation of Primary Breast Cancer Treatment. Gnant M1, Harbeck N2, Thomssen C3. 'The questions regarding multigene tests specifically addressed 5 tests, i.e. Breast Cancer IndexÂ®, EndoPredictÂ® (EPclinÂ®), MammaPrintÂ®, Oncotype DXÂ®,	

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			and ProsignaÂ®. The majority of panelists (86%) did not consider multigene testing necessary in pT1a-b pN0 ER+ PR+ HER2- low Ki67 and low grade EBC. Overall, outside of this low-risk subgroup, panelists agreed that all multigene tests provide valuable information on prognosis and risk, thus helping to omit chemotherapy in ER+ HER2- pN0 EBC. In pN+ disease (i.e. in 1-3 involved lymph nodes), agreement regarding prognosis was lower and some tests even received a 'no' vote for using it in order decide about chemotherapy in this population (table 2). Only 46% of the panelists (no 50%) believed that multigene signatures provide valuable information for decision regarding extended endocrine therapy.'	
20	NHS Professional	General	The consensus among the majority of international experts is that gene profiling has the highest level of evidence for use in predicting prognosis and selection for chemotherapy in the intermediate risk (node negative) group, which is consistent with the current NICE recommendation, though it stipulates only one test Oncotype DX to be useful. However, the draft recommendation stipulates that none of the tests are useful. This recommendation is concerning and inconsistent with the consensus and evidence accumulated thus far.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
21	NHS Professional	General	By backtracking the recommendation with a blanket approach in the same group (intermediate risk, node negative) of patients as opposed to the current recommendation which has already been implemented for some time in the NHS	Thank you for your comment which the committee considered.

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			will cause significant concerns for a number of stakeholders: - Public/Health care professionals - Can NICE confirm if the basis for the current recommendation was flawed? If not, can adequate explanation be given as to why the current recommendation is in place? - Patient groups: - The ongoing implementation of the current recommendation means that at least one assay is available in the NHS and patients have personally experienced its application in predicting their prognosis and informing the decision to receive chemotherapy or not. Can NICE provide adequate justification to our patients for stopping this current provision?	The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
22	NHS Professional	General	One of my clinical and research interests is in optimising the treatment of breast cancer in older patients. Evidence suggests that older patients are more likely not to be given adjuvant chemotherapy if such assays are not available, which could impact on survival. The use of these assays provides guidance to inform the clinician and patient in discussing the pros and cons of adding chemotherapy in this group of patients with intermediate risk. Otherwise older patients are more likely to suffer from potential 'under'treatment'.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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23	NHS Professional	2 (page 48)	It is contradictory to state that there is insufficient evidence to recommend routine adoption of Oncotype DX testing when the 2013 guidance issued a positive recommendation for the test; since then long term patient outcomes on over 63 000 patients have been published. The withdrawal of tumour profiling will have an adverse impact on breast cancer patients in the UK, subjecting more patients to 'unnecessary' treatment and 'over-treating' others.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
24	NHS Professional	General	I don't think that it is coast effecttive I aso can't see out come of patients who where supposed to be on low recurrwnce score (not benifiting from chemotherapy) had chemo left over with the complications	Thank you for your comment which the committee considered.
25	NHS Professional	General, page 1	‘There is not enough evidence to recommend the routine adoption of [ANY genomic or IHC test] to guide adjuvant chemotherapy decisions’ This statement does not fit with the available data in peer reviewed journals or with the international consensus regarding the use of genomic assays to guide adjuvant chemotherapy decision making in women with ER+ early breast cancer eg (1) Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology, Volume 26, Issue suppl_5, 1 September 2015, Pages v8â€“v30; (2) Use of Biomarkers to Guide Decisions on Adjuvant Systemic	Thank you for your comment which the committee considered. The EAG conducted an independent review of the evidence. Clinical guidelines do not always include an analysis of cost-effectiveness and as

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			Therapy for Women with Early-Stage Invasive Breast Cancer: American Society of Clinical Practice Guideline (Krop et al., July 10, 2017, doi: 10.1200/JCO.2017.74.0472)	such different decisions are to be expected from time to time.
26	NHS Professional	General	The current guidance if implemented and the 21 gene recurrence score removed from NHS patients will be a step backwards, and will inevitably mean many women are exposed to chemotherapy unnecessarily with all the related effects on their physical, psychological and social well being, To say nothing of the impact of the extra healthcare costs associated with delivering this unnecessary treatment and with all the related toxicities and hospital admission. Chemotherapy is associated with a very small risk of death and it can not be completely discounted that some preventable deaths could occur if the 21 gene recurrence score is withdrawn, and women treated unnecessarily with chemotherapy.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
27	NHS Professional	General	Section 1 ˜Draft recommendations", Page 2/48 NICE's draft recommendation states 'There is not enough evidence to recommend the routine adoption of the Oncotype DX test. In particular, more evidence is needed to prove that these tests have a positive effect on patient outcomes' In 2013 NICE made a positive recommendation for the adoption of the 21 gene recurrence score. The reversal of this positive finding is surprising to say the least. It can only be assumed this reversal is based on the flawed, selective analysis	Thank you for your comment which the committee considered. The EAG noted that all relevant studies were included in the clinical review. The committee considered the extensive comments on the draft recommendations, along with new value

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			(mentioned previously), it should be noted this analysis would not likely stand up to international peer review scrutiny by experts in the field.	propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
28	NHS Professional		There is evidence beyond doubt that patients with low recurrence Oncotype Dx score do not benefit from chemotherapy therefore the test is justified to avoid unnecessary chemo risks to these patients. Our institutions has used the test for 4 years and avoided unnecessary harm to many patients. Withdrawing the opportunity to perform the diagnostic assay will be a big step backwards.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
29	NHS Professional	General	The conclusions of this document from the large body of evidence that shows that tumour profiling tests in breast cancer identify patients who traditionally would receive chemotherapy but due to the low risk of recurrence the absolute benefit of chemotherapy is outweighed by chemotherapy toxicity. There is a need for it to be applied only to groups that are being considered for chemotherapy and not every breast cancer patient. These tests are prime example of personalised medicine and to remove NHS	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			access is a backward step and can lead to more patients undergoing unnecessary toxic and potentially life threatening treatment when several validated tests may have shown that chemotherapy's absolute benefit would not have been clinically significant. this would be an injustice. The impact of chemotherapy on those patients, relatives, their employers and the wider community is very great indeed.	1 in the second diagnostics consultation document.
30	NHS Professional	General	I am deeply disappointed by draft document. The oncotype test (previously recommended by NICE in 20143) has been used extensively within my unit and has spared unnecessary chemotherapy for breast cancer patients at low risk of recurrence. It is an essential tool in this era of personalised medicine. I believe the methodology used in this assessment is flawed. Firstly it assumes that all patients derive the same benefit from chemotherapy. We know that not to be true. The model overestimates the risk of recurrence in the lower risk women. This overinflation of risk gives the impression that omitting chemo in this group is more detrimental than is the case. I am concerned that this is a retrograde step in the individualisation of breast cancer adjuvant treatment decision making and would urge NICE to reconsider. I would also ask that when reconsidering the Israeli dataset and the TAILORx dataset are included in the analysis. Cytotoxic chemotherapy has untold effects on fertility, cognitive function, patient well being. Oncotype has allowed our MDT to tailor individual chemotherapy decisions and to direct chemo where it will give the best benefit.	Thank you for your comment which the committee considered. The EAG performed additional analyses on risk of recurrence, differential chemotherapy benefit, and adverse events associated with chemotherapy (see the third addendum to the diagnostics assessment report). These were considered by the committee. The EAG noted that the clinical review in the diagnostics assessment report includes all relevant available data, including TAILORx. The committee considered the extensive comments on the draft

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				recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
31	Private sector professional	General	I was extremely surprised by your recent draft guidance, which contradicts the guidelines issued by leading bodies, such as the American Society of Clinic Oncology. The modern era of cancer medicine treatment needs to be personalised and, therefore, genomic profiling for ER positive disease has become an integral part of modern breast cancer management, so that the right patient will receive chemotherapy. I acknowledge that your data was based on the use of Oncotype and overall the use of chemotherapy was not reduced. Even in this setting, some patients who received chemotherapy would have been otherwise deprived from it since standard pathological parameters do not accurately predict the disease behaviour in relation to relapse. The data regarding these genomic tests were derived from patients who have already participated in randomized clinical trials and, therefore, the level of evidence of considered one. The Multi-Disciplinary Team at the London Breast Institute has been using the EndoPredict Clinical genomic score for patients with early ER positive breast	Thank you for your comment which the committee considered. Clinical guidelines do not always include an analysis of cost-effectiveness and as such different decisions are to be expected from time to time. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			cancer. The score combines standard pathological parameters with the expression of genes which reflect proliferation and responsiveness to endocrine therapy and this has been shown to be superior to Oncotype DX in post-menopausal patients participating in the ATAC trial. We acknowledge that some patients, who are identified as low risk by conventional algorithms and scores, such as NHS Predict and NPI will yield a high genomic score and will be advised to receive adjuvant chemotherapy. We believe this will lead to a survival benefit, since there is a growing body of evidence that tumours can metastasise at a very early stage of development, ie, one measuring 5mm. The advantage of Endopredict Clinical is the lack of intermediate group, since the test is binary (low risk or high risk). We would be very grateful if you could reconsider your decision regarding the use of genomic profiling, since this will represent a step backwards for the country when the whole world is moving towards personalised cancer medicine. We believe that a statement similar to the American Society of Clinical Oncology, regarding the use of genomic profiling assays, such as Endopredict, Oncotype, Mammaprint, etc would be more objective and evidence based. Yours faithfully [redacted] MS FRCS on behalf of the MDT at The London Breast Institute	

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			Consultant Oncoplastic Breast Surgeon Professor of Breast Cancer Surgery	
32	NHS Professional	General	In the UK, we have spent the past 4-5 years using oncotype as an aid in intermediate prognosis breast cancer which is now at risk in this new guidance with many of these patients going on to receive unnecessary chemotherapy. This will place substantial increased demands on NHS services in the UK. The guidance has stated that low-recurrence score patients derive substantial relative benefit from chemotherapy which is simply not evidence based and our local audit has shown that these woman (after testing) choose not to have chemo. Your analysis states that these patients are being denied substantial chemotherapy benefit and implies that all patients should be given chemotherapy to receive the benefit which is not in line at all with current UK practice This is a unexpected conclusion, given that in 2013 NICE made a positive recommendation for the routine adoption of the Oncotype DX test and since then the evidence base for the test has been strengthened by long term patient outcomes evidence in thousands of patients. We believe NICE should therefore revise this recommendation as a matter of urgency	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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33	NHS Professional		"The basis of the NICE decision is based on a diagnostic assessment report written by ScHARR. The DAR report is fatally flawed in several areas and should not be the basis of any NICE decision as it is incorrect. For most Clinicians the most important thing is to be able to decide whether a patient will benefit from chemotherapy and prognosis is assessed in other ways. The only two assays which are of any value therefore and claim predictive evidence for chemotherapy are MammaPrint and the Oncotype DX assay. The Oncotype DX assay has made a huge difference in the UK because it has increased both patient and Oncologists confidence in the decision made about chemotherapy and reduced chemotherapy usage by 70% in the UK. Patients do not like having to undergo unnecessary debilitating side effects and potential long term harm. There is a large economic cost to them and their families. The calculations and assumption are based on a post-menopausal dataset, yet use premenopausal mortality assumptions on a postmenopausal dataset but the main economic benefit to either patients or the country is in a premenopausal group of patients.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
34	NHS Professional	General	"The assumption that genomic analysis of tumours does allow prediction of differential sensitivity to treatment is accepted internationally, such that MammaPrint and Oncotype DX are now part of international (ASCO,St Gallen,NCCN) guidelines. It is disappointing and surprising that a non-cancer EAG	Thank you for your comment which the committee considered.

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			has misinterpreted 10 years of research evidence, which is internationally accepted. The basis of this review is poor oncological advice and incorrect assumptions and bias. The fact that 99% of patients who are low RS do not get chemotherapy in the UK indicates the test is accepted evidence in the UK by patients and Oncologists alike.	The EAG noted that the 99% rate of no chemotherapy in the low RS group is only meaningful when it is linked to patient outcomes. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
35	NHS Professional		"The international community has examined these tests at length notably ASCO and St Gallen Consensus Group and has agreed that the validation studies on ONCOTYPE DX allow the use of this test for the intermediate/ equipoise group (PREDICT 3-5% abs benefit /LN negative NPI>3.4) to add further information to the clinical parameters to guide chemotherapy use. It is thus in this particular group that we should use this particular test and continue to gain further information on the other tests and risk groups from clinical studies. It would be a retro grade step to be overtreating this particular group of patients without the extra information from this test, with all the long and short term toxicity chemotherapy entails. The analysis makes reference to AML as a toxicity cost but	Thank you for your comment which the committee considered. Clinical guidelines do not always include an analysis of cost-effectiveness and as such different decisions are to be expected from time to time. The EAG performed additional analyses on risk of recurrence and adverse events associated with chemotherapy (see the

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			not to long term cardiac toxicity which is well publicised together with loss of earnings and increased social costs whilst on chemotherapy. The analysis seems to assess the whole issue of LESS chemotherapy for this equipoise group as detrimental because, it uses unpublished low number data (bespoke NCRAS TransATAC data) to achieve an artifically high risk of relapse for this group, making the risk of NOT giving chemotherapy more significant than it should be.	third addendum to the diagnostics assessment report). These were considered by the committee. The NICE reference case excludes productivity costs and other societal costs were therefore not included in the EAG economic model. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
36	NHS Professional	General	It has been falsely considered that all patients could derive a benefit across the 3 recurrence score groups but this is not the case. Only patients with high recurrence scores are likely to benefit. In addition, those who have lower scores and have not been tested may well have ""routine"" adjuvant chemotherapy with its associated toxicity when they actually were very unlikely to have any benefit.	Thank you for your comment which the committee considered. The differential benefit of chemotherapy is discussed in detail in the third

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			Not have access to any personalised molecular-based assay is a retrograde step and will result in increased use of unnecessary chemotherapy and reduced quality of life for our patients. It is a step backwards and an embarrassment to our international colleagues where these tests have been part of routine practice for a while.	addendum to the diagnostics assessment report. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
37	NHS Professional	General	The proposal by NICE (DG10) has many incorrect assumptions about the utility of adjuvant chemotherapy in patients with early breast cancer and in particular the potential benefits patients derive from genomic assays in guiding the use of adjuvant chemotherapy, particularly in patients considered to have a low risk of cancer recurrence, where chemotherapy can be omitted thus reducing the morbidity associated with treatment. The proposal also has made incorrect assumptions about the economic benefits to the NHS in terms of costs saved for low-risk patients avoiding chemotherapy which can be substantial. Finally the evidence has disregarded significant real-world data collected internationally involving thousands of women and data from the TAILOR X trial. The assumptions made in the document and evidence review are questionable and need to be reviewed again.	Thank you for your comment which the committee considered. The EAG noted that all available published data from TAILORx were included in the diagnostics assessment report. It also noted that TAILORx uses different cut points to those specified in the NICE scope. The committee considered the extensive comments on the draft recommendations, along with new value

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				propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
38	NHS Professional	General	At St Helens and Knowsley Breast MDT we are worried about the future implications for the proposed guidance regarding genomic testing. We have been using Oncotype testing from 2013 when it was first approved by NICE and have found it invaluable when discussing adjuvant chemotherapy. Not only is it useful for the Oncology decision process but the graphs are helpful in discussing risks with patients in the intermediate category. Not only would we urge NICE to rethink the plan for withdrawal but we would have hoped NICE would consider expanding the indications for Oncotype to include patients that are 1-3 nodes positive. This would save more patients from potentially harmful chemotherapy and would reduce considerable costs for the NHS. The Manchester data on node positive patients shows that 66% of patients did not require chemotherapy due to their low recurrence score from Oncotype. From our own data, using only node negative patients, in the last year we ordered 33 tests. Only two of these had a high recurrence score and therefore majority of patient who were likely to undergo chemotherapy by traditional predictive criteria did not.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			This test not only saves cost but also saves a lot of patients the unnecessary side effects of chemotherapy when the benefits are likely to be marginal. We implore you to rethink your recommendations Best wishes, [redacted] and [redacted], on behalf of the St Helen and Knowsley Breast MDT	
39	NHS Professional	General	Adjuvant chemotherapy carries a significant risk with a death rate of approximtely 1 in 400, those with a demonstrably low risk of recurrence at diagnosis as demonstrated by these tests (and there is a large amount of data to support this for oncotype dx) have very little likelihood of benefit from chemotherapy, which should be avoided to save pateints the morbidity of chemotherapy and this iatrogenic reisk of death, oncotype dx idefntifies significant numbers of patients at at ow riks and in whom chemotherapy can be avoided and is therefore of ennormous beneifit. IT would be very disappointing if this test was no longe ravailable.	Thank you for your comment which the committee considered. The EAG did additional analyses on the adverse effects of chemotherapy which are detailed in the third addendum to the diagnostics assessment report. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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40	NHS Professional	General	I was a Specialist Member on the original NICE DAC which considered the available Gene Expression Profiling tests and produce the guidance in 2013. Since this time I have delivered a small number of talks and sat on Advisory Boards for which I have received honoraria from Genomic Health, and so did not put myself forward for this review. I think the latest guidance is a regressive step and do not agree with the conclusions reached. In a time when tumour biology is gaining increasing importance in helping to guide appropriate treatment and avoid unnecessary treatment, this appears to be heading in the wrong direction. I do not agree with the premise that use of the Oncotype Dx test leads to reduced use of chemotherapy and thus increased levels of recurrent disease with attendant costs. Rather, the test has led to reduced use of unnecessary chemotherapy, with its financial implications and significant morbidity both in the short term (during treatment) and the long term; bone marrow and cardiac toxicity as well as persistent quality of life issues (neuropathy, cognitive function ...). The results of the NHS audit of the initial use of the Oncotype Dx test confirm how much the clinical community has valued the resuts of the test - 99% of patients with a low recurrence score receiving no chemotherapy.	Thank you for your comment which the committee considered. The EAG noted that the 99% rate of no chemotherapy in the low RS group is only meaningful when it is linked to patient outcomes. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			I hope that this contribution is helpful. I would be happy to comment in more detail if this were felt to be beneficial.	
41	NHS Professional	General	The UHNM Breast unit use the present NICE guidelines to determine chemotherapy use for ER positive HER2 negative patients without lymph node metastases. As a result of using Oncotype DX, the experience of this unit has been that many patients have been treated WITHOUT chemotherapy, who would otherwise have been offered chemotherapy by relying on NHS predict as a guide. As a team we are disappointed that an advance in cancer management, by assessment of the genetic and biological profile of individual cancers, rather than statistical evaluation of histological appearance, should be abandoned by the proposed alteration. We are unable to see what evidence has overturned the previous NICE decision to approve Oncotype DX in the node negative subgroup. We believe that not enough weight has been given to the morbidity (and occasional mortality) from chemotherapy. This will again be a problem for many more women if the draft guidance is enacted because patients at present recognised as not requiring chemotherapy based on Oncotype DX will again be treated. We would submit: Scientific analysis of individual tests should not be grouped together to develop a blanket policy.	Thank you for your comment which the committee considered. The EAG did additional analyses on the adverse effects of chemotherapy which are detailed in the third addendum to the diagnostics assessment report. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			The use of Oncotype DX (which is the only assay of which we have experience) has reduced the amount of chemotherapy which would otherwise have been used, by avoiding chemotherapy. The reduction in the amount of unnecessary chemotherapy, if mirrored nationally would lead to considerable saving in drug costs and additional costs to hospital trusts and NHS as a whole. The reduction in the amount of unnecessary chemotherapy would also reduce the significant unnecessary comorbidity caused by chemotherapy which is not only of major detriment to individual patients, but a substantial cost pressure on the NHS locally and nationally. Although our experience is of using Oncotype DX, we continue to support research studying the other assay techniques. Overall we believe that the new advice, if instigated, would lead to unnecessary overtreatment by chemotherapy, of patients with early ER positive, HER2-ve cancers who are only likely to come to harm from the treatment, and not benefit, and this is something which we believe should be avoided. We declare that we were able to use Oncotype DX in a number of cases before the NICE ruling was formally agreed by the NHS after funding was provided by Genomic Health.	
42	British Association of Surgical	General	One of us ([redacted]) has written a detailed letter from the University Hospitals of North Midlands detailing concerns about the Draft Consultation Document issued by The National Institute for Health and Care Excellence for the Diagnostics consultation	Thank you for your comment which the committee considered.

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	Oncology ~ The Association for Cancer Surgery		document Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. We are writing on behalf of the British Association of Surgical Oncology to forward a view from Surgical Oncology to highlight concerns from the wider surgical community about a proposed cessation of genomic testing for early ER positive, node negative HER2 negative cancer. We believe that: Scientific analysis of individual tests should not be grouped together to develop a blanket policy. The use of Oncotype DX in a large number of centres has reduced the amount of chemotherapy which would otherwise have been used, by avoiding chemotherapy. The reduction in the amount of unnecessary chemotherapy, should lead to considerable saving in drug costs and hospital expenditure to individual hospital trusts and the NHS as a whole. The reduction in the amount of unnecessary chemotherapy would also reduce the significant unnecessary comorbidity caused by chemotherapy which is not only of major detriment to individual patients. The short notice of this consultation has	The EAG noted that the paper referred to was included in the diagnostics assessment report. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			precluded an overall assessment of the UK experience, but it is to be expected that there will have been substantial savings both financially and in reduced unnecessary chemotherapy induced morbidity for local health economies and nationally A demonstration of the benefit of Oncotype DX was published by the Manchester group in The European Journal of Surgical Oncology in January 2017. Impact of Oncotype DX breast Recurrence Score testing on adjuvant chemotherapy use in early breast cancer: Real world experience in Greater Manchester, UK http://www.ejso.com/article/S0748-7983(17)30037-9/pdf The conclusion of this study is: Using the RS assay in routine clinical practice in the UK, even in node-positive patients, could help maintain patientsâ€™ quality-of-life and reduce the economic burden of breast cancer care. BASO~ACS agrees with this conclusion and supports the continuing use of Oncotype DX in NHS practice. [redacted]	

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43	NHS Professional	General	In Nottingham we have been using Oncotype dx as an additional decision tool for helping patients to decided whether or not to have chemotherapy for early breast cancer and have found it to be very helpful for some patients. The current document appears to focus on comparing assays and due to lack of concordance arrives at the decision that Oncotype Dx should no longer be funded or used in current clinical practice. The article does not however appear to have looked sufficiently thoroughly at the evidence for Oncotype Dx as a useful tool. I am requesting that a separate review of just Oncotype dx with clinician in-put is considered prior to making a final decision	Thank you for your comment which the committee considered. The EAG noted that the diagnostics assessment report did not solely focus on comparing assays, but considered each test individually both in terms of clinical evidence and cost-effectiveness. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
44	NHS Professional	Section 1, pages 2-48	Having worked with women who have been diagnosed with breast cancer and those who have been treated with chemotherapy for many years I have seen the enormous toll receiving chemotherapy has on some women's lives ; hair loss , nausea, hospital admissions, missed family events, work absences to name but a few. Since 2013 as clinicians we have had the ability to separate those who do need chemotherapy from those who do not. As such I have seen large groups of women benefit from being spared the side effects and missed life events that	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the

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			chemotherapy brings. Alongside this the use of chemotherapy has of course been significantly reduced bringing inevitable cost improvements. We know that only a small amount of women (8-10%) will benefit from chemotherapy as shown in the Oxford trialist's data. How disappointing that we are now looking at giving chemotherapy to more women and putting more women at risk from side effects than we need. Moreover we are already heavily overstretched to provide care for our patients and increasing chemotherapy use will undoubtedly put more strain on already stretched NHS recourses'. The NHS is usually at the forefront of developing services to improve people's lives. This proposal is in my view a retrograde step based on data which implies that if you haven't received chemotherapy (as those in the low recurrence risk group), then benefit has been prevented.	companies, and decided to revise section 1 in the second diagnostics consultation document.
45	Roche Products Ltd UK	General	General Comment: The combined strength of pharma and diagnostics under one roof means that personalised healthcare is a key focus for Roche. Itâ€™s been reflected in our portfolio which has helped change the way many diseases are diagnosed, aiming to ensure the right treatment to the right patient. However, many available drugs are currently prescribed with a one-size fits all approach. Harnessing genomic science, will represent a huge advance, allowing us to tackle the root cause of cancer at a genomic level, rather than the disease location in the body.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			Despite significant spend on cancer services in the NHS, there remain substantial opportunities to improve the outcomes achieved. From a scientific standpoint, we have in recent times seen a rapid improvement in our understanding of cancer, with treatment options rapidly evolving from one size fits all, to biomarker selected subgroups and now individualised treatments based on the tumour profile. We believe that for patients to optimally benefit, a broad coalition is required to transform care. General: How HTA bodies respond to the growing number of genomic tests that will be entering the market. Ultimately given the importance of genomics to the Government and the ambitions of the LSIS it's vitally important to ensure the HTA system doesn't become a blocker to adopting new innovative genomic tests. Is there a need for NICE to be looking at this in the round rather than product by product? Would NICE extrapolate on what specific clinical evidence they want genomic tests to show? This would support companies to ensure trial protocols can be set up to generate this evidence?	1 in the second diagnostics consultation document. The committee would ideally like to see evidence that tests have an effect on subsequent patient outcomes, that is, the change in treatment decisions when a test is used results in improved clinical

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				outcomes. This is described in section 5.5 of the second consultation document.
46	Macmillan Cancer Support	General	Macmillan Cancer Support is a registered charity providing support for people affected by cancer. Macmillan wants every one of the 2.5 million people living with and beyond cancer in the UK today to get the highest standard of care and support, so that they can have the best possible quality of life. Key messages - We are disappointed with some of the conclusions that have been reached around the value of tumour profiling tests. We question whether in all cases sufficient regard has been given to the benefits of tests in lowering an assessment of risk. This particularly applies in the case of Onctoptype Dx. - We had expected that access to GEP tests would be extended to patients at higher risk, but for whom a test would help guide decision-making around not receiving adjuvant chemotherapy. - The consultation places a lot of emphasis on evidence on survival outcomes but we believe more consideration needs to be given to issues relating to quality of life and the impact on patients of undergoing chemotherapy	Thank you for your comment which the committee considered. The EAG did additional analyses on the adverse effects of chemotherapy which are detailed in the third addendum to the diagnostics assessment report. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			- If, as recommended, these tests are not extended and are not made routine, we are concerned the consultation outcome would represent a break with important developments in personalised medicine. - Significant work would need to take place in our view to help rationalise to patients why these tests won't in future get routinely used. The three main questions we comment on in the consultation response 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?	
47	Macmillan Cancer Support	General	*Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?* If, further to this consultation, the recommendations are to be approved and form updated guidance, we believe NICE will need to provide a clear rationale for its recommendations. The rationale would need to be easily understood by patients, who may in some cases need reassurance why potential treatment options may occur when they could have been better decided on and informed through routine	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			availability of GEP tests. Removing these tests also affects treatment options and the best guidance that can be provided by clinicians where PREDICT is not a useful tool as it gives a percentage result, making it difficult for clinicians to advise. GEP testing is extremely useful to determine need among patients with 'intermediate' risk of recurrence. NICE will clearly need to explain any further research that is required and what the timeframe would be for any future reviews.	1 in the second diagnostics consultation document.
48	NHS Professional	General	I am writing as a Consultant Clinical Oncologist to express my dismay at the proposed withdrawal of NHS funding for tumour profiling tests for breast cancer as outlined in the draft consultation document DG10. It is accepted by the International oncology community that such tests are a cost effective and clinically proven way of determining the optimal deployment of adjuvant chemotherapy. The Oncotype DX test (for example) has been shown to not only predict prognosis but also which patients will benefit from chemotherapy. In an era where we are trying to be more conservative with toxic treatments such as chemotherapy, I consider it vital to continue to have access to these tests in everyday clinical practice.	Thank you for your comment which the committee considered. The EAG did additional analyses on the differential benefits of chemotherapy which are detailed in the third addendum to the diagnostics assessment report. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			I do believe like many that the methodology and assumptions made in this document are flawed and I urge you to delay your final decision until further evidence has been submitted and assessed. Yours sincerely, [redacted] Consultant Clinical Oncologist.	1 in the second diagnostics consultation document.
49	NHS Professional	General	We are writing to express our dismay and extreme concern at the proposals to stop funding the Oncotype DX test for NHS patients in England. As an MDT, we frequently request these tests to risk stratify and allow patients to avoid chemotherapy for early stage breast cancer. The Oncotype test has had a significant impact on our ability to appropriately deliver chemotherapy, avoiding need for treatment in many of our patients. Adjuvant breast chemotherapy is associated with significant morbidity and a risk of fatal adverse reactions. As a direct result of the OncotypeDX test, we have reduced chair occupancy in our chemotherapy unit, need for on-treat clinic appointments and blood tests, and potentially avoided significant toxicities from unnecessary chemotherapy. We should be doing all we can to prevent patients from avoidable harms, and give the most appropriate treatments for their condition. The decision to reverse NICE approval for this test is a retrograde step based on flawed assumptions and we believe that it is a very short-sighted one.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			We urge you to reconsider and allow us to continue offering this important part of our treatment. Kind Regards [redacted] MCRP FRCR Consultant Clinical Oncologist On behalf of the Doncaster and Bassetlaw Teaching Hospitals NHS Trust Breast MDT [redacted] Consultant Medical Oncologist [redacted] Consultant Breast Surgeon and MDT Lead [redacted] Consultant Breast Surgeon and Professor of Breast Cancer Surgery Sheffield Teaching Hospitals [redacted], Consultant Breast Surgeon [redacted] Consultant Histopathologist	
50	NHS Professional	General	In our practice at James Paget university Hospital in Great yarmouth, the use of Oncotype DX testing for all ER +ve, HER2-ve, LN-ve tumours has resulted in an increase in uptake of chemotherapy in our older population (aged >70yrs), and a decline in the use of chemotherapy in our younger patients (<40 years). Both clinicians and patients prefer an individualised and targeted approach to developing management plans, which provides greater evidence in specific cases than the use	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the

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			of Predict, which provides categorical scoring. In summary, the use of Oncotype DX has benefited younger and older patients in our practice, and I would recommend that these subgroups, at the very least, continue to have access to this test.	companies, and decided to revise section 1 in the second diagnostics consultation document.
51	NHS Professional	General	The guidance suggests that testing helps decide if patients may benefit from chemotherapy if found to be at high risk of recurrence. I believe this data has been looked at the wrong way round. In our MDT experience we use Oncotype DX to spare patients chemotherapy as we are reassured by scores of less than 18. This in turn prevents chemo related morbidity and has cost benefit implications. We have data to this effect that could be provided if required. We as an MDT strongly support the use of Oncotype DX or other validated profiling test in order to spare patients from chemotherapy where possble and to bring down the high percentage of patients who are over treated.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
52	Association of Breast Surgery	Whole document	The Association of Breast Surgery (ABS) is extremely disappointed with the conclusion that NICE has drawn from reviewing the evidence for use of these novel technologies in the NHS. NICE suggest that there is not enough evidence to recommend the routine use of these tests. However, one such test, Oncotype DX,	Thank you for your comment which the committee considered. The EAG noted that all references cited (with the exception of Klang et al.) are

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			has been available in the NHS since it was recommended for clinical use by NICE itself (DG10, 2013). There is clear evidence that the use of these tests can reduce the burden of chemotherapy in women with oestrogen positive lymph node negative breast cancers, with the outcome of the tests having real world impact on decision making in the clinic (1-5) including clear examples from the NHS (1). The evidence favours use of tumour profiling in those groups of patients where the benefits of chemotherapy were previously uncertain and where targeted use of chemotherapy in appropriate patients (as identified by these tests) can result in individualised treatment (6, 7). This results in financial savings for the health service (1) but more importantly, it also allows women to be spared the consequences of unnecessary chemotherapy (1 – 7). ABS is of the opinion that the withdrawal of the availability of these tests in the NHS will have a significant impact on our ability to tailor treatments to the individual patient and be a retrograde step in the management of breast cancer. Patients will be denied the opportunity to avoid unnecessary chemotherapy and the toxicity accompanying this. In addition, those women identified as high risk by genomic testing will be denied this extra valuable information to help them make their choices (10).	either included in the diagnostics assessment report, or excluded with justification in Appendix 2 of the diagnostics assessment report. Klang et al. was identified by the EAG's searches but was excluded from the review at the title/abstract screening stage because only decision impact studies from the UK and Europe were included. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			The analysis performed by NICE is flawed as described above. We hope that this decision will be reconsidered. The Association of Breast Surgery represents almost 1600 surgeons and nurses involved in the diagnosis, treatment and management of women with breast cancer throughout the United Kingdom. The above statement distils the widespread concerns relayed to us by our members. References: 1) Loncaster J, Armstrong A, 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. Eur J Surg Oncol 43:931-937, 2017. 2) Geffen DB, Abu-Ghanem S, Sion-Vardy N, et al: The impact of the 21-gene recurrence score assay on decision making about adjuvant chemotherapy in early-stage estrogen-receptor-positive breast cancer in an oncology practice with a unified treatment policy. Ann Oncol 22:2381-2386, 2011. 3) Joh JE, Esposito NN, Kiluk JV, et al: The effect of Oncotype DX recurrence score on treatment recommendations for patients with estrogen receptor-positive early stage breast cancer and correlation with estimation of recurrence risk by breast cancer specialists. Oncologist 16:1520-1526, 2011. 4) Lo SS, Mumby PB, Norton J, et al: Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. J Clin Oncol 28:1671-1676, 2010.	

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			5) Partin JF, Mamounas EP: Impact of the 21-gene recurrence score assay compared with standard clinicopathologic guidelines in adjuvant therapy selection for node-negative, estrogen receptor-positive breast cancer. Ann Surg Oncol 18:3399-3406, 2011. 6) de Boer RH, Baker C, Speakman D, et al. The impact of a genomic assay (Oncotype DX) on adjuvant treatment recommendations in early breast cancer. Med J Aust, 199 (2013), pp. 205-208 7) Eiermann W, Rezai M, Kummel S, et al.The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. Ann Oncol, 24 (2013), pp. 618-624 10) Klang SH, Hammerman A, Liebermann N et al. Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. Value Health. 2010 Jun-Jul;13(4):381-7	
53	Genomic Health UK Ltd.	Section 1, Page 2/48	If upheld, the recommendations would lead to many more UK EBC patients receiving chemotherapy. A significant proportion of whom will derive no benefit but will endure debilitating short and long-term side-effects. Many patients will also be missed who do need chemotherapy, who will consequently suffer a preventable recurrence. The recommendations run contrary to the international oncology community consensus; to target chemotherapy to the ~10% (Oxford Overview) chemo-	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			sensitive EBC patients, and spare the ~90% non-chemo-sensitive patients from unnecessary toxicity. The NHS has achieved noteworthy success at advancing EBC care (based on NICE DG10) by reducing chemotherapy (as shown in the NHS audit data) in patients who will derive no benefit. This has unfortunately been entirely misinterpreted in the EAG analysis; concluding that these patients were harmed by not receiving chemotherapy. This is due to the incorrect assumption that all patients are chemo-sensitive and derive a large relative risk reduction (RRR) of distant recurrence across all RS groups. Level 1 validation evidence, supported by long-term patient outcomes evidence in >63,000 patients, clearly show that patients with RS<18 in fact derive negligible or no benefit. It is highly unlikely that the ~10% chemo-sensitive patients are in this group, whilst patients with RS>30 derive a very large RRR. The evidence supporting the use of Oncotype DX is even stronger now than when previously recommended by NICE.	1 in the second diagnostics consultation document.
54	Genomic Health UK Ltd.		References can be provided for all comments, as needed	Thank you for your comment which the committee considered.
55	UK Breast Cancer Group	5.1	There is a strong drive internationally to de-escalate breast cancer treatment in a safe manner. Since the introduction of these tests the proportion of patients	Thank you for your comment which the committee considered.

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			receiving chemotherapy for node negative disease has fallen. The NHS audit in 2016 showed quite clearly that since use of Oncotype DX there has been a reduction of approximately 25% in the use of adjuvant chemo in the eligible population. Genomic tests have been shown robustly to identify a sub-group of node negative patients with low risk of recurrence with endocrine therapy so this de-escalation in chemotherapy and hence reduction in excess toxicity has been done in a safe manner. It is reasonable to assume that breast cancer mortality has not been compromised and that acute chemotherapy-related mortality of approx. 0.25%, acute chemotherapy-related admissions affecting approximately 35% of breast cancer patients have been reduced and that long-term morbidity and late excess mortality from chemotherapy will fall. The MINDACT study also demonstrated safety in de-escalating low risk patients in a randomised trial setting. We have had access to prognostic tools for many years, namely 'Adjuvant! Online' in the past and currently 'PREDICT'. However, prior to genomic tests clinicians clearly struggled to recommend no chemotherapy in 'intermediate' risk patients.	The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
56	UK Breast Cancer Group	5.1	If we revert to an era of more chemotherapy-giving, we will encounter capacity issues in already stretched chemotherapy units. This has not been factored in.	Thank you for your comment which the committee considered. The EAG noted that some of the tests may be expected to increase chemotherapy use within particular

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				patient subgroups (see section 4.48 of the second consultation document).
57	UK Breast Cancer Group	5.1	Most major guideline producing groups now recommend these assays in the node-negative population, including NCCN, St Gallen, ASCO, ESMO. The decision will result in a return to NHS patients self-paying for the test creating a two-tier system.	Thank you for your comment which the committee considered. Clinical guidelines do not always include an analysis of cost-effectiveness and as such different decisions are to be expected from time to time.
58	UK Breast Cancer Group	-	In a survey* to breast Oncologists undertaken by UKBCG open over just 48 hours, of 75 responses, 100% reported using Oncotype regularly in their NHS practice and 100% supported its continuing use in node negative disease. This is an indication of the strength of feeling amongst Breast Oncologists in the UK towards securing continued access to these assays in the setting of node positive disease. *The survey was distributed by email to 200 members of UKBCG (breast oncologists) with a 37.5% response rate in 48 hours.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
59	Breast Cancer Now	General	While we welcome the opportunity to respond to this consultation, and appreciate that NICE has a diagnostics programme manual guideline which sets out the	Thank you for your comment which the committee considered.

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			timeframes for the consultation period, this is a particularly complex consultation which includes an 817 page DAR report and in this instance 20 days has not been long enough to fully consider this.	
61	Breast Cancer Now	General	We are very disappointed to see that NICE has been unable to recommend any of the prognostic tools to help guide chemotherapy use on the NHS. This appears to be a backwards step for some patients (patients with hormone positive, HER2 negative, lymph node negative breast cancer assessed using current tools as being at intermediate risk of recurrence) at a time when the NHS is looking towards personalising treatment. When NICE issued its 2013 guidance, they estimated that around 9,700 people could fall into the specific group of breast cancer patients that they recommended Oncotype DX as an option for. The ability to personalise treatment based on tumour profiling and as a result reducing unnecessary chemotherapy and enabling patients to avoid its gruelling side effects is a key part of improving patient care and has the potential to reduce associated costs with chemotherapy. At a time when healthcare professionals tell us that chemotherapy units have limited capacity, reducing the number of patients who need to receive chemotherapy would free up space for those that would benefit from receiving it in a timely manner.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
62	Breast Cancer Now	General	This new draft guidance reverses a decision made by NICE in 2013 which recommended the use of Oncotype DX. We do not feel that the diagnostics consultation document is clear enough on the reasons behind not recommending	Thank you for your comment which the committee considered.

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			Oncotype DX in this updated guidance. It is unclear whether this is a result of additional clinical evidence, the cost or a combination of both. The previous guidance referenced a patient access scheme for Oncotype DX, and we are aware that NHS England agreed an access programme. However, there is no mention of this in the current document. Having contacted NICE to ask further questions on the consultation document, we have been instructed to insert them into this consultation response. Therefore, we would welcome clarity on these points. In addition to this, it was only recently that NICE included Oncotype DX as a priority area for quality improvement in the breast cancer quality standard [QS12] in 2016. It recommended that people with ER positive, HER2 negative an lymph node negative early breast cancer who are at intermediate risk of distance recurrence are offered gene expression profiling with Oncotype DX.	The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
63	Breast Cancer Now	6.1	We welcome the recommendation for further research comparing the tumour profiling tests with the PREDICT tool, however, collecting this data could take a significant amount of time. In the meantime, there are already tests, such as Oncotype DX which has been available on the NHS which have been shown to allow patients to avoid unnecessary adjuvant chemotherapy (Loncaster, J. Armstrong A. et al 'Impact of Oncotype DX breast recurrence score testing on adjuvant chemotherapy use in early breast cancer: real world experience in Greater Manchester). This gives patients and clinicians invaluable reassurance that they may safely not have chemotherapy and has a result not have the side-effects,	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			therefore, helping to maintain patients' quality of life and reduce the costs associated with chemotherapy.	1 in the second diagnostics consultation document.
64	Breast Cancer Now	4.8 and 4.9	*In addition to the point above, the NICE consultation document itself highlights that analysis has indicated that Oncotype DX provided statistically significant additional prognostic information over most commonly used clinical and pathological variables to assess risk. Therefore, again we are concerned that the decision to not recommend any tumour profiling tests is a step backwards.*	Thank you for your comment which the committee considered.
65	NHS Professional		The NICE draft document supports overtreatment of many hormone receptor positive, HER2 negative early breast cancer patients. This is especially true in the node negative group. Use of theses assays reduces the number of women who undergo adjuvant chemotherapy with minimal chance of benefit. It does NOT increase the chance of women having chemotherapy a definite decision for treatment is made with PRECICT. In Oxford, we have been using Oncotype Dx for several years to the great benefit of patients. The data are immature, but I am not aware of any patients who avoided adjuvant chemotherapy because of a low RS score and whose disease has relapsed. Again, we would welcome an opportunity to share our data with NICE. In summary, we think this guidance has not reached the right conclusions and would welcome it being reconsidered and altered. There are further data to come	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			soon from the upcoming practice-changing prospective TAILORx trial. Any guidance should wait and incorporate these data.	
66	NHS Professional	General	I am writing on behalf of the Worcestershire Breast Multidisciplinary Team concerning your diagnostic consultation document on tumour profiling tests, specifically Oncotype DX. As a service we manage over 625 new breast cancers annually. Our experience of using genomic testing in our intermediate risk patients (and some node positive patients) has been extremely positive. Importantly we have seen a significant reduction in those patients having or needing chemotherapy. Nationally the introduction of this test has resulted in greater standardization and reduced variability of care across all areas of healthcare (99% of low scores not having chemotherapy). Your decision to not recommend the use of Oncotype DX and increase chemotherapy use seems a major step backwards for patient care and would have massive implications to our oncology services that barely cope at present. The report does not take into account the significant implications of chemotherapy to the patient, the family and loss of income to the individual and economy â€“ this is a major omission to the review.	Thank you for your comment which the committee considered. The consideration of broader impacts on family members and productivity are excluded from the NICE reference case, and therefore were not included in the EAG's economic analysis. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			Obviously with the limited timeline to respond I have not had time to draft a full response but we as an MDT would not support the suggestion of removing access to a genomic test for suitable patients.	
67	NHS Professional	General	Are the provisional recommendations sound, and a suitable basis for guidance to the NHS? This will lead to many patients to endure debilitating side-effects, and potential long-term harm which can be avoided. This will also place substantial increased demands on already stretched NHS resources. The 2016 NHS audit showed that clinicians and patients are deciding to forego chemotherapy in 99% of cases of low-Recurrence Score	Thank you for your comment which the committee considered. The EAG noted that the 99% rate of no chemotherapy in the low RS group is only meaningful when it is linked to patient outcomes. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
68	NHS Professional	General	The main UK use of genomic tests has, and would be, to avoid the overuse of chemotherapy in low risk patients. Indeed, since the previous NICE recommendations, this has been widely applied without detriment.	Thank you for your comment which the committee considered.

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			As stated" In lymph node negative patients, using the test in clinical practice appeared to result in low rates of chemotherapy use in low-risk patients (2% to 12%), with acceptable outcomes (distant recurrence-free survival, distant recurrence-free interval or invasive disease-free survival 96% to 99.6%)". Rescinding this guideline is likely therefore to lead to a reversion with a return to a recommendation for chemotherapy in this lower risk group.	The EAG noted that some of the tests may be expected to increase chemotherapy use within particular patient subgroups (see section 4.48 of the second consultation document). The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
69	NHS Professional	General	Elsewhere: ".. we cannot conclude whether patient outcomes would be affected, or even in which direction they would be affected. This conclusion is based on the clinical evidence, not on the economic modelling. â€¦â€¦ This is especially true given the lack of clarity over how intermediate patients would be treated in clinical practice; whether the test would be used in isolation of clinicopathological factors, and how clinicopathological factors would be used in clinical practice; ….' This is particularly disingenuous; as per the previous guidance (NICE DG10), the Oncotype Dx test is not used independently of clinicopathological factors in the UK (based on that guidance, in the NHS setting the test may only be requested based	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			on ER and HER2 status, node negativity and grade and tumour size, the latter 3 incorporated into NPI and all 5 features in Predict) and it is being widely used and applied to manage this intermediate group of patients.	1 in the second diagnostics consultation document.
70	Patient	General	To the honorable members of NICE advisory committee regarding Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. My name is [redacted], Medical Oncologist Specialist in Breast Cancer at the Hospital Universitario Virgen del Rocio in Seville Spain. I am also a Breast Cancer Patient since 2013. Therefore I believe that I have a unique perspective on the management of breast cancer from both the clinical and patient point of view. I also am president of the 'Actitud Frente al Cancer' Organization which seeks to educate, empower, and provide emotional support to patients (http://actitudfrentealcancer.org/). I thank the committee for this opportunity to submit comments regarding the recent publication of the draft of the Diagnostic Consultation Document regarding Tumour Profiling tests to guide adjuvant decisions in people with breast cancer and congratulate the group for its in-depth analysis of this issue. However, I wish to present my concerns, in support of other breast cancer patients in England, regarding the committee's decision to not recommend any tumour profiling test for routine use in the NHS.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			In Spain, these tumour profiling tests have been used in routine practico since 2011-12. Since then I have been using 1st generation genomic testing to selected groups of breast cancer patients for informing chemotherapy decisions in early stages. I had my own surgically-removed tumour tested by Oncotype in 2013 and then by the PAM50 Prosigna test for 10 years prognostic confirmation and research purposes. Unfortunately, in both tests I got same results, my risk of recurrence was high and I performed Chemo in 2013. Anyway that was a very valuable lesson to me, a very reliable prognostic test and a very important experience facing other patients in similar conditions. I am convinced that Genomic Testing are an excellent tool for the quality of care regarding breast cancer patients. I am very convinced of the clinical utility of genomic testing and added prognostic value provided by biological biomarkers over clinic-pathological factors. The best treatment decision should be based considering all possible information. Above all, knowing an accurate prognosis improves patient's ability to organize their lives during the years after primary treatment.	
71	NHS Professional	General	The prospective validated data from clinical trials shows that the use of genomic profiling (Oncotype DX or endopredict / others) helps patient with low risk scores avoid chemotherapy. The cost of the test is counterbalanced by the savings from avoiding chemotherapy. To stop clinicians using the test within the NHS would a retrogressive step for the patients.	Thank you for your comment which the committee considered. The EAG noted that some of the tests may be expected to increase chemotherapy use within particular

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				patient subgroups (see section 4.48 of the second consultation document). The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
72	NHS Professional	General	As one of 3 consultant breast surgeons treating over 600 breast cancers a year in an already over stretched service I am deeply concerned regarding the proposed recommendation on breast tumour profiling. Within the field of breast cancer we are fortunate to have achieved a relatively high success rate in curing this disease but this has been at the expense of 1; ever increasing morbidity of treatments to patients and 2; ever increasing financial and resource demands on the NHS. There has been a considerable drive over the last 10 years to reduce this burden on both the patients and the NHS by ever improving the targeting of treatments to the patients that will benefit and avoiding the over treatment of others. This recommendation would be entirely contradictory to these efforts.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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73	NHS Professional	General	The draft recommendation 'there is not enough evidence to recommend the adoption of any genomic or IHC test to guide adjuvant therapies' flies in the face of the objective of all healthcare professionals which is to maximise benefit whilst minimising morbidity of the treatments for this disease. Its suggestion raises one of 2 accusations a; the guidelines of 3 years ago were flawed and we have been significantly under treating and harming many patients since its adoption, or b; this recommendation is flawed. After much experience in the use of Oncotype DX aid to treatment decision making and real world experience of the outcome of care I suggest that it is this current recommendation that is deeply flawed.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
74	NHS Professional		Are the provisional recommendations sound, and a suitable basis for guidance to the NHS? These recommendation would put the NHS at the â€˜back of the queueâ€™ in terms of developing a modern oncology service built on â€˜personalizedâ€™ medicine. These recommendations would put the NHS at odds with the recommendations of most of the developed world in the management of breast cancer. The American Society of Clinical Oncology recommend the use of GEP testing to aid decision making https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/breast-cancer	Thank you for your comment which the committee considered. Clinical guidelines do not always include an analysis of cost-effectiveness and as such different decisions are to be expected from time to time. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			The European Society of Medical Oncology recommend the use of these tests: â€œGene expression profiles, such as MammaPrint, Oncotype DX Recurrence Score ,Prosigna and Endopredict may be used to gain additional prognostic and/or predictive in-formation to complement pathology assessment and to predict the benefit of adjuvant chemotherapyâ€ http://www.esmo.org/Guidelines/Breast-Cancer/Primary-Breast-Cancer The NCCN have also included the use of Oncotype in their guidelines for women with node negative disease https://www.nccn.org/patients/guidelines/stage_i_ii_breast/index.html	1 in the second diagnostics consultation document.
75	NHS Professional	General	General comment To give chemotherapy to all intermediate risk patients is a retrograde step particularly at a time when over-diagnosis and over-treatment in breast cancer is accepted as being a major problem. 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. This recommendation represents a backward step which makes no sense in the clinics we conduct every day. At a common-sense level, it seems very doubtful that these recommendations represent good value for money at a time when the NHS is under such financial and workforce pressures.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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76	NHS Professional	General	General comment TailorX (run by the NCI independently of GHI) may well report at ASCO in June 18. If the results show that the threshold for recommending chemotherapy is an RS of 26 or over, then 85% of patients will be able avoid this treatment. This is will mean the over prescription of chemotherapy can be substantially reduced. Since only about 5% of patients in this intermediate risk category actually benefit, it will reduce the over-prescription of chemotherapy to 3x instead of the 10x currently recommended (and probably more if the proposed recommendations are adopted). Women of the UK will be very poorly served (and angry) if this is the case and we have to wait a further 3 years for the next NICE review.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
77	NHS Professional	2, page 1	The document states that 'there is not enough evidence to support routine adoption of any genomic test to guide chemo decision' I whole-heartedly disagree and if this guidance goes ahead then 4 years of progress will be lost and 10% more patients will be made to endure short and life-long side-effects of chemo for minimal benefit. If the guidance goes ahead then the UK will be forced to fall behind the rest of the developed world with chemotherapy prescribing practice. At a time when all the International Conferences are focusing on 'down-scaling' treatment, why should the UK be forced to upscale chemo treatment?	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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78	NHS Professional	General	Please do not reverse this recommendation which will have the knock on effect to reverse the progress made by NHS in breast cancer treatment in the UK and have a huge negative impact on so many ladies who do not need or deserve the terrible impact they will endure in both short and long-term from having chemotherapy.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
79	NHS Professional	General	With improving breast cancer survival rates attention has turned to de-escalating adjuvant treatment and avoiding unnecessary treatment, and thus debilitating side effects and potential long term harm. Personalised molecular profiling has become routine practice in the UK for those at Intermediate risk of recurrence, as defined by NPI score with node negative ER+ breast cancer. Using such tests in our Centre has led to 75% of patients tested avoiding chemotherapy by virtue of low recurrence scores. Lack of access to these tests would mean an increase in patients receiving chemotherapy and consequent strain on already stretched chemotherapy units.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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80	NHS Professional	General	The reversal of the recommendation to adopt Oncotype Dx testing for those at intermediate risk in 2013 is surprising and unexpected. The document does not explain clearly why the previous decision to recommend the tests has now been overturned for node negative cancers.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions, and decided to revise section 1 in the second diagnostics consultation document.
81	NHS Professional	General	As a clinician working in the NHS I have grave concerns about the contents of this document and its implications that genomic tests to aid decision making will not be available in the future. These tests are not for everyone, but used carefully where the decision to give chemotherapy based on clinico-pathological criteria is borderline they can give valuable information to help decision making, which may save a women undergoing all the toxic effects of chemotherapy, hair loss, sickness, infection risks, infertility and long term consequences where it gives them no addition benefit for recurrence. More data is always welcome and the OPTIMA trail and other prospective trials are underway, such as TAILORX , but there is always extensive data, especially with Oncotype Dx and these tests are incorporated into all major International Guidelines.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			In 2018 we cannot ignore the advances technology has given us and go back to the dark ages of giving chemotherapy to everyone 'just in case' . Our day units are too full, lets target our resources wisely and save patients from undergoing unnecessary treatments.	
82	NHS Professional	General	We have been using Oncotype Dx in our MDT ever since it became available in the NHS access scheme for the intermediate risk group as per NICE guidance. In our use, it has reduced use of chemotherapy by 35-40% (when compared with using NPI and/or PREDICT). Oncotype Dx testing has helped the clinical team significantly with decision-making in an otherwise difficult (intermediate-risk) group. The resultant benefit in terms of reduced toxicity/side effects, reduced costs is self-explanatory. Critics of breast cancer screening & treatment consistently make the over-diagnosis and overtreatment argument. Genomic tests have helped reduce some of this overtreatment. The draft recommendation, if it goes ahead will make UK practice as an outlier compared to other similar guidelines in western countries, all of which recommend genomic tests in the ER +, HER-2 neg, node negative patients (ASCO, St Gallen, NCCN guidelines).	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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83	NHS Professional	4.36	NICE places undue importance on decision impact studies. If, as the conclusions of this report state, more evidence is needed to prove that these tests have a positive effect on patient outcomes then such studies merely demonstrate that clinicians are willing to believe the clinical validity of the tests in the absence of robust data. Were decision impact studies able to provide outcome data then they would be far more meaningful.	Thank you for your comment which the committee considered. The committee noted that none of the tests had strong enough evidence to demonstrate an effect on patient outcomes (see section 5.5 of the second diagnostics consultation document).
84	NHS Professional	5.5, 5.15	Notwithstanding the deficiencies in the individual studies reviewed by the EAG and the lack of prospective studies, the totality of evidence demonstrates that chemotherapy use has been reduced through using the tests in a number of healthcare jurisdictions without any demonstrable increase in adverse disease outcome for LN0 tumours. The evidence that this applies to LN1-3 tumours is much weaker.	Thank you for your comment which the committee considered.
85	NHS Professional	5.16	Please note that uniquely amongst the prospective RCT's, OPTIMA is a trial being conducted within the NHS	Thank you for your comment which the committee considered.
86	NHS Professional	5.16	Comment [163] applies to other prospective studies.	Thank you for your comment which the committee considered.

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87	NHS Professional	General	I am writing on behalf of the MDT at the Royal Surrey County Hospital NHS Foundation Trust to express my concern at the methodology used in the recent draft guidance for these tests. NICE approved Oncotype DX for use in intermediate risk patients in the NHS with node negative ER/PR+, Her2- breast cancer in 2013 (DG10, 2013). Since then it has helped to ascertain the benefit of chemotherapy for many patients in the UK and helped us ensure that this toxic and potentially life threatening treatment is used where clinically appropriate. The consultation chose to ignore North American data due to the issues with analysing cost effectiveness. This has led to a wealth of quality clinical data being excluded from the analysis. The analysis assumes a one size fits all benefit to all comers which we know is clinically not correct – as such this has been treated as a statistical exercise rather than a clinical exercise. The statistical review has been highly critical of the methodology used in the RCTs and of potential bias and as such has elected to dismiss some of the clinical evidence included. Many RCTs have methodological issues if scrutinised in this detail - this reflects the reality of conducting trials in a clinical context with	Thank you for your comment which the committee considered. The EAG noted that the clinical review of prognostic and predictive studies did not restrict by country; all relevant studies were included. It noted further that the review of decision impact studies was restricted to the UK and Europe (i.e. excluded North America) due to the large differences in baseline chemotherapy rates between countries. The EAG did additional analyses on the adverse effects of chemotherapy which are detailed in the third addendum to the diagnostics assessment report. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section

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			reasonable numbers of patients but it does not necessarily make the findings invalid. In addition, the cost benefit analysis ignores the late and often debilitating effect on patients from chemotherapy treatment (cardiomyopathy, neuropathy, second cancers) which not only trivialises the impact of these treatments but also ignores the survivorship agenda. In short, we feel that there are issues with the methodology in this review and that to stop using Oncotype Dx in routine clinical use for the intermediate risk patients is a retrograde step and one which risks harming patients.	1 in the second diagnostics consultation document.
88	NHS Professional	General	As Oncologists treating breast cancer, 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. From the Oxford overview, only 10% of breast cancer patients will benefit from adjuvant chemotherapy, so any tests that allow us to identify these patients are very welcome. Since the last NICE Guidance was issued, Oncologists in Newcastle have been using Oncotype Dx testing routinely for node negative patients with Grade 3 or large Grade 2 tumours and believe that this has been beneficial. Patients who have a low recurrence score, who might in the past have been offered chemotherapy, can be reassured that this is not required. Those with a high recurrence score can be more confident that the chemotherapy will be of benefit. The proposed withdrawal of this testing on the NHS is, we believe, a retrograde step and is at	Thank you for your comment which the committee considered. The EAG noted that data on the percentage of patients receiving chemotherapy conditional on genomic test results is only meaningful when it is linked to patient outcomes. The committee considered the extensive comments on the draft recommendations, along with new value

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			odds with what is being done in other countries. The guidance therefore goes against international oncology best practice. The result of having no genomic testing will be an increase in the number of patients receiving chemotherapy, which is not only inappropriate, but will also add to the current stresses on NHS services. We have already seen the Churchill Hospital in Oxford delaying chemotherapy due to lack of resources. Many chemotherapy units are overstretched and the guidance being suggested would make the situation even worse. There are a number of inappropriate clinical assumptions made in the guidance and also some important issues that have not been taken into account. 6) There is 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 patients who can't afford £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. However we strongly support continuing NHS funding for tumour profile testing for node negative, grade 3	propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			and large grade 2 tumours, which we all believe has been an important advance in the management of our breast cancer patients. [redacted] Consultants in Clinical Oncology Newcastle Hospitals NHS Foundation Trust	
89	NHS Professional	General	As a Breast MDT Surrey and Sussex Hospital Trust would not support the withdrawal of oncotype DX testing for ER+ve node negative breast cancer patients on the NHS. There are many patients with questionable chemotherapy benefit in whom oncotype has proved invaluable in guiding management.	Thank you for your comment which the committee considered. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
90	Royal College of Pathologists	General	We appreciate the effort and comprehensive review of literature, analysis and interpretation of findings that were carried out by the EAG in this document. However, we would like to raise some concerns regarding the health economic models including some likely irrelevant items with subsequent biased interpretation of the results.	Thank you for your comment which the committee considered.

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91	Royal College of Pathologists	1.1	Our main comment is on the final recommendation stating that "There is not enough evidence to recommend the routine adoption of EndoPredict, MammaPrint, Oncotype DX Breast Recurrence Score, Prosigna and IHC4+C to guide adjuvant chemotherapy decisions for people with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer with 0 to 3 positive lymph nodes. In particular, more evidence is needed to prove that these tests have a positive effect on patient outcomes. Their cost effectiveness compared with current practice is highly uncertain.". In fact the published data reviewed by the EAG and presented in the document indicates, as highlighted in many places in the document, a prognostic value of some of these multigene tests and some were superior to the available clinicopathological variables in use in the current practice specifically in the clinically indeterminate risk groups. These tests are meant to provide more accurate prediction of risk that can help determining the use of systemic therapy and in this context the use of chemotherapy. Unlike therapeutic agents, the use of these tests is mainly to refine the prognostic stratification of the clinically indeterminate risk group which they provide with acceptable degree of accuracy. Recommending to use or not to use such multigene tests should not be bases solely on the estimated QALY and ICER. Mixing lymph node negative with lymph node positive (0-3 nodes) may undervalue the use of these tests in the lymph node negative disease. Relying of the quality of data providing evidence for the chemotherapy predictive power of some test can bias the recommendation since	Thank you for your comment which the committee considered. The EAG noted that the economic model analyses LN negative and LN positive patients separately. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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			the main use of these tests is to provide level of risk which should be appreciated. Chemotherapy predictive power can be an added value of some tests but should not be used as the main reason to approve or disprove using the test. We expected the final recommendation based on the current review of literation and the data presented in the document is to limit the use of these multigene tests to the clinically indeterminate risk group, as complementing test(s) to the current practice and providing valuable additional prognostic information on the level of risk. It is acknowledged that the use of chemotherapy in these borderline risk cases using the available clinicpathological parameters is challenging and the available risk tools are often insufficient to accurately guide decisions about chemotherapy in such specific subgroups of breast cancer patients; applying a molecular test in such situations is likely to improve patients management and make treatment decision more objective and evidence based rather than being opinion based which may vary in different centres in the UK	

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92	Patient organisation	General	At Breast Cancer Care we speak to thousands of women and men diagnosed with breast cancer each year. Deciding whether or not to have chemotherapy can be a difficult decision for many of these people. Having the opportunity to be informed about their risk of recurrence, and the potential level of benefit of chemotherapy, equips patients with information to help them make a decision about the best treatment for them. We are therefore disappointed that NICE has not recommended the use of these tests on the NHS in England. This decision will be a huge blow to many thousands of breast cancer patients, both now and in the future, who could avoid unnecessary chemotherapy and its associated side-effects. It is particularly frustrating that a decision about Oncotype DX has been overturned, as this test was recommended in the previous 2013 guideline: Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat (DG10). To now have this decision overturned in updated guidance, due to a change in the comparator, seems unfair and a backwards step in the progress towards more tailored treatments. We would urge NICE to reconsider this decision.	Thank you for your comment which the committee considered. The committee noted the potential benefits of tumour profiling tests for people with early breast cancer who are deciding whether to have adjuvant chemotherapy (section 5.2 of the second consultation document). The committee considered additional analyses done by the EAG on adjuvant chemotherapy benefit (section 5.10 of the second consultation document) and access proposals submitted during the first consultation, and decided to recommend Endopredict, Oncotype DX and Prosigna as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (ER)-positive, lymph node (LN)-negative and human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (see section 1.1 of the second consultation document). The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the

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				companies, and decided to revise section 1 in the second diagnostics consultation document.
93	NHS Professional		As an overall sentiment the surgical team and MDT have found the use of oncotype invaluable in the informed discussions had with patients regarding treatment options. It provides greater evidence regarding prognosis and crucially predicting treatment response, which we believe the validation studies have provided clinical confidence to conclude. I have had a very positive personal experience with the use of this assay in discussions with patients, where the recommendation of chemotherapy is uncertain. It has provided greater information, which patients can weigh up to make a more complete informed decision on whether or not to consider chemotherapy. In my experience the possibility of chemotherapy is quite often a major reason for patient anxiety and fear regarding a diagnosis of breast cancer. Patients in general would like to avoid chemotherapy if they are able to without significant detriment to their prognosis and quality of life. Some patients even when recommended for chemotherapy still make an informed decision not to have chemotherapy despite a great than 3% or even higher absolute risk reduction in disease specific mortality or recurrence due to the fear of chemotherapy side effects. Chemotherapy has a significant side effect profile and I have personally seen several patients with side	Thank you for your comment which the committee considered. The committee noted the potential benefits of tumour profiling tests for people with early breast cancer who are deciding whether to have adjuvant chemotherapy (section 5.2 of the second consultation document). The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It concluded that it was important to consider potential adverse events that could be caused by chemotherapy, but that reduced occurrence of adverse events due to reduced exposure to chemotherapy was unlikely to affect conclusions on cost effectiveness of the tumour profiling tests. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the

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			effects that have significantly compromised their quality of life. Some of these patients having been independent and with rewarding and productive professional lives have no longer been able to work and deteriorated to the point of requiring assistance in their daily lives. I do not believe that we should be hasty to recommend chemotherapy without the greatest possible information available to each patient so that they can make a truly informed choice.	companies, and decided to revise section 1 in the second diagnostics consultation document.
94	Health Outcomes Researcher	General	I am writing on behalf of my research team at SHORE-C who have many decades of experience researching the profound impact of systemic therapies on patients' quality of life and on helping healthcare professionals communication regarding the harms and benefits of different treatments and decision-making. We have recently completed a training programme on helping HCPs to explain risk in the context of gene expression profiling tests especially OncotypeDX and Endopredict. we also conducted the psycho-social elements of the 'Bloomfield et al study, 2017) looking at pre and post test decision-making and impact on anxiety. We are especially concerned that the last bullet in 4.1 on p12 implies that the only research conducted has looked at how test scores influence the decision-making of the doctor. There are several studies eg Holt et al, BJC, 2013 (looking at OncotypeDx and Fallowfield et al (Esmo ,2017) Psycho-oncology 2018 (in press) looking at Endopredict, showing the impact on the decision-making of	Thank you for your comment which the committee considered. The outcomes of interest were defined in the NICE scope, and included health-related quality of life (HRQoL). The EAG noted that it did include studies that quantified decision changes, and this could include decision changes because of patient preference. The EAG also included quantitative studies on pre and post-test anxiety and HRQoL, for example Holt 2013 and Bloomfield 2017. The EAG noted that in the diagnostics assessment report it concluded: “Genomic testing may reduce state anxiety in some

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			patients and resolution of decision conflict. In section 4.39 regarding anxiety and health-related quality of life, the EAG seem troubled by the lack of a comparator in studies which seems to ignore that fact that the Bloomfield Endopredict study for example looked at 1) patients' decision conflict and anxiety after a decision about chemotherapy had been made and then again when a test result was available. This showed a significant reduction in decision- conflict and reduction of anxiety in those who either had their decision for no chemo confirmed or had their treatment downgraded as low risk. We have many studies on thousands of women with breast cancer showing that anxiety does have a major impact on quality of life and furthermore that fear of recurrence is a primary contributor to that anxiety. We will leave some comments about some of the interpretations of trials and the science behind genomic tests to others with more clinical science credibility but feel that there were some inaccuracies regarding utility and the emerging predictive rather than just prognostic abilities of genomic testing. We feel deeply concerned that the EAG decision and comments will encourage serious over treatment of ER+, HER2- early breast cancer patients and sincerely hope that sufficient numbers of people make their objections to the document clear and convincing enough for NICE to reconsider. we	patients in some contexts, but generally there was little impact on HRQoL". The committee considered the extensive comments on the draft recommendations, along with new value propositions from some companies, and decided to revise section 1 in the second diagnostics consultation document.

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			are happy to supply any extra documentation you might be interested in receiving.	
95	NanoString Technologies	4.58, pages 30-31	NanoString disagrees with the Committee that improved risk predictors based on the biology of the tumor do not provide additional reassurance and reduced strain to breast cancer patients when compared with tools based on traditional factors such as PREDICT, A!O, or NPI. This is not the case and there is good evidence (e.g. Marshall et al.) to demonstrate that, from a personal utility perspective, a gene expression test result is the most important factor for determining chemotherapy treatment choice, over and above input from a clinical doctor. This value is greatest in the intermediate clinical risk group. Marshall DA, Deal K, Bombard Y et al. How do women trade-off benefits and risks in chemotherapy decisions based on gene expression profiling for early stage breast cancer? A discrete choice experiment BMJ Open 2016:6;e010981. Doi 10.1136/bmjopen-2015-0109181	Thank you for your comment which the committee considered. The committee noted the potential benefits of tumour profiling tests for people with early breast cancer who are deciding whether to have adjuvant chemotherapy (section 5.2 of the second consultation document). The EAG noted that Marshall et al. is a discrete choice experiment based on the stated preferences of Canadian women from the general public. This study does not provide any direct information on how women with breast cancer trade off benefits and risks of treatment.
96	NanoString	General	NanoString believes that obtaining the best possible understanding of one's individual prognosis represents a continuing unmet need for breast cancer patients as accurate knowledge of prognosis provides extremely important information to patients when considering treatment decisions and life planning. This belief is reinforced by our	Thank you for your comment which the committee considered. Clinical guidelines do not always include an analysis of cost-effectiveness and as such

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			discussions with patients and patient advocacy groups in this area. Further, inclusion of gene expression tests in all major clinical treatment guidelines and consensus panel recommendations (ESMO, ASCO, St. Gallen, SEOM-Spain, AGO-Germany, and NCCN-USA) demonstrates international recognition of the value of gene expression testing amongst caregivers. The worldwide utilization and widespread reimbursement of gene expression tests in early stage breast cancer over the past decade, provides further support of the recognition of the existence of an unmet need.	different decisions are to be expected from time to time. The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.
97	Breast Cancer Now	4.39	Patients with breast cancer are faced with a difficult choice when considering chemotherapy which can have a huge emotional toll. It is therefore very concerning that no tumour profile testing is being recommended as evidence suggests that it may reduce anxiety in some patients in some context. This removes an opportunity to improve quality of care and also increase both clinicians and patients' confidence in their treatment decision.	Thank you for your comment which the committee considered. The committee noted the potential benefits of tumour profiling tests for people with early breast cancer who are deciding whether to have adjuvant chemotherapy (section 5.2 of the second consultation document).
98	Patient		Finally, I would like to draw the committee's attention to some recent studies that have been published in Spain regarding the impact of genomic testing on both physician decision to treat patients with hormone receptor positive/HER2- early breast cancer with or without chemotherapy, as well as the impact these tests have on the quality of life of patients. I believe these studies demonstrate not only the	Thank you for your comment which the committee considered. The EAG notes that: - Martin et al. 2015 is included in the EAG report

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			clinical value of genomic testing but also the societal benefit through a decrease in anxiety levels that patients suffer due to uncertainty surrounding their treatment decision. M.Martin et al (Curr Med Res Opin. 2015 Jun;31(6):1129-37 Prospective study of the impact of the Prosigna assay on adjuvant clinical decision-making in unselected patients with estrogen receptor-positive, HER2-negative, node-negative early-stage breast cancer) Rodriguez CA et al, Ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e12062 Impact of the Prosigna (PAM50) assay on adjuvant clinical decision making in patients with early stage breast cancer: Results of a prospective multicenter public program. S. Shak, M. Roberts, D. Miller, A. Kurian3, V. Petkov (Annals of Oncology (2017) 28 (suppl_5): v511-v520. 10.1093/annonc/mdx385). 1451P - Breast cancer specific survival (BCSS) in young woman ESMO 2017 Congress. Madrid www.aetsa.org/.../plataformas-genomicas-de-segunda-generacion	- Rodriguez et al. was not identified in the searches, but, the results appear to be in line with other Prosigna decision impact studies - Shak et al. 2017 was published after the date of the searches and is a reanalysis of the SEER database, the primary reference for which is included in the diagnostics assessment report.
99	NHS Professional		My personal experience with the test, and that shared by my colleagues in the Norwich MDT, is that it has been of great benefit. The discussion with a patient who finds themself in this grey area for	Thank you for your comment which the committee considered.

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			recommendation of chemotherapy can be very difficult, especially for the patient. They are torn between not wanting to go through an unpleasant 4 month course of treatment with potential for significant long-term side effects, and the desire to do as much as possible to maximise their chance of survival. The making of the decision can be a source of significant psychological trauma and potentially feelings of guilt. It was interesting to see the reaction of our Specialist Breast Care Nurses when they were informed of the latest draft guidance, certainly not a positive one.	The committee noted the potential benefits of tumour profiling tests for people with early breast cancer who are deciding whether to have adjuvant chemotherapy (section 5.2 of the second consultation document). The committee considered the extensive comments on the draft recommendations, along with new value propositions from some of the companies, and decided to revise section 1 in the second diagnostics consultation document.

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THEME: Use of bespoke TransATAC analysis

Comment number	Name and organisation	Section number	Comment	NICE response
100	NHS Professional	General	Relating to Section ˜Probability of developing distant metastases (without chemotherapy) “Oncotype DX, Prosigna, IHC4+C, EPClin” Table 124, Page 356/510 This analysis appears to be statistically flawed and selected group of patients as evidenced by the use of the word 'bespoke', the use of data in this fashion is scientifically unsound. The 'bespoke' dataset is unpublished, involves small patient number, only 254 patients had tissue available for testing with all four assays in the NPI>3.4 subgroup). The resulting confidence intervals for the point estimates which NICE used are broad. The confidence intervals overlap between test risk groups, and tests, therefore point estimates should not be used to draw conclusions about differences between tests or base assumptions on for the analysis. There are possible intrinsic bias in the selected patients as selected cases had to have enough tissue available, and therefore these tumours could be very different from the rest of the patient group. No data is presented comparing the clinic-pathological data for the patients used in the bespoke analysis vs not.	Thank you for your comment which the committee considered. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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Comment number	Name and organisation	Section number	Comment	NICE response
101	NHS Professional	Pages 356-510	The dataset used from the TransATAC study is a very small subgroup with wide confidence intervals. It seems that an unexpectedly high recurrence rate was applied to the low RS group based on this small unpublished dataset, thereby exaggerating the theoretical chemo benefit in this low risk group. This does not reflect peer-reviewed evidence or clinical experience.	Thank you for your comment which the committee considered. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
102	NHS Professional		Document 2 (DAR) Section ˜Probability of developing distant metastases (without chemotherapy) “Oncotype DX, Prosigna, IHC4+C, EPClin” Table 124, Page 356 Comment: bespoke data request provided by the TransATAC team to the EAG, restricts the analysis of the full TransATAC dataset to HR+, HER2-, LN0-3 patients, as well as analysing by three patient sub-groups; pN0 NPI≤3.4, pN0 NPI>3.4, LN1-3. The bespoke unpublished dataset involves relatively small patient numbers (254 patients with tissue available for testing with all four assays in the NPI>3.4	Thank you for your comment which the committee considered. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available

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Comment number	Name and organisation	Section number	Comment	NICE response
			subgroup). The resulting confidence intervals for the point estimates which NICE used are broad.	data for use in the model (section 5.8 of the second consultation document).
103	NHS Professional	General	"Reduced TransATAC Dataset used in EAG analysis The EAG used a reduced, TransATAC dataset but the TransATAC reduced dataset is unpublished, has not been shown to be comparable with the general population in the UK. Their own data suggests it is an inappropriate dataset to use and their findings are therefore invalid. Table 124 states 10 year recurrence rates in a “bespoke reduced” TransATAC database. TransATAC 10 year survival published by Dowsett et al in JCO 2010 [2] gave 10 year survival for 513 low RS Oncotype DX cancers as 96% (95%CI 93-97%) yet the dataset used here is further reduced and the EAG authors claim a 85% 10 year DDFI for Low RS from this small TransATAC historical dataset. This raises issues of validation and bias in the reduced TransATAC dataset not addressed by the EAG authors. Further in the trials run by NSABP, an independent highly respected USA group including B14, B20 (and SWOG 8814 analysed by statisticians from another respected independent USA group in node	Thank you for your comment which the committee considered. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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THEME: Use of bespoke TransATAC analysis

<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>positive patients) ,the 10 year recurrence in 338 and 218 low RS patients (out of a total of 668 and 651 analysed respectively) was 6.8%(95%CI96-90.4%) in B14 and 3.2%(95%CI 6.3%-0.1%) in B20 ,with confidence intervals that do not overlap the reduced TransATAC figures . Indeed the 10 year recurrence in the node positive SWOG 8814 trial was only 8% in the Low RS group but 46% in high RS patients treated with Tamoxifen alone.

Further nearly all distant recurrence had occurred by 5 years and there was no increase in recurrence in the low RS group between 5 and 10 years whereas there was in the High RS group (as stated in the EBCTCG meta-analysis).

Table: Published recurrence rates for Oncotype DX RS on Tamoxifen alone (no CT)

<table>
<tr><td></td><td>NPI >3.4 Node -ve</td><td>Node negative</td><td></td></tr>
<tr><td>p124 EAG review</td><td>Low RS OncotypeDX</td><td>Intermediate Risk</td><td>High Risk</td></tr>
<tr><td>Reduced TransATAC Data (n=not stated)</td><td>0.884 (0.776-0.907)</td><td>0.798 (0.694-0.865)</td><td>0.749 (0.598-0.851)</td></tr>
</table>
</td><td></td></tr>
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Original TransATAC Data 2010 (n=872)</td><td>0.96 (0.93-0.97)</td><td>0.88 (0.82-0.92)</td><td>0.75 (0.66-0.83)</td></tr>
<tr><td>B14 (n=668)</td><td>0.932 (0.904-0.968)</td><td>0.857 (0.917-0.797)</td><td>0.695 (0.626-0.764)</td></tr>
<tr><td>B20 (n=651)</td><td>96.8 (93.7-99.9)</td><td>90.9 (82.5-99.4)</td><td>60.5 (46.2-74.8)</td></tr>
</table>
The confidence intervals between the original TransATAC dataset and reduced dataset do not overlap, yet the EAG ignored this comparing assays from a dataset provided by the IHC+4 team."

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.
</td><td></td></tr>
</table>

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104	NHS Professional	General	In the SEER USA dataset of 21,023 node negative Low RS score cancers the 5 year Breast cancer specific mortality was 0.4%(95%CI 0.3-0.6).In the same SEER database for the 2,810 women with micrometastases in their nodes, the 1,644 Low RS women had a breast cancer free survival of 98.9%(95%CI 97.4-99.6%) both with confidence intervals well above the DAR reviews claim of a 85% 10 year recurrence derived from the very small sample in the TransATAC database. This data from randomised trials verified by independent trials groups should have made it obvious to the EAG that the reduced TransATAC dataset was not fit for purpose, inherently biased and too reduced to be a viable dataset particularly for the EAG to use as an economic testing dataset. The EAG authors have exhibited groupthink and much as they have criticised the literature for potential bias in selection of tumour blocks from the various trials, yet they have used a reduced set biased by data loss and far smaller than data sets published in the literature. They have ignored clear discordance on survival in the Low RS group between the reduced dataset and the original TransATAC dataset, the latter which provides results closer to the published trials encompassing far greater numbers of patients and inherently more	Thank you for your comment which the committee considered. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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			accurate. Their assumptions and analysis are incorrect. Another more appropriate dataset needs to be used for their economic analysis and the incorrect assumption that 5 year distant disease free data is "unreliable" needs to be corrected. The authors claim the TransATAC data was useful to compare four of the five tests and data was available to allow subgrouping by NPI status but if the data set is too small or unrepresentative it is inappropriate to use and provides an invalid comparator. Moreover since the TransATAC authors developed IHC4 as a test, there have been several publications which have misrepresented the advantages of IHC4 against the other tests raising publication bias and conflicts of interest. I am surprised and alarmed this dataset was considered for use.	
105	NHS Professional	General	"1. The use of the Transatac study dataset is not appropriate for the economic analysis as it is not representative of the majority population in which gemoic testing would be employed. As noted in the EAG report Transatac includes only postmenopausal women who had already been deemed by their oncologists not to be suitable for chemotherapy (the 20% of women in the ATAC study who did receive chemotherapy were excluded from the analysis). Thus all women who may have been "saved" from chemotherapy are, by definition,	Thank you for your comment which the committee considered. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee

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			excluded from the analysis. The potential reduction in chemotherapy usage is thus underestimated. Furthermore the population is solely postmenopausal women. Premenopausal women are far more likely to be treated with chemotherapy and thus have reduced usage following genomic testing with a “low” score. Simply stating that “this assumption introduces an additional degree of uncertainty with respect to the generalisability of the analysis” is not sufficient"	concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
106	NHS Professional	General	Re the use of the sub-group from TransATAC The economic analysis (and risk classification probabilities etc) based on the bespoke sub-group of TransATAC is of methodological concern. This has been based this on a small sub-group from the trial and is stated to be a pragmatic decision (as 4 of the 5 tests could be assessed). However, this is a cohort of post-menopausal, low risk patients, the majority of whom are likely to not have been indicated for chemotherapy, and is thus not applicable to the broader spectrum of how the tests would be (and are presently) used. This also seems an unusual cohort in some ways since the 10 year DFS are not what would anticipate from other series of such good prognosis post-menopausal patients. Is this data correct? Can a larger more representative cohort not be modelled?	Thank you for your comment which the committee considered. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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			As a pathologist I would also note that there is a possible bias in that cases in this bespoke sub-group were indeed those in who 4 of the 5 tests could been conducted and thus were those in whom tumours of sufficient size and had material in available paraffin wax blocks for such testing. [Indeed, elsewhere the EAG note "The EAG maintain that it is not wrong to point out the limitations of the evidence base with regard to patient spectrum and loss of samples" but they have heavily weighted this particular evidence in their own analysis].	
107	NHS Professional		The summaries are not reasonable because the main model is based on an unpublished, unplanned subset of patients from the TransATAC study who did not receive chemotherapy.	Thank you for your comment which the committee considered. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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108	NHS Professional	General	Sestak 2017 data request: The major part of the economic analysis seems to be based on this data. Using NICE's own criteria for excluding the results of the B20 and SWOG 8814 trials, this data should have been rejected. It appears these data have not even been published in a peer reviewed journal. 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. The numbers in each group are not stated, only the wide confidence intervals and much of the information was redacted. 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 (reference above). 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. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
109	NHS Professional		The unpublished Trans-ATAC data used by NICE, quotes recurrence rates for low risk disease in very small patient groups (250 patients!)	Thank you for your comment which the committee considered.

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			with huge confidence intervals and that are out of sync with other published data. Why are NICE using this data?	The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
110	NHS Professional		4) We are concerned about the emphasis on data from the ATAC trial. This is an old study and many of the patients would not have been considered suitable for chemotherapy. The trial is also an outlier with respect to recurrence rates, which were much lower in studies rejected in the guidance.	Thank you for your comment which the committee considered. The committee considered the bespoke TransATAC analyses, including additional work done by the EAG in response to consultation comments (detailed in the third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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THEME: Distant recurrence rates by risk classification

Comment number	Name and organisation	Section number	Comment	NICE response
111	NHS Professional	4.4.7 (page 26)	The probability of developing distant metastases was based on a 'bespoke' data analysis of TransATAC which is unpublished and not yet subject to peer review. The 15% distant recurrence rate for the low risk recurrence score group is unusually high, in comparison with other data sets (published TransATAC data Dowsett et al JCO 2010; Paik NEJM 2004). The higher recurrence rate may therefore have over inflated the potential benefit of chemotherapy in this low risk recurrence score group.	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
112	NHS Professional	General	The point estimates used in the NICE analysis are outliers compared with multiple published peer-reviewed trial evidence. Most importantly, the 15% 10 yr risk of distant recurrence (DR) for low-Recurrence Score patients in the NPI>3.4 subgroup is very different to the recently presented 9+ yr real-world follow up of patients from the Clalit registry (4% DR: Stemmer SABCS 2017), the TransATAC full dataset (9% DR: Dowsett JCO 2010 â€“ used for the previous NICE assessment), and the NSABP B-14 trial (7% DR: Paik N Eng J Med 2004). NICE should	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when

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			base this critical assumption in the analysis on published peer-reviewed evidence which is representative of clinical experience.	all clinical risk groups were pooled together (see third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
113	NHS Professional	General	We feel the model used by NICE over-estimates the benefit of chemotherapy in the low recurrence risk group. Over 90% of patients in this risk group do not receive chemotherapy within the NHS, published data demonstrates that there is negligible benefit of chemotherapy in this group. However the model used by NICE using bespoke TRANSATAC data estimates the risk of recurrence to be 15% compared to 4% and 7% in other series. This therefore over-estimates the benefit of chemotherapy in low recurrence risk group.	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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114	NHS Professional		Adding further evidence to the value of the test in the recurrence score low and intermediate risk group is the reported low risk group cohort from TailorX and the publication of the Clalit services health registry data. TailorX reported a 93.8% 5 year disease free survival in the low risk recurrence score group who did not receive additional chemotherapy. The Clalit services health registry data although a retrospective analysis was of prospectively collected data. It confirmed the findings of the original validation studies (B-14 and B-20 patients) that distant recurrence rates observed were similar, where low risk recurrence score groups did not receive chemotherapy and most of the intermediate risk recurrence score groups also did not receive chemotherapy. It is here that I contest the conclusions of the draft document, which extrapolated that from the Oxford overview data that the 8-10% benefit patients receive from chemotherapy is distributed across all recurrence score groups. One should also be very clear of the absolute risk reduction when observing any benefit in the low and intermediate recurrence score groups. I also contest the extrapolated TransATAC data used to conclude that the NPI>3.4 low risk patient cohort have a 15% 10 yr recurrence when the studies already discussed do not conclude that. NSABP B-14 study concludes a 4.6% 10 yr recurrence risk in ER+ve Her 2-ve node -ve patients.	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document). In terms of differential chemotherapy benefit, 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 5.4 of the second diagnostics consultation document).

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Comment number	Name and organisation	Section number	Comment	NICE response
115	NHS Professional		I terms of the modelling used on this occasion: - the baseline risk of recurrence, taken from a small subset of patients from a previous study, appears too high and is not consistent with larger 'real world' datasets - eg. the Clalit database.	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
116	NHS Professional		Significant weight is given to unpublished transATAC data and particularly subgroup analysis. This is contrary to the usual principles of NICE. The distant recurrence for low risk patients is higher than published data included the full transATAC dataset publication by Dowsett 2010.	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when

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Comment number	Name and organisation	Section number	Comment	NICE response
				all clinical risk groups were pooled together (see addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
117	Association of Breast Surgery		b) NICE calculate an artificially high rate of recurrence even in the lower risk patients, creating an erroneous impression that withholding chemotherapy even to these women is detrimental to patient outcome (in absolute and relative senses). We know that this is not true. The TaylorX, a multicentre prospective study of over 10 000 women, showed that low risk patients, as identified by a low Oncotype DX score, could be safely treated with hormonal therapy alone. These patients avoided the need for chemotherapy yet had a less than 1% risk of distant recurrence at 5 years (8). 8) Sparano JA, Gray RJ, Makower DF et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer N Engl J Med 2015; 373:2005-2014, 2015	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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THEME: Distant recurrence rates by risk classification

Comment number	Name and organisation	Section number	Comment	NICE response
118	Genomic Health UK Ltd.	Diagnostic Assessment Report Section 'Probability of developing distant metastases (without chemotherapy) – Oncotype DX, Prosigna, IHC4+C, EPClin'	10-year rates of DR by RS group, based on the bespoke unpublished non-peer-reviewed dataset (DAR Table 124), which would be deemed of low quality according to NICE's own criteria for evidence inclusion, are outliers versus published evidence. In particular, the 15% DR rate applied to the RS<18, NPI>3.4 subgroup in Table 124 is incorrect & greatly exaggerates the theoretical potential for chemotherapy benefit in these patients. Oncotype DX classifies ~50% of patients in RS<18 group and the NHS audit showed that clinicians and patients choose to forgo chemotherapy 99% of the time with this result. So the unrepresentative dataset is a significant contributor to the incorrect conclusion that Oncotype DX testing results in patients being prevented benefit (dominated) vs. current practice. Whilst we understand wanting to analyse test risk group distribution by subgroup, the point estimates used for DR rates are clearly not reliable. Confidence intervals are excessively wide and overlap between assays & test risk groups. The point estimates for DR used also conflict with available published evidence. The rate of DR at 10 years for the RS<18 group was 4% in	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document). The EAG noted that its probabilistic sensitivity analysis takes account of the uncertainty surrounding all model parameters, including the uncertainty surrounding distant recurrence estimates.

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		Table 124, Page 356/510	recently presented real-world patient outcomes data from the Clalit registry. This is more closely in line with the data from the independently conducted NSABP B-14 trial or the full TransATAC dataset used in the 2013 assessment. Therefore, we would suggest that NICE base this important model input on one of these published datasets	
119	Genomic Health UK Ltd.	Diagnostic Consultation Document Section 1 'Draft recommendations', Page 2/48	There is an urgent need to utilise tumour biology to also spare many LN+ EBC patients from unnecessary chemotherapy toxicity. Evidence shows many LN+ ER+ EBC patients have good prognosis when treated with endocrine therapy alone. DR rates from the Clalit registry for the RS<18 group, were 1.2%/4.4%/5.4% at 5 yrs for patients with N1mi/1LN+/2-3LN+. The Plan B trial reported 5 yr OS of 99% for patients with N1 disease RS<18. 5 yr BCSS reported from the SEER registry was 98.9% for N1mi and 95.1% for 3LN+ patients. The Oxford Overview highlights that any chemotherapy benefit occurs in the first 5 yrs of follow up so it is appropriate that NICE include data from SEER, Clalit and Plan B. Withholding chemotherapy for patients with less than a 5% risk of DR is not clinically controversial, as it is	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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			unlikely that chemotherapy will provide additional benefit that outweighs the risks from side effects. Crucially, the independent SWOG-8814 trial also reported a statistically significant Recurrence Score by treatment interaction in 1-3LN+ patients, and reinforced the finding from NSABP B-20 and 5 neoadjuvant trials that patients with RS<18 derive negligible or no benefit from chemotherapy. We would encourage the Committee to reconsider making a recommendation for certain patients with LN+ EBC, where there is treatment uncertainty, to also have access to the important prognostic and predictive information provided by the Oncotype DX assay.	
120	UK Breast Cancer Group	4.47 5.8	The modelling used the TransATAC data which is a small data set. Based on this study, it assumes a 15% recurrence at 10yrs for all risk categories. This seems flawed.	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see

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				third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
121	NHS Professional		The report also appears to contradict itself by acknowledging the predictive value of genomic testing in the Mindact study (using Mammoprint) and then dismisses it on the basis of short follow up although the benefits of chemotherapy generally appear early. The dataset you have used to determine chemotherapy benefit does appear higher than our clinical experience of recurrence rates in the low recurrence score group and the 4% seen in the Clalit registry (Stemmer SABCS 2017). In using the TransATAC data, this high rate will exaggerate the chemotherapy benefit in this group. The use of this small, unpublished dataset seems against normal NICE protocol, especially when the main author advocates another genomic predictor.	Thank you for your comment which the committee considered. The EAG noted that MINDACT showed that patients with high modified Adjuvant! Online and low MammaPrint scores had little benefit from chemotherapy. However, MINDACT did not assess whether the relative benefit of chemotherapy differed by test risk group, since only discordant-risk patients were randomised to chemotherapy or no chemotherapy. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see

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				third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
122	NHS Professional	General	Another falsehood contained within this analysis if the ridiculously high recurrence rate for the low risk subset that is used to inform the analysis. The figure of a 15% 10 year distant recurrence risk (DRR) in this low risk group contradicts all current peer reviewed trial evidence and clinical “coal face” experience. Many currently recruiting trials are being redesigned directly because of the diminishing DRR seen in this patient group which is leading to a significant under powering of these trials. This 15% estimate is clearly an outlier biased results due to the small retrospectively tested group of patient which happened to have enough residual breast cancer tissue to be included in this analysis. This error in estimation compounds the previous flaws in the analysis and again suggests that many patients have been harmed by the denial of systemic therapy to this group of low risk group, this is untrue. Since the 2013 recommendation there has been a strengthening of the evidence for the use of Oncotype DX with its use in over 60,000 patients. Locally we have seen the reduction in the over use of systemic therapy and its targeting to the population clearly identified as	Thank you for your comment which the committee considered. The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see third addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).

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			deriving benefit from the therapy. The reversal of the recommendation will do nothing more that harm many patients and increase the resource and financial burden on the NHS.	

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123	NHS Professional	General	The assumption appears to be made that the benefits of chemotherapy are constant across the recurrence risk profiles for the Oncotype score. This is incorrect. Together with the biological rationale that higher proliferative rate tumours are likely to be more chemosensitive, the previous analyses of B20, SWOG 8814 and data of Oncotype in the neoadjuvant setting clearly show that this assumption is incorrect. This will overestimate the benefits of chemotherapy in the low RS group.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
124	NHS Professional	4.4.9 (page 27)	The guidance states that 'Benefit of chemo assumed to be the same across all test risk groups'. The evidence available is contradictory to this (Paik et al JCO 2006, Albain et al Lancet 2010). The data supports both the prognostic and predictive value of genomic profile testing in patients with ER positive breast cancer, and clearly demonstrates the differential relative benefit across recurrence groups. The guidance uses EBCTCG Lancet 2012 as a reference, the authors of this publication have stated in their conclusion 'Information was lacking about tumour gene expression markers, or quantitative immunohistochemistry that might	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which

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			help to predict risk, chemosensitivity for both', clearly recognising the importance of such tests in clinical practice.	tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
125	NHS Professional	5.4 (page 38)	The document states that 'it is likely some patients could have a greater relative benefit from chemotherapy than others, for example, patients with hormone receptor-positive cancer that is insensitive to endocrine therapy but that evidence is not available to support this'. There is published data (Prat et al BMC Medicine 2015; Prat et al Clin Cancer Research 2016) which demonstrate firstly, the variation of intrinsic subtypes in a particular subset of breast cancer (e.g. HR+, HER2- BC) and secondly the ability of intrinsic subtyping (in these studies, including the use of gene expression tests) to provide prognostic and predictive information for patients receiving neoadjuvant chemotherapy. The document continues to state that, while the Paik and Albain study analyses showed a statistically significant prediction of differential relative treatment effect, the studies did not adjust for hormone receptor status. However the patient cohort in these studies were all hormone receptor positive. It is also stated that 'hormone receptor status may also predict	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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			chemotherapy benefit'. This is indeed correct, in that HR-ve tumours would have greater chemotherapy benefit compared to HR+ve tumours. However the subgroup in question here, where the greatest benefit of gene expression tests lie, is the HR+ve group where the available data supports the ability of gene profiling tests in predicting chemotherapy benefit (Paik et al JCO 2006, Albain et al Lancet Oncol 2010)	
126	NHS Professional		The original NSABP B-14 and B-20 validation studies for the prognostic and predictive function of the test provided robust long-term evidence of genomic profiled groups where the omission of chemotherapy provided no detriment to overall survival. It also indirectly emphasised the great benefit of anti-oestrogen (Tamoxifen in the studies) in this ER+ve node -ve group of patients with intermediate risk of disease recurrence and prognosis.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
127	NHS Professional		2. Document 1 (DCD)	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
			Section 4.49, Page 27/48 Section 4.50 (sensitivity analysis assuming differential relative chemotherapy benefit across Recurrence Score groups), Page 28/48 Comment: Low-Recurrence Score patients are assumed to derive substantial relative benefit from CT by NICE panel which is NOT correct. 2016 NHS audit data shows 99% of low-Recurrence Score patients forego chemotherapy (as expected), The analysis (as a consequence of the assumption) concludes that these patients are being denied substantial chemotherapy benefit and implies that all patients should be given chemotherapy to receive the benefit which is not in line with current clinical practice- COMPLETELY WRONG ASSUMPTIONS by NICE panel members I am afraid, Section 'Adjuvant chemotherapy treatment effect on distant recurrence', Page 364/510 Comment: Both published validation trials and real-world outcomes evidence demonstrate that low-Recurrence Score patients derive negligible / no relative or absolute benefit from chemotherapy (Paik et al. 2006, Albain et al. 2010, Sparano et al. 2015, Stemmer et al. 2017, Petkov et al. 2016, Nitz et al. 2017)	The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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			So, the analysis over-states the benefit from chemotherapy for patients in the low-Recurrence Score group The evidence supports that the analysis also under-states chemotherapy benefit to patients with high-Recurrence Scores	
128	NHS Professional	4.49 (page 48)	The document assumes that low risk patients derive similar benefit from chemotherapy. It is known that most low-risk patients are not treated with chemotherapy. The document implies that low risk patients are being denied chemotherapy (not the reality) and that all patients should be treated with systemic chemotherapy. This is clearly flawed. It is well recognised that low RS patients derive negligible benefit from chemotherapy yet the guidance overestimates the chemotherapy benefit in this low risk group and overestimates benefit in high RS patients. The differential benefit seen across risk groups should be used in the modelling.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
129	NHS Professional	2.4.2 (page 18ff)	Most clinicians do not recommend chemotherapy in low RS patients.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict

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				the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
130	NHS Professional	General	Document 1 (DCD) Section 4.49, Page 27/48 Section 4.50 (sensitivity analysis assuming differential relative chemotherapy benefit across Recurrence Score groups), Page 28/48 NICE are incorrect in their assumption that the same sensitivity to chemotherapy exists for women with breast cancer across each Recurrence Score group. The analysis concludes that these patients are being denied substantial chemotherapy benefit and implies that all women should be given chemotherapy to receive the benefit, this is not in line with the evidence base nor accepted clinical knowledge (please see comment [25] for	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative

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			ESMO and ASCO guidelines). Published clinical trials and real-world outcomes evidence demonstrate that low-Recurrence Score patients derive negligible / no relative or absolute benefit from chemotherapy.	chemotherapy benefit for different Oncotype DX risk groups.
131	NHS Professional		The analysis assumes that all breast cancers will have a benefit from chemotherapy which is the underlying basis of its economic assessment. The basis of this assumption is claimed to be the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis data. All genomic tests being assessed determine ER positive, HER-2 negativity cancers for selection for chemotherapy and a similar population should have been studied from available patient data. It is noticeable that the authors of the meta-analysis quote 'In low risk ER positive disease treated with effective endocrine therapy, further risk reduction from adding chemotherapy cannot, in absolute terms, be large, and patients not helped by chemotherapy will be harmed by its toxicity'. The reduction in distant recurrence is far less in node negative patients and it is incorrect to assume they achieve a risk reduction similar to node positive patients. For a small node negative tubular cancer, the absolute benefit of chemotherapy is less than 1% but toxicity (death, Thromboembolic	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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			events, cardiotoxicity, leukemia induced by anthracyclines) is greater than 1% so no oncologist would propose chemotherapy in this case. Unfortunately if NICE sticks to this decision increased harm will occur to node negative breast cancer patients!"	
131	NHS Professional	General	"Prediction of chemotherapy benefit The prediction of chemotherapy benefit is different between the low risk patients in whom reducing the risk from 5% at 10 years to 3% (particularly in the 26% UK patients over 60 years of age) is overwhelmed by the mortality (2% UK data) and toxicity of the treatment, even if there was any benefit to chemotherapy in the low risk groups, indicates toxicity would be greater. Personalisation of treatment according to individuals risk is crucial. The lack of differential relative risk reduction from chemotherapy is not accepted by all Oncologists, unlike the advisors to the NICE Guidelines. There is evidence from a number of papers, such as the SEER database where OncotypeDx low RS patients, both node positive and node negative were not given chemotherapy, but had a 4.4% 5 year risk of recurrence in the node negative low recurrence score and a 1.1% 5 year recurrence in the node positive. The German Plan B trial found a 3% distant recurrence at 5 years in the low RS score less than 12(not given CT) and the TAILORx study found a	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG agreed that the absolute benefit is lower for low-risk patients, but it noted that the relative benefit across risk groups is uncertain.

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			similar recurrence rate. Moreover, the absolute benefit from chemotherapy in these women with such low recurrence rates and low distant recurrence rates is minimal and clearly indicates a sub-set who have no benefit from chemotherapy, which has been shown previously in other trials comparing Tamoxifen alone verses Tamoxifen and chemotherapy internationally (ie B20). Thus the data should have been modelled separately in both the node negative and node positive assuming no absolute benefit in the node negative, compared to the node positive. Neoadjuvant Chemotherapy data, (Gianni L et al in JCO 2005 paper [3]) which analysed Oncotype DX scores before neo-adjuvant chemotherapy in analysis to predict chemotherapy benefit. No patients had a pathological complete response (accepted evidence of chemo sensitivity) with an Oncotype DX score <28 and a high recurrence score(absolute value) was positively associated with the likelihood of pCR (p=0.005), there are other neo-adjuvant chemotherapy studies that have similar findings and equally endocrine neo-adjuvant studies, such as Ueno et al in IJCO 2014 [4] which showed that the response rate in patients undergoing neo-adjuvant endocrine therapy led to tumour responses of 60% in the low RS group, but 20% in the high RS group, leading to breast conserving surgery in 90.6% in the low RS patients, but only 46.7% in the high RS patients. Akashi-Tanaka et al in Breast 2009	The EAG noted that data were modelled separately for node-negative and node-positive patients. Neoadjuvant chemotherapy and adjuvant endocrine therapy are out of scope for this assessment.

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			[5] found a 54% clinical response rate in the low RS cancers given neo-adjuvant endocrine treatment, compared to 31% in the high RS group. None of these studies are randomised, but nonetheless indicate a differential sensitivity according to recurrence score for treatment before surgery, which fits with the predictive analyses from both the B20 and the SWOG-8814 trials. It is notable that both B20, found an RS interaction with chemotherapy of p=0.038 and the SWOG-8814 study, an RS interaction with chemotherapy of p=0.029 indicating the predictive benefit of the RS score for predicting chemotherapy benefit , when performed by two independent Trials groups in the United States and Canada." **References** 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. 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®	

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			as a predictor of clinical response to 24 weeks of 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. 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: 0.1016/j.breast.2009.03.005. Epub 2009 May 2.	
132	NHS Professional		In UK practice we do not use the relative benefits of chemotherapy but the absolute benefits to the patient in terms of 5 and 10 year survival. From this we derive the equipoise group (standardely the 10 year as above) in whom we need the extra information. The interpretation of relative similar benefit across all test risk groups is thus flawed and does not represent how we would ever utilise these tests. Table 1 in the consultation document actually illustrates this point by showing that there is a reduction of unnecessary chemotherapy for some patients ie 0.43 v 0.33 and 0.01 from the CQUIN NHSE access scheme, but also the APPROPRIATE use of chemotherapy for the high risk group. Many clinicians took part in this scheme and the data has	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative

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			never been fully published. This is some of the best data we have on how the test is used in the UK and it is referred to but equally dismissed in this document. Full disclosure of this data set is long overdue.	chemotherapy benefit for different Oncotype DX risk groups. The committee concluded that the Genomic Health access scheme dataset (on use of Oncotype DX in the NHS) was an important piece of real world evidence for use in the economic model. It concluded further that future data collection should be done as part of a national database, rather than by individual companies, in order to increase transparency and linkages with outcome data.
133	NHS Professional	General	3. Whilst we accept that the scope of the update had to include the low, intermediate and high classifications proposed by the manufacturers, it is clear that modern application, particularly of the Oncotype DX test, has changed. Two large prospective studies (PlanB and TailorX) demonstrate an almost complete lack of distant recurrence in women with up to 3 ALN involved with a RS<12 or 11 respectively at a median follow up of 3-5 years. As the benefit of chemotherapy is seen during this period, irrespective of whether or not this test offers predictive value, the excellent prognosis must completely obviate any potential chemotherapy benefit. This is the clear path of usage of such tests and	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict

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			we wish to formally call for an additional analysis of the data to be performed with these cut points, such that the full utility of ODX can be assessed. This is particularly important as the Markov model assumes that all subgroups gain benefit from chemotherapy (based on EBCTCG analysis) which is clearly flawed in these two prospective clinical trials providing level 1 evidence.	chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The scope specified that tests should be assessed in accordance with their CE marks, and at the cut-off points specified by the manufacturers. The EAG noted however, that data using thresholds of RS<11 or 12 from PlanB and TAILORx were included in the clinical review for additional information.
134	NanoString	4.72, page 35	The predictive ability of a test was identified as having a strong impact on the test's cost-effectiveness (Sec. 4.70). Neoadjuvant chemotherapy response data has been reported for Prosigna by Prat and colleagues. The results of this study support Prosigna's ability to predict which hormone receptor-positive breast tumors are more likely to respond to chemotherapy. While the study does not meet the Committee's evidence requirements, we believe that the study supports the assertion that base case estimates of Prosigna's cost effectiveness are conservative. Prat A, Galvan P, Jimenez B, et al. Prediction of Response to	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but

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			Neoadjuvant Chemotherapy Using Core Needle Biopsy Samples with the Prosigna Assay. Clin Cancer Res. Feb 1 2016;22(3):560-566	that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The neoadjuvant setting was not within the scope of the assessment. The EAG noted that advice it received suggested that data from a neoadjuvant setting cannot be generalised to the adjuvant setting.
135	NHS Professional	General	Not entirely clear why benefit derived from chemo is uniform across all groups. We are being asked to use more chemotherapy without evidence for benefit is lower risk groups. Practice not in keeping with international guidelines.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 14 March 2018

THEME: Adjuvant chemotherapy benefit

Comment number	Name and organisation	Section number	Comment	NICE response
136	NHS Professional		- The assumption remains that all patients receive the same relative benefit from adjuvant chemotherapy, regardless of tumour biology. This is clearly not the case, with much evidence and experience to the contrary. I accept that there are methodological issues with some of the data put forward as evidence for the predictive value of Oncotype Dx, one would hope that the forthcoming TailorX study - which I believe is due to report later this year - will help clarify this. It would be difficult to withdraw the test and then receive clear evidence as to its value.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
137	NHS Professional		In consideration of the draft consultation document: - page 27 of 48, point 4.49. This is flawed to state “the benefit of chemotherapy was assumed to be the same across all test risk groups”. This misses the point of genomic testing and the biology of each cancer. The predictive importance of the Oncotype DX is missed here. To make an assumption that low risk patients gain a significant benefit from chemotherapy is not supported by evidence.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which

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				tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
138	NHS Professional		- NSABP B20 and SWOG8814 are independent studies that used Oncotype DX. The results are similar and robust in showing the value of the 3 recurrence score groups. - TAILORx have not reported the results from their study of the intermediate group patients after a median follow up of over 8 years due to lack of events. This provides a very significant finding in that there cannot be a significant benefit of chemotherapy because lack of events in both groups. - The NCI (USA) considers it unethical to include a chemotherapy arm for the low recurrence score group in the setting of a clinical trial.	Thank you for your comment which the committee considered. The committee reconsidered the published evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
139	Royal Marsden Hospital	4.49	The following is copied from the discussion section of the 2012 EBCTCG publication:	Thank you for your comment which the committee considered.

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			Multiplying together breast cancer mortality RRs for the first and third of these findings (standard CMF or standard 4AC vs no chemotherapy, and more effective regimens vs either of these; 0.775 x 0.825 = 0.64) would suggest about 36% breast cancer mortality rate reduction for the more effective regimens versus no chemotherapy. This supports a substantially larger reduction in risk from cytotoxics than the 0.76 hazard ratio than has been applied. Discussion with multiple colleagues indicates that those regimens that are more effective are in much greater use than the lower efficacy treatments.	The EAG conducted additional sensitivity analyses accounting for a wider range of potential relative risks of relapse for chemotherapy versus no chemotherapy (see third addendum to the diagnostics assessment report).
140	Royal Marsden Hospital	4.50	Whether or not the Oncotype predicts for increased relative benefit from chemotherapy is highly contentious. It may be worth noting that the data cited to support this from Paik 2006 rely in part on the 1.31 hazard ratio in the low risk group, ie that added chemotherapy is associated with increased recurrence in this group. There are no other data or biological explanation to support such an effect.	Thank you for your comment which the committee considered. The EAG performed additional analyses to show the impact on the ICERs if a smaller differential relative chemotherapy benefit than that taken from the B-20 study (Paik et al. 2006) was applied in the model in the LN negative, NPI>3.4 group for Oncotype DX. The committee concluded that although these analyses were associated with considerable uncertainty, they gave an indication of Oncotype DX's likely cost

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				effectiveness if the relative chemotherapy benefit differed between Oncotype DX risk groups, but not to the extent reported in the Paik et al. (2006) study (section 5.10 of the second consultation document).
141	Association of Breast Surgery		ABS feels that the calculations utilised by NICE in their cost effectiveness analysis are flawed for the following reasons; a) NICE do not accept that any of the tests predict chemotherapy effect, but apply a model where there is equal benefit of chemotherapy to all patients – we know that is not true eg, histological grade 1 vs grade 3; c) NICE assume that, in an economic sense, giving chemotherapy is inherently a "good" thing across the board if a patient's risk of recurrence is high enough. This does not apply universally. Multidisciplinary teams will have in depth knowledge of individual patients and be able to assess, with the addition of tumour profiling test outcomes, the value of chemotherapy in individual patients (9). 9) Losk K, Freedman RA, Lin NU, et al: Implementation of surgeon-initiated gene expression profile testing (Oncotype DX) among patients with early-stage breast cancer to reduce delays in chemotherapy initiation. J Oncol Pract 13:e815-e820, 2017.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG notes that the economic model is not predisposed to find chemotherapy an inherently good intervention in all patients (for

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				details see the addendum to the diagnostics assessment report).
142	Genomic Health UK Ltd.	DCD Section 4.49, Page 27/48 DAR Section 'Adjuvant chemotherapy treatment effect on distant recurrence', Page 364/510	Level 1 evidence is available from multiple high-quality independent RCT trials using archived samples, showing that pN0-3 patients with RS<18 have little or no chemo-sensitivity and so derive negligible relative risk reduction (RRR) from chemotherapy, whereas patients with RS>30 have much greater chemo-sensitivity and derive a very large RRR from chemotherapy. Indeed, this was acknowledged in both the TAILORx and OPTIMA trial protocols (Section 4.4 of OPTIMA protocol: Differential sensitivity of breast cancer subtypes to chemotherapy). If the EAG had engaged with the internationally renowned study groups; NSABP & SWOG, as they did with study groups for other technologies under assessment, all of the EAGs uncertainties about the conduct of the independent NSABP B-20 or SWOG-8814 trials would have been addressed before the DCD publication. Five RCT neoadjuvant chemotherapy trials also support differential chemo-sensitivity across RS groups. These trials show that tumours with RS<18 are not chemo-sensitive (tumour responses were not likely), but	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG have engaged with study authors as far as was possible within this assessment. During this consultation the EAG have been in contact with authors of the NSABP-B20 study and the SWOG-8814 study.

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		Table 128, Page 363/510	are endocrine therapy-sensitive (measurable clinical and pathological responses) (visa versa for RS>30 tumours). We would encourage the NICE committee to revisit the conclusion about the strength of evidence supporting differential RRR from chemotherapy for patients across RS groups, as it is fundamental to the outcome of the assessment and future access of NHS EBC patients to critical personalized tumour biology information.	The neoadjuvant setting was not within the scope of the assessment. The EAG noted that advice it received suggested that data from a neoadjuvant setting cannot be generalised to the adjuvant setting
143	Genomic Health UK Ltd.	Diagnostic Consultation Document Section 1 'Draft recommendations', Page 2/48	The recommendation that more outcomes evidence is needed for Oncotype DX is surprising, given the existing NICE recommendation, which led to thousands of NHS patients being tested, and given the subsequent availability of outcomes evidence from >63,000 patients. We assume the Committee's change in perspective is a result of a combination of the incorrectly assumed uniform chemo-sensitivity across patients, the inaccurate DR point estimates, and the greater chemo-sparing impact of Oncotype DX testing shown by the NHS audit data. The NHS data showed that clinicians and patients are choosing to forgo chemotherapy in 99% of cases of RS<18, which is precisely what would be expected when the test was adopted in the NHS on NICE's recommendation in 2013.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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			The fact that this is concluded to lead to patients being prevented benefit in the EAGs analysis (Oncotype DX 'dominated'), highlights that the uniform chemotherapy benefit assumption is distorting the analysis. The NHS data also showed huge variation in baseline chemotherapy prescribing across the country (pre-RS chemotherapy rates ranged from 0% to 94%); this inequity of care we understood was the reason for the NICE Breast Cancer Quality Statement for Oncotype DX. If the aforementioned incorrect underlying assumptions were revised, the analysis would correctly support a clear improvement in patient outcomes, as well as economic benefits to the NHS, for Oncotype DX testing	The committee considered the distant recurrence rates by risk classification. It heard from the EAG that the distant recurrence-free rates from the bespoke TransATAC analysis used in the model are consistent with results from other studies, both when subgrouped by clinical risk group and when all clinical risk groups were pooled together (see addendum to the diagnostics assessment report). The committee concluded that the bespoke TransATAC analysis has some limitations, but was the best available data for use in the model (section 5.8 of the second consultation document).
144	NHS Professional		There are a number of concerns with the analysis and the assumptions of the draft recommendations. Firstly, all hormone receptor positive, HER2- early breast cancer patients are assumed to derive a large & equal benefit from chemotherapy. This is not true. In our practice, only those women with equivocal benefit according to PREDICT go forward with oncotype Dx and this score then aids the decision as to whether to reccomend chemotherapy or not.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded

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			Thus the RS helps some women avoid chemotherapy by identifying women at very low chance of benefit....but equal chance of the mortality and morbidity associated with treatment. This also results in significant cost savings. The guidance has not acknowledged the ability of the Oncotype DX assay to predict the likely benefit of chemotherapy and to have a positive effect on patient outcomes, despite substantial evidence. We are also keeping our local data from the past few years and would be very willing to share this with NICE.	that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
145	Lead Biostatistician (public university)	4.24 and 4.6, pages 17-18	I am the NSABP Lead Biostatistician and co-author responsible for analysis of the NSABP B-20 study published by Paik and colleagues in the Journal of Clinical Oncology (JCO) 2016 (Paik et al. JCO 2006;24:3726). The NSABP B-20 trial was performed with pre-specified endpoints and was independently analyzed by NSABP. [Comment 1.1] The Diagnostics Consultation Document (DCD) was not accurate in concluding that the evidence obtained in the NSABP B-20 clinical trial did not strongly support the conclusion that the Oncotype DX assay predicts the benefit of chemotherapy. The DCD stated in this short section that they relied on the EAG and their Diagnostics Expert Report (DAR) in questioning the results and conclusions of NSABP B-20 and	Thank you for your comment which the committee considered. The EAG noted that the B20 study (Paik 2006) reported interaction tests between Oncotype score and chemotherapy benefit, some of which were adjusted for clinicopathological factors. The diagnostics assessment report stated that it was unclear whether these factors were adjusted for individually or simultaneously. It has now been clarified that adjustments were simultaneous. This has been updated in

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			that the "EAG concluded that the significant results could be because potentially important covariates were omitted from the statistical model." All important and relevant covariates were included in the regression analyses. As the EAG cited "Paik et al 2006 performed several Cox regressions adjusting for age, tumour size, ER, PR, tumour grade, Recurrence Score as a continuous variable, treatment and the interaction between treatment and Recurrence Score (interaction p-values 0.035 to 0.068); thus, there is weak evidence for an interaction between treatment and continuous Recurrence Score." [Comment 1.2] Because tumour grade is subject to intra- and inter-observer misclassification, two independent centralized tumour grades and the site tumour grade were assessed and considered in the B-20 data analyses as a sensitivity measure. Each Cox regression model corresponds to one of these tumour grades assessed in B-20: two independent centralized tumour grades and the site tumour grade. Consistency of these results demonstrated the strength of the evidence, contrary to the conclusion drawn by the EAG ("thus, there is weak evidence for an interaction between treatment and continuous Recurrence Score"□). It would be ill-advised to hold p-value=0.05 as the watershed in sensitivity analyses when one of many did not make the cut. Rigidly interpreting scientific findings based on p-value=0.05 as a hard threshold has recently been clearly disputed in a position paper by	section 5.4 of the second diagnostics consultation document. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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			the leadership of the American Statistical Society (Wasserstein RL, Lazar NA. The ASA's Statement on p-Values: Context, Process, and Purpose. Am Stat. 2016;70(2):129). [Comment 1.3] The requirements of JCO constrained the number of tables and figures that could be included in the 2006 publication. However, as is the case for all NSABP studies, we conducted extensive analyses and are pleased to share many of those with you that address the questions raised by the DCD and EAG regarding the Oncotype DX assay and prediction of chemotherapy benefit. [End Comment 1]	
146	Lead Biostatistician (public university)	4.3.3, pages 97-112	[Begin Comment 2] Current use for Oncotype DX in clinical practice is restricted to hormone receptor positive (HR+) HER2 negative (HER2-) breast cancer. The Paik NSABP B-20 publication in 2006 included patients with HER2+ disease. The EAG questions whether the conclusions regarding prediction might be driven by the HER2+ patients with high Recurrence Scores. HER2 values by IHC or FISH are not available for the NSABP B-20 patients because HER2 testing was not standard practice when these patients were diagnosed. However, the Oncotype DX assay includes a quantitative assessment of HER2 expression, which can be used to	Thank you for your comment which the committee considered. The EAG noted that the diagnostics assessment report stated that “other potential biases in the reanalyses of RCTs included attrition of samples; exclusion of patients due to missing data for covariates; and inclusion of HER2+ patients (who are out of scope for this assessment).”

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			identify HER2+ patients. Kaplan-Meier plots were used to assess the evidence of chemotherapy prediction after exclusion of HER2 positive disease (defined by quantitative RT-PCR >11.5; Baehner et al. JCO 2010;28:4300), by comparing the treatment benefit for all patients and for each Recurrence Score risk group (<18, 18-30, and >31) (Figure 1, available here: https://pitt.app.box.com/s/d2j4h0q3p0plbrmpgn7i7xw29uebbrmy). The plots to the left include all patients and the plots to the right exclude patients who are HER2+. [Comment 2.1] As reported in the Paik NSABP B-20 2006 publication, for all patients there is little or no benefit of chemotherapy with RS <18 and clear benefit of chemotherapy with RS >31. The results for the analyses after exclusion of HER2+ patients are very similar to those for all patients (Figure 1, available here: https://pitt.app.box.com/s/d2j4h0q3p0plbrmpgn7i7xw29uebbrmy). There is no evidence from unadjusted K-M plots that the inclusion of patients who had HER2+ disease accounted for the predictive power reported by Paik NSABP B-20 publication in 2006. There were also very few HER2+ patients in the similar B-14 tamoxifen-treated patients with Oncotype DX testing: 60 out of 668 based on NSABP Pathology IHC assay. We would anticipate the same in the B-20	Thank you for the additional data on the HER2- subgroup and for the adjusted hazard ratio data. The EAG agreed that these show a similar pattern to the full cohort. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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			study population. [End Comment 2]	
147	Lead Biostatistician (public university)	4.3.3, pages 97-112	[Begin Comment 3] The EAG reported that the impact of potential imbalances in baseline covariates were not addressed in the Paik NSABP B-20 publication since demographic information by treatment and multivariable models that simultaneously adjusted for the covariates were not detailed in the publication. They also noted that the inclusion of clinicopathological variables alongside RS in the RSPC algorithm (Tang et al. JCO 2011;29:4365) resulted in a loss of predictive ability (p=0.10), and suggested that these uncertainties substantially weaken the conclusion that the RS is predictive of chemotherapy benefit. [Comment 3.1] Although not presented in detail in the JCO 2006 publication due to space limitations, analysis of baseline covariates by treatment and additional multivariable models were fit that simultaneously adjusted for patient age, tumour size, ER, PR, and tumour grade. The range of the interaction p-values (according to different tumour grade readings) were reported in the JCO 2006 publication. To provide additional evidence regarding the value of Oncotype DX beyond tumour grade, tumour grade was assessed separately by two central laboratory pathologists	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG noted that the B20 study (Paik 2006) reported interaction tests between Oncotype score and chemotherapy benefit, some of which were adjusted for clinicopathological factors. The diagnostics assessment report stated that it was unclear

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			(identified as Pathologist A and Pathologist B) in addition to the pathologist at each patient's investigational site. Table 1 (available here: https://pitt.app.box.com/s/d2j4h0q3p0plbrmpgn7i7xw29uebbrmy) provides a summary of baseline covariates by treatment arm in the 651 patients included in the study. Overall, the treatment arms were well balanced except for the grade as defined by Pathologist B, for whom there were more lower and higher grade and fewer moderate grade tumours. [Comment 3.2] Multivariable models for the Recurrence Score by treatment interaction that are simultaneously adjusted for baseline covariates are shown below in Tables 2, 3, and 4 (available here: https://pitt.app.box.com/s/d2j4h0q3p0plbrmpgn7i7xw29uebbrmy) for the 3 different tumour grades. In addition, similar multivariable models that are adjusted for baseline covariates were obtained in the HR+ HER- patients by excluding the HER2+ patients. The results in Tables 2, 3, and 4 (available here: https://pitt.app.box.com/s/d2j4h0q3p0plbrmpgn7i7xw29uebbrmy) in all	whether these factors were adjusted for individually or simultaneously. It has now been clarified that adjustments were simultaneous. This has been updated in section 5.4 of the second diagnostics consultation document. The EAG noted that RSPC (a score which combines RS, age, tumour size, grade, nodal status and endocrine treatment) has been shown to have prognostic ability, but not to be statistically significantly predictive for chemotherapy benefit. The EAG agreed that the suggestion in the diagnostics assessment report that this 'raises questions regarding the predictive effect of RS over clinicopathological variables' was incorrect. However, the EAG noted that the Oncotype RS score is recommended to be interpreted alongside clinical factors when making treatment decisions, and therefore the final decisions may have increased prognostic

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			patients and those in the patients relevant to current practice (excluding HER2+ disease) are summarized in Figure 2 (available here: https://pitt.app.box.com/s/d2j4h0q3p0plbrmpgn7i7xw29uebbrmy). If anything, the multivariable results where HER2+ disease is excluded even more strongly support that the Recurrence Score is predictive of chemotherapy benefit in NSABP B-20. The EAG should review these results and revisit their conclusions regarding the strength of the evidence. [Comment 3.3] One other point, the EAG comments implies that the results for RSPC by treatment interaction in Tang et al 2011 (interaction p-value = 0.1) raises questions regarding chemotherapy prediction. However, RSPC is a fundamentally different measure as an attempt to synthesize and consolidate the independent prognostic utility of the traditional clinicopathologic factors and the Recurrence Score so that patients and their treating physicians are provided with a unified disease prognosis. This effort is similar to the creation of a risk index of breast cancer developed by Mitch Gail et al for high-risk women. The test on treatment interaction was performed as a secondary/exploratory analysis. The result is consistent with abundant other evidence that the traditional clinicopathologic covariates themselves are not predictive of chemotherapy benefit and would add “noise” when treatment interaction	relevance but decreased predictive relevance.

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			is concerned. [Comment 3.4] The impact of clinicopathologic covariates on the Recurrence Score by treatment interaction and potential confounding by clinicopathologic variables is appropriately explored by fitting models of the Recurrence Score by treatment interaction, with covariate adjustment for the clinicopathologic variables, as presented above. In addition, when fitting statistical models, it is standard practice at NSABP to also perform exploratory analyses to examine alternate functional forms, including non-linear effects, to ensure that the models used are appropriate for the data. Based on these exploratory analyses, the pre-specified statistical model to evaluate the Recurrence Score by treatment interaction was deemed to be appropriate. [Comment 3.5] In summary, these multivariable results in Figure 2 (https://pitt.app.box.com/s/d2j4h0q3p0plbrmpgn7i7xw29uebbrmy) for Recurrence Score by treatment interaction are very consistent with the published results of the primary model with no covariate adjustment, HR = 0.32, 95% CI = (0.11, 0.94), p = 0.038 (Table 2 in Paik NSABP B20 publication in 2006), and support the conclusion that the statistically	

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			significant interaction in the unadjusted analysis is not due to confounding from clinicopathologic factors. [End Comment 3]	
148	Lead Biostatistician (public university)	Section 4.3.3, pages 97-112	[Begin Comment 4] The EAG raises a potential concern that the performance of the Recurrence Score to predict chemotherapy benefit is uncertain because the tamoxifen alone arm of NSABP B-20 was used previously in the development of the Recurrence Score. To address the magnitude, if any, of any exaggeration in the prognostic results for the tamoxifen alone arm in NSABP B-20, we compared the risk profile of the Recurrence Score in the NSABP B-14 clinical validation study, which was a completely independent set of patients treated with tamoxifen alone, with the risk profile of the tamoxifen alone arm of B-20 (Figure 3, available here: https://pitt.app.box.com/s/d2j4h0q3p0plbrmpgn7i7xw29uebbrmy). [Comment 4.1] It is important to note that the analysis of the NSABP B-14 patients treated with tamoxifen alone was done after and independently of the use of the NSABP B-20 tamoxifen alone patients for assay development. In addition, the values of the Recurrence Score that were used in the analysis for prediction of chemotherapy benefit in the Paik NSABP B-20	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG noted that this analysis (which used continuous Oncotype DX scores) is interpreted by the commentator as suggesting that the range of distant recurrence risk estimates, and slopes, are

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			publication in 2006 were based, as noted in the Methods, on re-running the assay using the standardized analytically validated methods that were used in the NSABP B-14 study, replacing the analytical results on the tamoxifen arm from the Oncotype DX development phase. The orange lines in Figure 3 (available here: https://pitt.app.box.com/s/d2j4h0q3p0plbrmpgn7i7xw29uebbrmy) depict the 10-year risks of distant recurrence (solid line) and the associated 95% confidence intervals (dashed lines) for 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. [Comment 4.2] The range of these distant recurrence risk estimates are very similar between NSABP B-20 and B-14. The slopes are similar as well, suggesting that the magnitude of any exaggeration of the results in the NSABP B-20 tamoxifen alone arm is small or non-existent. These results suggest that use of the NSABP B-20 tamoxifen alone arm to develop the Recurrence Score does not weaken the conclusion that the Recurrence Score is predictive of chemotherapy benefit. [End Comment 4]	very similar between B20 and B14. However, the EAG note that recurrence rates per risk group do appear to show greater separation in B20 than B14 (see the third addendum to the diagnostics assessment report).

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149	Lead Biostatistician (public university)	Section 4.3.3, pages 97-112	[Begin Comment 5] As reported in the Paik NSABP B-20 2006 publication, only a subset of all enrolled patients in the parent NSABP B-20 study had tumour blocks and were eligible for analysis in the NSABP B-20 study of the Recurrence Score. RT-PCR was successful in more than 97% of the blocks analysed. The Paik NSABP B-20 publication in 2006 noted that patients in the parent study were not included if their blocks were either never obtained by NSABP or, less commonly, exhausted from use in prior studies. Appendix Table A1 of the publication provided the distributions of patient age, tumour size, tumour grade, and hormone receptor status for patients who were assessable for the Recurrence Score and for those who were not. Tumours that were assayed for Recurrence Score had a wide distribution of tumour size, but the proportion of small tumours (<1 cm) were slightly lower (17% vs 21%). Tumours that were assayed were also less commonly graded by the site as well differentiated (13% vs 18%). Age, ER, and PR were similar between groups. [Comment 5.1] Simon et al published criteria for levels of evidence determination (Simon et al. JNCI 2009; 101(21):1446), which considered this issue of potential bias in the use of “prospective-retrospective” studies of archival tissue for tumour marker validation. A high level of evidence (Level IB)	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG noted that the SWOG-8814 study reported interaction tests which were individually adjusted for baseline covariates (age, ethnic origin, tumour size, progesterone status, grade, P53, and HER2; p-value not reported but stated to be significant for all). It noted further that when ER was included the analysis as the only baseline covariate, the p value was non-significant (p=0·15).The EAG

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			can be obtained when there are one or more (preferably more than one) "prospective-retrospective" studies of clinical trial patients with consistent results. It is thus very reassuring that the independent, rigorously performed study of Oncotype DX in the SWOG S8814 clinical study in node-positive breast cancer (Albain et al. Lancet Oncol 2010;11:55) showed predictive results for the Recurrence Score consistent with the results of NSABP B-20. [Comment 5.2] 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. It is only by study of randomized patients that conclusions regarding treatment benefit can be rigorously made. The results of the published NSABP B-20 and SWOG S8814 studies indicate that the Recurrence Score is predictive of chemotherapy benefit, with much greater relative risk reduction for high Recurrence Score disease than for low Recurrence Score disease. [End Comment 5]	does not agree that SWOG-8814 supports the claims of prediction of chemotherapy benefit for Oncotype DX.
150	NHS Professional		The recurrence score helps us identify those who benefit from chemotherapy - as shown by several validation studies. It has also identifies those who previously would not have been given	Thank you for your comment which the committee considered.

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			chemotherapy but need it. The implication from your interpretation that all patients, independent of recurrence score, benefit from chemotherapy (section 4.49) does not fit with the published data or other reviewers (e.g. the TAILORx trial was only allowed to randomize the intermediate group as independent reviewers felt in unethical to give chemotherapy to the low score group and not give chemotherapy to the high risk group).	The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG noted that there are only 2 reanalyses of RCTs relating to the ability of Oncotype DX to predict the relative treatment effect from chemotherapy in the adjuvant setting (1 in LN negative and 1 in LN positive patients), and patients in the no-chemotherapy arm of the B20 study (LN negative) were used to derive the Oncotype score. Evidence from observational studies is inconclusive due to the limitations of the analyses performed.

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				The EAG noted that TAILORx used a cut point of RS<11, whereas the cut point for this assessment is RS<18, in accordance with the scope.
151	NHS Professional	General	Has all of the relevant evidence been taken into account? From recent trials , node negative gene predictive & prognostic data and real-world outcomes evidence, all demonstrate that low-Recurrence Score patients derive negligible / no relative or absolute benefit from chemotherapy (Paik et al. 2006, Albain et al. 2010, Sparano et al. 2015, Stemmer et al. 2017, Petkov et al. 2016, Nitz et al. 2017). This evidence needs to be considered.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG noted that all the articles listed are included in the review.

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Comment number	Name and organisation	Section number	Comment	NICE response
152	NHS Professional	General	(i) Comment that: "We also note the fact that giving chemotherapy to everyone is a cost-effective option compared with giving chemotherapy to a subset of patients does not invalidate the model as it is plausible that chemotherapy is cost effective" is a highly worrisome view to anyone involved in breast cancer care and highlights a disconnect between this analysis and modern clinical management. Present practice aims not to overtreat patients and the UK can be considered at the forefront of this in many ways. This lack of recommendation for any genomic test is a retrograde step in personalised medicine and patient 'outcomes'. (ii) In the base-case analysis, the benefit of 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, based on the Oxford overview. This is recognised to be simplistic and based on older chemotherapy regimens, and no clinician accepts that there is universal chemotherapy benefit across all patients. Recruitment of patients into a number of RCTs (OPTIMA, as one example) highlights clinicians' expert views that this is not the case. Indeed, whilst stated to be outwith the remit of this guideline, it is absolutely clear from neoadjuvant trials that tumours with different biology vary hugely in response. Methods for identification of which	Thank you for your comment which the committee considered. The EAG noted that the model is not predisposed to automatically find chemotherapy to be cost-effective within all patient subgroups. Further details explaining the use of chemotherapy in the model can be found in the third addendum to the diagnostics assessment report. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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			patients benefit and which suffer only side-effects are essential, and without any of these assays available to UK clinicians the UK will be an outlier in international practice.	
153	NHS Professional	General	My concerns regarding the evidence used in coming to this recommendation is based upon the following; An assumption has been made that the benefit of chemotherapy is universal across all risk groups, this is not the case. There is a considerable amount of data that show a differential benefit of chemotherapy between the low risk group and the high risk group. This overestimation of the benefit of chemotherapy to the low risk group invalidates much of the following evaluation. This assumption suggest that all patients with an NPI of 3.4> derive benefit from chemo therefore all of these patients require treatment with chemotherapy rather than further stratification. This is clearly not what is practiced in the real world of breast cancer management as we know as clinicians this would lead to significant over treatment of the population in this NPI group. This assumption also under values the benefit of chemotherapy in the high risk group so a differential analysis should be applied to the different risk groups. This would show the true case that the results of a low risk score isn't the denial of benefit to that patient but actually results in the safe omission of a toxic morbid therapy. The assumption that the use of a "low" risk score is the denial of benefit to a patient also jaundices the	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG noted that the model does not assume that all patients derive benefit from chemotherapy; it applies a treatment effect. Further details explaining the use of chemotherapy in the model can be found in

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			cost effeteness results. It is the safe reduction of the suggested blanket use of chemotherapy in this low risk group that is core to the cost benefit to both the patient and the NHS.	the third addendum to the diagnostics assessment report.
154	NHS Professional	Section 4.3, page 99	Chemotherapy prediction for Oncotype DX: To reject the results of the B20 and SWOG 8814 trial based on the possibility of spectrum bias is not scientifically valid. These trials were both conducted by organisations with very high scientific standards independent of Genomic Health, using pre-specified endpoints, using independent statistical analysis, with central histopathologic review by 3 highly respected practitioners (in the case of B20) and with sound statistics showing that the subset of patients from the initial trial were not significantly different. The chances of both trials arriving at the same conclusions is less then 1%. The Simon (Simon R. Roadmap for developing and validating therapeutically relevant genomic classifiers. J Clin Oncol. 2005;23(29):7332-41. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2009;101(21):1446-52.) criteria for inclusion of prospective-retrospective trials as 1A evidence demands that at least two such trials reach the same conclusion. (None of these criteria seem to have been applied the reworking of the Trans-ATAC data which is the basis of this report - see below).	Thank you for your comment which the committee considered. The EAG did not reject the B20 and SWOG-8814 studies from the review, or their results from their summary of the evidence. The risk of bias was highlighted, in accordance with usual quality assessment practices. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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Comment number	Name and organisation	Section number	Comment	NICE response
155	NHS Professional	General	Clinical utility: The Oxford overview shows that most chemotherapy benefit is seen in the first 5 years and to exclude the evidence from the SEER and CLALIT databases on the grounds of insufficient follow up is not logical.	Thank you for your comment which the committee considered. The EAG notes that these studies are included in the diagnostics assessment report. Whilst the SEER registry data did not officially meet the criteria for inclusion due to short follow-up length for survival outcomes, the EAG still reported this study.
156	NHS Professional	4.4.9, page 27	I believe NICE have incorrectly assumed that all patients have the same sensitivity to chemotherapy (relative risk reduction from chemo) within each risk group. For example it appears that NICE are assuming that pateints in the low RS score group derive 'substantial benefit' from chemo and in their analysis conclude that these patents are being denied substantial benefit from chemo. Both the SWOG and NSABP B20 trial datasets (both published and validated - Paik et al 2006, Albain et al 2010, Petkov 2016, Nitz 2017) suggest that all chemo benefit is in the high RS score group. And this is in line with clinical experience	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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			Hence the wrong assumption has been made about low RS score patients which overstates the benefit from chemo for this group, leading to the wrong conclusion. The NICE analysis is in my opinion flawed.	
157	NHS Professional		There are assumptions in this document that I believe to be incorrect. 1. The benefit to chemotherapy is the same for all patients. This in incorrect. Whilst proportional benefit maybe similar, ABSOLUTE benefit varies. A small node negative ER positive tumour has a very low risk of recurrence, often <5% at 10years, so there cannot possibly be a 15% gain to chemotherapy such that a patient as you quote. patient's with a higher risk of recurrence main gain more from chemotherapy than a low risk tumour, due to proportional risk reduction. 2. There is also an assumption that the use of these genomic tests might mean that a patient will forgo the gain from the benefit from chemotherapy if it is withheld due to a low risk score being identified. This is incorrect. The use of a genomic test in an ER positive/HER-2 negative population identifies patients whose tumour is BIOLOGICALLY low risk, where the additional benefit of chemotherapy over and above endocrine treatment is lower than the risk of chemotherapy, so where patients prognosis and risk of recurrence is the same regardless of chemotherapy and are therefore spared it's toxicity and harms.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG noted that the model attempts to quantify the trade-off between the advantages and disadvantages of receiving chemotherapy, the probability of which is driven by the genomic test and the way in

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				which that information is used to inform chemotherapy use. The recurrence rates are based on published data. Further details explaining the use of chemotherapy in the model can be found in the third addendum to the diagnostics assessment report.
158	NHS Professional		Point numbers 4.49 and 4.59 make an assumption that chemotherapy benefit is equivalent in all patient groups. This assumption is flawed (widely accepted as such) because this is not how we practice breast cancer treatment in the UK. We already use risk-stratification methods (such as NPI) to prevent chemotherapy use in some low-risk group patients and vice-versa. Genomic tests, such as Oncotype DX (the only one that we have experience of) help further in risk stratification, patient selection.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups. The EAG noted that the difference in relative benefit across risk groups is uncertain, but

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				the absolute benefit is lower for low-risk patients.
159	NHS Professional	5.4 & 4.24	A point not made in the EAG review is that the 2 historic clinical trials of chemotherapy vs no chemotherapy that were re-analysed according to Oncotype DX tests performed on a subset of participant tumour blocks (Paik 2006, Albain 2010), were conducted in an era prior to routine HER2 testing. Approximately 10% of ER-positive tumours are also HER2-positive – the proportion will vary slightly with population characteristics. The Oncotype DX algorithm, which is in the public domain, is strongly influenced by proliferation and HER2 related genes and therefore such tumours would be expected to have high Recurrence Scores. In Albain 2010, 12% of tumours were identified as HER2-positive by the HER2 test that is integral to the Oncotype DX test. I am not aware of any analysis of the effect that inclusion of these tumours had on the results of this study. The Paik 2006 study report makes no mention of HER2 status of any of the retrieved tumour blocks even though there would have inevitably been HER2-positive tumours present. This is possibly because the Oncotype DX test was not configured to report HER2 status at that time. It is likely that at least some of the differential chemotherapy benefit in the high Recurrence Score groups demonstrated in these two studies was driven by a disproportionate representation of HER2-positive tumours in the high-risk group. HER2-positive tumours have been reported to have	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.

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			increased chemotherapy sensitivity compared to HER2-negative tumours after adjustment for other clinic-pathology features	
160	NHS Professional	5.4 & 4.24	Albain 2010 were able to analyse only 227 LN1-3 tumours. The confidence intervals are consequently extremely wide.	Thank you for your comment which the committee considered. The EAG agreed that the confidence intervals for the hazard ratios (for chemotherapy vs. no chemotherapy) in low-risk and intermediate-risk groups are very wide in both B20 and SWOG-8814. This is discussed in the third addendum to the diagnostics assessment report.
161	NHS Professional		3) The guidance assumes the same relative benefit for chemotherapy for all risk groups, suggesting that sensitivity to chemotherapy is independent of other prognostic factors. There is, however, 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. In current US trials, such as the TAILORx study comparing chemotherapy with no chemotherapy, It was considered unethical to include patients with very low recurrence scores, who were assumed not to benefit from chemotherapy. There is no evidence to suggest that these patients are at increased risk of a late recurrence.	Thank you for your comment which the committee considered. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but

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			Patients with very high recurrence scores have also been excluded, as the evidence strongly suggests that their risk of recurrence is significantly reduced with chemotherapy and therefore their benefit from chemotherapy has been assumed to be proven.	that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.
162	Agendia N.V.	Comment no. 17 page 38 of 212 (NICE Addendum 2; 1.2)	Comment no. 17 page 38 of 212 (NICE Addendum 2; 1.2) It is important that the EAG are aware of the statistical flaw of the NSABP-B20 predictive study, and this has been specifically mentioned in the "NICE Addendum 2". 39/212 from *"Approximately 1/3 of the total number of patients in the trial was used as the training set"* To: "The study re-used the 233 samples from the B20 tamoxifen treated arm that were used for the development of the Oncotype test and compared these with the patients from the arm that had not been previously used, patients treated with chemotherapy added to tamoxifen." To underscore that the statistical issue is not merely "some patients", but really the entire arm, the comparative arm, which makes the statistical flaw much larger and more likely to have influenced the outcome of the study. Also, we wish to discuss the following statement written in the Addendum: "It is unclear whether inclusion of the derivation set patients	Thank you for your comment which the committee considered. The EAG agreed that overfitting of the tamoxifen arm of the B20 study is a limitation which could potentially overestimate the difference in relative chemotherapy benefit between risk groups. The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative

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			would augment or reduce any apparent interaction between chemotherapy and RS, but it does put the study at high risk of bias." We feel it does not highlight the flaws in this study clearly enough for readers and would like to provide more details. As the tamoxifen data were the training dataset for the Oncotype recurrence score, the ability to separate patients for the Oncotype Recurrence Score groups is a given. The true validation in the Paik et al study in the NSABP-B20 study is the independent data from the chemotherapy arm. And this data shows that the Oncotype Recurrence Score does not appropriately stratify the risk of recurrence in the true validation dataset. [Ioannidis, 2006, Nat Clin Pract Oncol], or this indicates that the observed difference in outcomes between the chemotherapy and tamoxifen arms might be "exaggerated". [Symmans et al, 2012, Oncology] To determine the extent of inflation of the data in the training set, one can compare the recurrence risks from similarly treated patients from the validation series with the training series. If these recurrences are the same for the 2 series, then one could accept the extent of overfitting to be small. Since the NSABP Study B14 compares tamoxifen to placebo, and NSABP Study B20 compares tamoxifen to tamoxifen plus chemotherapy; both studies have a Tamoxifen-only treated arm. The recurrence risk of the Low Recurrence Score 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 recurrence in the	chemotherapy benefit for different Oncotype DX risk groups.

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High Recurrence Score risk group is much higher in the development series, 39.5% compared with 30.5% in the B14 validation series. 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%.

We therefore disagree with the EAG that “it is unclear whether inclusion of the derivation set patients would augment or reduce any apparent interaction between chemotherapy and RS”. The impact of the re-use of the tamoxifen treated arm has a huge impact that can be inferred from comparison of the tamoxifen treated arms from NSABP-B14 and B20.
<table>
<tr><td rowspan="3">OncotypeDx RS score</td><td colspan="2">NSABP-B14</td><td colspan="4">NSABP-B20</td></tr>
<tr><td colspan="2">Tamoxifen treated</td><td colspan="2">Tamoxifen treated</td><td colspan="2">Tamoxifen +chemotherapy treated</td></tr>
<tr><td>Recurrence Risk</td><td>% of TAM treated patients in total study population (n)</td><td>Recurrence Risk</td><td>% of TAM treated patients in total study population (n)</td><td>Recurrence Risk</td><td>% of TAM+CT treated patients in total study population</td></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>
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<table>
<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>
TAM – Tamoxifen treated, TAM+CT – Tamoxifen plus chemotherapy treated
</td><td></td></tr>
<tr><td>163</td><td>Agendia N.V.</td><td>Comment no. 13 page 52 of 212</td><td>With the data provided above, we would like to argue that there is no evidence available that “the recurrence score may also predict the benefit of chemotherapy”, and would urge the EAG to remove this statement from the report. Given the arguments provided above, we do not agree with 4.23 and 4.24 on page 17 of 48 in the NICE diagnostic consultation document.</td><td>Thank you for your comment which the committee considered.

The committee reconsidered the evidence on whether the tumour profiling tests can predict the benefit of chemotherapy in light of consultation comments (section 5.4 of the second consultation document). It concluded that the evidence on the extent to which tumour profiling tests are able to predict chemotherapy benefit is highly uncertain, but that there may be some difference in relative chemotherapy benefit for different Oncotype DX risk groups.</td></tr>
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THEME: Risk of recurrence after 5 years

Comment number	Name and organisation	Section number	Comment	NICE response
164	NHS Professional	5.5 (pages 38-39)	The document states that 'the risk of recurrence often continues beyond 5 years' and that long term follow up and outcome data not available. However there is published data (Ohnstad et al Breast Cancer Res 2017; Laenkjolm et al JCO 2018) which confirms the utility of gene expression tests and intrinsic sub typing in providing prognostic information of long term outcome (e.g. up to 15 years in the Ohnstad paper).	Thank you for your comment which the committee considered. The EAG noted that there is uncertainty surrounding the duration over which the benefit of chemotherapy is sustained, hence constraining recurrence at 15-years reduces the likelihood of overestimating this benefit of chemotherapy. Sensitivity analyses were performed on this input and more details are available in the third addendum to the diagnostics assessment report.
165	NHS Professional	5.5, 5.16	It is incorrect to state that longer-term follow-up data will necessarily add to the value of MINDACT. The Oxford Overview 2005 & 2012 publications (EBCTCG, Lancet 2005, 2012) clearly demonstrates that chemotherapy has very little if any impact on recurrence events beyond 5 years. Late analysis of recurrence will therefore be confounded by events that cannot be influenced by chemotherapy.	Thank you for your comment which the committee considered. This issue was raised in the original EAG report (page 362) and in the response to consultation on the EAG report. For further discussion, please refer to EAG addendum point 4.
166	NHS Professional		The assumption that chemotherapy has any effect on relapse beyond 5 years cannot be justified from meta-analysis data and is incorrect. The prevention of relapse over 5 years is best achieved with extended adjuvant hormonal therapy.	Thank you for your comment which the committee considered. This issue was raised in the original EAG report (page 362) and in the response to consultation on the EAG

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THEME: Risk of recurrence after 5 years

Comment number	Name and organisation	Section number	Comment	NICE response
				report. For further discussion, please refer to EAG addendum point 4.

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THEME: Adverse effects of chemotherapy

Comment number	Name and organisation	Section number	Comment	NICE response
167	NHS Professional		The external assessment group analysis underestimated risk of the harms, as 1% of women under 60 and 2% of women 60 years and older die within 1 year of adjuvant chemotherapy according to UK and USA figures (Rosenstock A et Al,Breast Cancer Res Tmt 2016(157)339-50 :Wallington M et Al.Lancet Oncol 2016(17)1203-16) so there is not a universal benefit to chemotherapy as the EAG assume! The EAG review only really factored in AML as significant harm and ignored the 15%of women get permanent alopecia and 10-12% long term peripheral neuropathy with Taxane chemotherapy, and the 5% who get cardiac problems (heart failure) by 10 years after Anthracyclines. On top of that, all the patients who undergo chemotherapy lose 6 months of their working life and need other members of their family to take care of their children at immense expense to society.	Thank you for your comment which the committee considered. The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It 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.
168	NHS Professional		c. The probability of AML is flawed as in the same dataset (Wolf et al) the risk of AML was increased through the use of radiotherapy alone. This is also reported by Zeidan AM et al (Risk of myeloid neoplasms after radiotherapy among older women with localized breast cancer: A population-based study. PLoS One. 2017 Sep	Thank you for your comment which the committee considered. The use of the Wolff study was based on expert advice received by the EAG. Sensitivity analyses were conducted around the incidence rate for

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THEME: Adverse effects of chemotherapy

Comment number	Name and organisation	Section number	Comment	NICE response
			13;12(9):e0184747.). There is little evidence for an additive risk of chemotherapy and radiotherapy and thus the model requires recalibration. d. It seems odd that the only chronic toxicity considered for chemotherapy is AML. It is well known that chemotherapy, particularly taxane based chemotherapy induces permanent peripheral neuropathy in ~50% of women treated, inducing altered balance and gait. The impacts of such chronic toxicities as neuropathy are not included in Campbell et al which does not include any data on patients treated with weekly paclitaxel and assumes that all HRQoL issues return to baseline by 1 year. More recent data clearly demonstrate that this is fundamentally flawed and that the cost of chemotherapy continues well beyond this.	AML within the EAG report (see EAG report Tables 139, 142, 145, 148 and 151). The issues surrounding long-term AEs of chemotherapy were raised in the EAG report and in response to the consultation on the EAG report. Please refer to EAG addendum point 5 for additional analyses including CHF, alopecia and peripheral neuropathy.
169	Royal Marsden Hospital	4.1	A key feature of the clinical utility of the use of these tests is to avoid unnecessary toxicity when cytotoxic therapy can be safely avoided. This should be give equal weighting to measures of disease outcome.	Thank you for your comment which the committee considered. The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It concluded that it was important to consider potential adverse events

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THEME: Adverse effects of chemotherapy

Comment number	Name and organisation	Section number	Comment	NICE response
				that could be caused by chemotherapy, but that reduced occurrence of adverse events due to reduced exposure to chemotherapy was unlikely to affect conclusions on cost effectiveness of the tumour profiling tests.
170	UK Breast Cancer Group	4.52	Long term toxicities other than AML have not been factored into the economic model. Infertility, early menopause, peripheral neuropathy and occasional permanent hair loss are all commonly encountered in clinical practice. Chronic fatigue has been reported in up to 25% of patients. Cardiac toxicity (heart failure) arising from anthracycline use is a particular concern with reported excess mortality of 0.5-1.5%.	Thank you for your comment which the committee considered. The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It concluded that it was important to consider potential adverse events that could be caused by chemotherapy, but that reduced occurrence of adverse events due to reduced exposure to chemotherapy was unlikely to affect conclusions on cost effectiveness of the tumour profiling tests.
171	NHS Professional	General	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
			The Summary and analysis over-states the benefit from chemotherapy for patients in the low-Recurrence Score group. All the cost effectiveness should be taken in account including inpatient episodes while on chemotherapy and its huge impact on quality of life. For some patients especially for self employed and with co morbidities it also has significant implication both financial and health respectively.	The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It 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. Societal impacts (including productivity) do not form part of NICE's reference case and therefore were not included in the economic model.
172	NHS Professional	General	As a breast cancer oncologist who has used genomic testing (Oncotype and Endopredict) regularly to help patients make decisions around chemotherapy I am hugely disappointed in this provisional guidance. I would make the following specific comments:	Thank you for your comment which the committee considered. The EAG noted that none of the studies listed appear to report health-related quality of life estimates measured using a preference-based

Comment number	Name and organisation	Section number	Comment	NICE response
			Has all of the relevant evidence been taken into account? There has been a recommendation that more research is done. In respect of quality of life there is a wealth of evidence showing that the use of chemotherapy in the adjuvant setting is (at the very least temporarily) detrimental to quality of life. These publications would include (as a brief snapshot of a huge dataset) Broeckel JA1, Jacobsen PB, Balducci L, Horton J, Lyman GH. Quality of life after adjuvant chemotherapy for breast cancer. Breast Cancer Res Treat. 2000 Jul;62(2):141-50. Paraskevi T Quality of life outcomes in patients with breast cancer Oncol Rev. 2012 Mar 5; 6(1): e2. Martin M1, Breast Cancer International Research Group 001 Investigators. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005 Jun 2;352(22):2302-13.	instrument. As such, these studies cannot provide health utilities for inclusion in the model. The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It 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.

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Comment number	Name and organisation	Section number	Comment	NICE response
			Cameron D, Barrett-Lee P, Velikova G, Canney P, Moyses H, McDermaid M, Banerji J, Gaunt C, Reynolds C, Wardley A, Bowman A, Bertelli G, Murray N, Bliss J. TACT2 Randomised Adjuvant Trial in Early Breast Cancer (EBC): Tolerability and Toxicity of Standard 3 Weekly Epirubicin (E) Versus Accelerated Epirubicin (aE) in 129 UK Hospitals (4391 Patients) (CRUK/05/019). Cancer Res. 2010;70(24 Suppl):#P5-10-06 There is also a massive literature on the consequences of adjuvant breast cancer chemotherapy which includes (but is not limited to) problems of: â€¢ Cognitive impairment â€¢ Fatigue â€¢ Time off work and under / un employment â€¢ Depression â€¢ Infertility â€¢ Cardiac disease None of this morbidities have been included within the Markov model.	

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Comment number	Name and organisation	Section number	Comment	NICE response
			It is not scientifically plausible to assume that these same detriments in quality of life would occur in patients who did not receive chemotherapy. In this context it is fanciful and impractical to suggest that more research be done in this area. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The summaries of effectiveness are not reasonable interpretations of the evidence as they ignore the lack of detriment to quality of life in those who safely avoid chemotherapy. The summaries are not reasonable because they are modelled on a very limited â€˜costâ€™ of the impact of chemotherapy which ignores much of the toxicity.	
173	NHS Professional		There is a cost for chemotherapy per cycle in this document, costs for endocrine treatment and follow-up, but no assessment of the cost of chemotherapy in terms of other risks. Some assessment of the AML risk is included, but no assessment of long term cardiac toxicity of chemotherapy. It is often estimated 1-2 % of patients may have long term cardiac failure and all the costs associated with that. In addition to AML there is also a risk of myelodysplasia	Thank you for your comment which the committee considered. The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It concluded that it was

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Comment number	Name and organisation	Section number	Comment	NICE response
			long term. There are mental costs and financial costs of a patient unable to work during chemotherapy and recovering from treatment.	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. Societal impacts (including productivity) do not form part of NICE's reference case and are therefore not included in the economic model.
174	Patient		I was predicted a 70% survival rating by PREDICT (which you seem to think can take the place of genomic testing) as opposed to 98% by the Oncotype DX genomic test. I would have had to have chemo, the possible long-term drawbacks of which I do not think you have adequately taken into account in your documentation of the site. Not to mention the unquantifiable psychological effects of a relatively poor prognosis.	Thank you for your comment which the committee considered. The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It 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,

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Comment number	Name and organisation	Section number	Comment	NICE response
				was unlikely to affect its conclusions on the cost effectiveness of the tumour profiling tests based on the EAG's analysis.
175	NHS Professional	5.8, 4.52	The economic model excludes intangibles and unknowns which are nevertheless very real issues for chemotherapy treated patients. These include issues such as chronic fatigue affecting return to work, peripheral neuropathy and costs of fertility preservation. It is well established that the acute mortality of breast cancer chemotherapy is approx 0.25%. Estimates for the incidence of late anthracycline-induced heart failure and consequent excess mortality are variable but appear to lie in the range of 0.5-1.5%. With the exception of AML however none of the excess mortality is included in the model.	Thank you for your comment which the committee considered. The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It 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.
176	Macmillan Cancer Support		*Has all the relevant evidence been taken into account?* Macmillan believes the consultation is unduly focused on outcomes in terms of survival. In our view, this misses the point of	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
			tumour profiling tests, which is to guide patients and clinicians on avoiding chemotherapy, but without impacting on survival, and which drive better quality of life outcomes. It is difficult to design research that can link quality of life (QoL) directly with the test. We know that tumour profiling testing may mean chemotherapy is avoided and therefore improve QoL in those who would otherwise receive it unnecessarily. Equally, QoL may improve for those patients who know they are getting chemotherapy, when based on a clinical decision alone they would not have had it and that would affect survival. We are certain that what the evidence does show is that chemotherapy reduces QoL. So, our expectation was that rather than remove access to GEP tests, NICE would recommend extending it to include patients who are higher risk who decide not to have treatment. We also expected the recommendations to include extending tumour profiling tests to include Mammaprint. The use of Onctoptype Dx in lowering risk and therefore guiding patients and clinicians on appropriate circumstances for avoiding	The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It 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.

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Comment number	Name and organisation	Section number	Comment	NICE response
			the use of chemotherapy seems to have been largely overlooked. This has implications in terms of immediate financial savings, but longer-term too in terms of reduced financial impact on future health and social care services. Focusing specifically on Onctoptype Dx, we believe tumour profiling can lower risk. The evidence that needs more examination therefore concerns what quality of life improvements patients who face lower risk might benefit from by deciding not to undergo chemotherapy. Evidence on the additional quality of life impact of not receiving chemotherapy would consider reduced risks to patients themselves, in terms of effects of treatment. However, it is also important to understand the evidence on health care provision and what chemotherapy can mean in terms of impacts on individuals' working lives.	
177	NHS Professional		5) We are also concerned that the morbidity and mortality of chemotherapy has not been taken into account in the costing. While the long-term risk of leukaemia is mentioned, there does not seem to be an allowance for the costs of inpatient care for side-effects of chemotherapy, such as sepsis, blood clots, line infections etc . There is also the cost of increased staff time	Thank you for your comment which the committee considered. The EAG notes that: - the costs associated with chemotherapy-related toxicity were included in the total

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			dealing with patient concerns about side effects. The increase in the use of chemotherapy that would result if this guidance is implemented would also mean more patients having to take time off work and an increase in stress for their families.	chemotherapy costs used in the model which were estimated by Hall *et al*. - AML was assumed to be associated with a mortality impact.
178	NHS Professional		The opinion that all patients should be considered for chemotherapy as there is benefit for all in the NICE guidance does not take into account the risk of second malignancy induced by chemotherapeutic agents. As this risk is in the order of 2-3% and many patients benefit of chemotherapy is of similar magnitude according to the PREDICT V2 criterion. We would be over-treating patients if we offered them all chemotherapy and putting them at risk of a life changing diagnosis. Moreover there is the risk of serious cardiac complications and neutropenic sepsis with the chemotherapy regimens used in breast cancer. We would urge you to reconsider the recommendation to withdraw support for Oncotype DX.	Thank you for your comment which the committee considered. The EAG notes that the economic model included AML, based on the study reported by Wolff *et al*. The committee considered additional analyses done by the EAG on adverse events and added a new consideration to the second consultation document (section 5.11). It 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.

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THEME: Probability of having chemotherapy

Comment number	Name and organisation	Section number	Comment	NICE response
179	NanoString Technologies	1.2, pages 2-3	The DCD indicates that the Committee concluded that there is a high degree of uncertainty as to how the probability of chemotherapy differs between tests, compared to current practice. The EAG provided sensitivity analyses to its model, based on alternative sources for the pre-test (baseline) and post-test probability of chemotherapy by subgroup (Table 145, p389 EAG report). For the LN0 NPI<3.4 subgroup, this group of sensitivity analyses increased the ICER; however, in the LN0 NPI>3.4 subgroup this group of sensitivity analyses all reduce the ICER compared to the EAG base case, and the same is true for the single sensitivity analysis in the LN+ (1-3 nodes) subgroup. It is reasonable to conclude, therefore, that the base case analysis represents a conservative estimate of Prosigna's cost effectiveness. Scenario ICER Subgroup: LN0 NPI>3.4 Base case (deterministic) - Â£25,857 LN0 NPI>3.4 post-test P(chemo) Holt et al - Â£19,356 LN0 NPI>3.4 post-test P(chemo) Loncaster et al - Â£21,216 LN0 NPI>3.4 post-test P(chemo) UKBCG survey - Â£22,420 LN0 NPI>3.4 baseline P(chemo) NCRAS, post-test P(chemo) Holt	Thank you for your comment which the committee considered. The committee considered the data on pre- and post-test chemotherapy decisions used in the model. It concluded that there was much more uncertainty around chemotherapy decision making for 2-level tests, and for the subgroups that were not included in the original recommendation from NICE on tumour profiling tests (LN negative, NPI 3.4 or less, and LN positive) (see section 5.9 of the second consultation document). The committee also concluded that the Genomic Health access scheme dataset was an important piece of real world evidence for use in the economic model (section 5.6 of the second consultation document).

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Comment number	Name and organisation	Section number	Comment	NICE response
			et al - Â£18,288 LN0 NPI>3.4 baseline P(chemo) NCRAS, post-test P(chemo) Loncaster LN0 - Â£20,971 LN0 NPI>3.4 baseline P(chemo) NCRAS, post-test P(chemo) UKBCG survey - Â£20,774 Subgroup: LN+ (1-3 nodes) Base case (deterministic) - Â£28,666 LN+ post-test P(chemo) UKBCG survey - Â£20,427	
180	NHS Professional	General	I append details of UHNM experience of using Oncotype DX, and the benefit to our patients. **Impact of Oncotype Dx® on MDT Decision for the need of Adjuvant Chemotherapy in patients with Early Breast Cancer UHNM Experience** Introduction Oncotype Dx® is a validated multiple gene assay to predict recurrence and benefit of adjuvant therapy for breast cancer patients. NICE guidelines recommend its use in hormone receptor	Thank you for your comment which the committee considered. The committee heard from the EAG that this information could not be included in the economic model because estimates of the probability of receiving chemotherapy pre- and post-test conditional on test risk score are needed.

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Comment number	Name and organisation	Section number	Comment	NICE response
			(HR) positive, Her-2 negative early breast cancer (EBC). Oncotype Dx use has been shown to reduce chemotherapy use in EBC. Financial constraint is a major barrier limiting its use in developing nations. The objective of this analysis was to study the impact of Oncotype scores on pre-Oncotype adjuvant therapy decisions made by clinicians. Methods All patients with HR positive, Her-2 negative EBC fit for adjuvant chemotherapy and advised an Oncotype Dx were included in the study. An initial treatment decision taken by the treating oncologist (without Oncotype score) was documented as hormone therapy only, chemotherapy and hormonal therapy or could not decide. The decision was compared with the need for chemotherapy based on Oncotype score. The decision of adjuvant treatment was compared pre and post-Oncotype testing. Results Eighty-three patients were evaluated. Mean pathological tumor size was 25.8 mm. Oncotype Dx changed adjuvant decision in 39.8% of patients. Moreover, of the patients planned for adjuvant chemotherapy, 74% did not receive it based on their Oncotype scores. Similarly, of the patients planned for hormonal therapy,	

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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>12% did receive chemotherapy as they had a high Oncotype score. There were 7 patients in the â€˜could not decideâ€™ group, of whom 5 (71%) needed only hormonal therapy. Eight patients had a node positive disease. Of these, 3 patients needed adjuvant chemotherapy

Conclusions
Oncotype Dx significantly impacts treatment decisions for adjuvant therapy in EBC. Adjuvant chemotherapy can be avoided in majority of patients with EBC based on Oncotype scores as compared to traditional clinicopathologic criteria

ONCOTYPE DATABASE

Total patients = 83
Nov 2009 to May 2017
Nodal status

<table><tr><td>Nodal status</td><td></td></tr><tr><td>Negative</td><td>75</td></tr><tr><td>Micrometastasis</td><td>4</td></tr><tr><td>Positive</td><td>4</td></tr><tr><td>Total</td><td>83</td></tr></table></td><td></td></tr>
</table>

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THEME: Probability of having chemotherapy

<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>
Mean age = 56.4 yrs (39 â€“ 75)
Median = 55 years
Median tumor size = 22mm (pT)
Mean tumor size = 25.8 mm (pT)

<table>
<tr><td>Nodal status</td><td></td></tr>
<tr><td>Up to 50</td><td>26</td></tr>
<tr><td>51 - 65</td><td>35</td></tr>
<tr><td>>65</td><td>22</td></tr>
<tr><td>Total</td><td>83</td></tr>
</table>

Tumor stage and grade

<table>
<tr><td>pT</td><td>Grade I</td><td>GII</td><td>G III</td><td></td></tr>
<tr><td>T1</td><td>3</td><td>21</td><td>15</td><td>39</td></tr>
<tr><td>T2</td><td>0</td><td>29</td><td>10</td><td>39</td></tr>
<tr><td>T3</td><td>0</td><td>4</td><td>1</td><td>5</td></tr>
<tr><td></td><td>3</td><td>54</td><td>26</td><td>83</td></tr>
</table>

Change in decision as per pT stage and grade
pT1 - GI - 2/3
pT1 G II - 9/21
</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>pT1 G III - 7/15
pT2 G II - 6/29
pT2 G III - 5/10
pT3 G II - 3/4
pT3 G III - 0/1
Change in decision = 33/83 (39.8%)

MDT decision for adjuvant Rx * Adjuvant Rx given Crosstabulation
Count

<table>
<tr><td colspan="2"></td><td>Adjuvant Rx given</td><td></td><td>Tota</td></tr>
<tr><td colspan="2"></td><td>Hormonal therapy</td><td>Chemo-therapy</td><td></td></tr>
<tr><td rowspan="3">MDT decision for adjuvant Rx</td><td>Hormonal therapy</td><td>43</td><td>6</td><td>49</td></tr>
<tr><td>Chemotherapy</td><td>20</td><td>7</td><td>27</td></tr>
<tr><td>No definite decision</td><td>5</td><td>2</td><td>7</td></tr>
<tr><td colspan="2">Total</td><td>68</td><td>15</td><td>83</td></tr>
</table>

Chemo to hormone = 74%
Hormone to chemo = 12.2%
No decision to hormone = 71%</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>Score category * Grade Crosstabulation
Count
<table><tr><td></td><td></td><td colspan="3">Grade</td><td rowspan="2">Total</td></tr><tr><td></td><td></td><td>I</td><td>II</td><td>III</td></tr><tr><td rowspan="3">Score category</td><td>Low</td><td>3</td><td>35</td><td>9</td><td>47</td></tr><tr><td>Interme diate</td><td>0</td><td>18</td><td>9</td><td>27</td></tr><tr><td>High</td><td>0</td><td>1</td><td>8</td><td>9</td></tr><tr><td colspan="2">Total</td><td>3</td><td>54</td><td>26</td><td>83</td></tr></table>[redacted]</td><td></td></tr>
</table>

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Comment number	Name and organisation	Section number	Comment	NICE response
181	Myriad Genetics	4.73	As shown in the deterministic sensitivity analysis results, the probability of receiving chemotherapy conditional on test results is a key driver of the ICER, with some sensitivity analyses reducing the ICER for EndoPredict by 57%. There is a reliance on the recent Bloomfield et al. (2017) abstract reference to inform the probability of receiving chemotherapy conditional on test results for EndoPredict in the base case economic analysis (1). Despite the study by Bloomfield et al. (2017) with 149 patients being UK-based, Myriad Genetics questions whether this is the most appropriate source for the base case. Myriad Genetics suggests that this model parameter is investigated further by the EAG, given that it is a key ICER driver. To support this, Myriad Genetics has provided the data of the prospective Penault-Lorca et al (2018) decision impact study with 200 patients (2) in a draft, full-text form in academic in confidence, as only an abstract for this study (3) was available at the time of the systematic review stage of the DAP process. [redacted] (2). Furthermore, the prospective decision impact study by Ettl et al (2015) (4) was	Thank you for your comment which the committee considered. The committee considered the data on pre- and post-test chemotherapy decisions used in the model. It concluded that there was uncertainty around chemotherapy decision making for 2-level tests, and for the subgroups that were not included in the original recommendation from NICE on tumour profiling tests (LN negative, NPI 3.4 or less, and LN positive) (see section 5.9 of the second consultation document). The EAG used the Bloomfield study in the base case for the 2-level tests as this was the only UK study. However, further sensitivity analyses were undertaken using the Penault-Llorca study (the data in the full-text draft match those from the published abstract which were included in the EAG report). The committee heard from the EAG that the Ettl *et al.* study could not be use in the model as it does

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Comment number	Name and organisation	Section number	Comment	NICE response
			also only available in abstract form at the time of the systematic review stage; a full text of this study has subsequently been published (5). Ettl et al (2017) reported that availability of the EPclin score in 395 patients resulted in a percentage decision change of 41%, favouring avoidance of chemotherapy 150 times (38%) and its addition 20 times (5%) resulting in a net reduction of 33% (5). [redacted] *References:* Bloomfield DJ, et al. Patient/oncologist decisions about adjuvant chemotherapy in ER+ ve, HER2-ve early breast cancer following endopredict testing. *American Society of Clinical Oncology*; 2017. [redacted]Penault-Llorca F, et al. A prospective multicenter non-randomized trial evaluating the effect of EndoPredict® (EPclin®)	not report pre- and post-test probabilities of receiving chemotherapy conditional on test risk score.

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 14 March 2018

THEME: Probability of having chemotherapy

Comment number	Name and organisation	Section number	Comment	NICE response
			clinico-genomic test on treatment decision making among patients with intermediate clinical risk. *San Antonio Breast Cancer Symposium;* 2016; San Antonio, Texas, USA Ettl J, et al. Prospective comparison of conventional clinicopathological factors, uPA/PAI-1 and EndoPredict clin score (EPclin) for adjuvant clinical decision making in ER-positive, HER2- negative breast cancer: Progesterone receptor expression is strongly associat. Cancer Research Conference: *37th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States Conference* Start 2015;75. Ettl J, et al. Decision impact and feasibility of different ASCO-recommended biomarkers in early breast cancer: Prospective comparison of molecular marker EndoPredict and protein marker uPA/PAI-1. *PLoS One*. 2017 Sep 6;12(9)	
182	NHS Professional	General	Evidence of decision impact of Oncotype DX: [redacted] (Holt et al) was based on testing all ER+ PR+ HER2- node -ve patients and not a selected group at intermediate risk. The decision changes in our current practice (review of 80 patients selectively tested with Oncotype DX) are as follows: 36.2% decisions unchanged, 73.8% changed, 6 of 80 to HT plus chemotherapy	Thank you for your comment which the committee considered. In the base case, the EAG's model used the Genomic Health access scheme dataset as the source for the pre- and post-test probability of having chemotherapy in the intermediate clinical

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			and 45 of 80 to HT alone). This is significantly different to your estimation and to other similar published analyses done on selected patients in the UK.	risk group. Other sources were used for other risk groups and the 2-level tests (see table 1 in the second consultation document). The committee concluded that the access scheme dataset was an important piece of real world evidence for use in the economic model. It noted that alternative sources of data were used in sensitivity analyses.
183	NHS Professional	2.4.2, page 18	The lower use of chemo following use of genomic assessment is cited as the 'key driver for reversal of recommendation' for use of genomic testing. the NHS Audit in 2016 showed that clinicians are not using chemo in the Low RS score group. as stated above, the published validated data described above suggests that with-holding chemo in this group of patients is entirely appropriate (the Oncotype assay is modelled on the basis that the low RS score group derive negligible benefit from chemo as confirmed in the SWOG and NSABP B20 datasets cited above)	Thank you for your comment which the committee considered. The committee concluded that the access scheme dataset was an important piece of real world evidence for use in the economic model. It considered the modelled impact of these data on chemotherapy use (see section 4.48 of the second consultation document).
184	NHS Professional	4.48	Table 1 shows the reduction in chemotherapy use resulting from the NHS Access scheme which is a model input. The fall in proportion of eligible patients treated with chemotherapy by an	Thank you for your comment which the committee considered.

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			absolute figure of 10% is likely an underestimate because although the data collection started with the scheme launch, there was a time lag required to implement the scheme at individual trusts, in some cases running into many months.	The committee concluded that the access scheme dataset was an important piece of real world evidence for use in the economic model. The EAG noted that their model only uses data for which there was a pre- and post- test chemotherapy decision, which would not be affected by a lag in implementation.
185	NHS Professional	6	*The data on chemotherapy use from the NHS England access scheme prior to and in the first year of its implementation when combined with outcome data collected routinely by the NHS offer the ability to answer questions on the clinical and cost effectiveness of the tests that is highly relevant to the NHS.*	Thank you for your comment which the committee considered.

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186	NHS Professional	General	"The meta-analysis data is not the best published evidence, as it is a series of trials, some of which are historical (pre 2006) and irrelevant to the current standards of care. Some of the trials did not use chemotherapy or endocrine therapy in their randomisation. It is an incorrect assumption that there is a uniform 10 year risk reduction due to chemotherapy in all risk groups. In the meta-analysis [1] in node negative patients, who were also ER positive, there was no significant difference between 5 years of Tamoxifen alone and 5 years of chemotherapy and Tamoxifen. chemotherapy does not benefit all women and whilst node negativity is not the only factor (cf, young age and tumour size), it is a key factor, which meant the model should have been run with different assumptions for node negative and micro-metastatic patients, compared to those with node positive disease. Importantly all patients node negative and positive are at risk of the complications and mortality from chemotherapy but the benefit is minimal for most ER positive, HER2 negative node negative cancers. The meta-analysis suggests that the benefit of chemotherapy in ER strong, HER-2 negative patients is largely only from the addition of Taxane chemotherapy, which NICE only recommends for node positive	Thank you for your comment which the committee considered. The EAG noted that the 10-year relative risk of relapse for adjuvant chemotherapy versus no chemotherapy is based on the annual event risks for distant recurrence reported in the EBCTCG meta-analysis. Alternative relative risks were presented in diagnostics assessment report. Separate analyses are presented for lymph node negative and lymph node positive subgroups.

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Comment number	Name and organisation	Section number	Comment	NICE response
			patients. The EAG assumptions and conclusions are not valid for a node negative population. Very few of the historical trials reported in the meta-analysis had HER-2 status available and it is clear that HER-2 positivity affects responsiveness to chemotherapy and thus the meta-analysis which does not separate out these ER positive, HER-2 positive patients from the HER-2 positive, ER negative patients, is not the best evidence available. Indeed that is the case for nearly all screen detected Hormone receptor positive HER-2 negative cancers (12000 cases annually ,yet only 12% currently are given chemotherapy) and is the reason NICE stated only node negative intermediate risk breast cancer patients should undergo genomic testing. It is concerning that benefit and economic analysis was not performed separately in intermediate risk node negative and positive cohorts." "**Reference** 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	

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Comment number	Name and organisation	Section number	Comment	NICE response
			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	
187	Myriad Genetics	1.1	The diagnostics consultation document (DCD) states that *'there is not enough evidence to recommend routine adoption'* of the five tests assessed. However, as part of the diagnostics assessment programme (DAP) manual there is recognition in the process guidance that 'e*vidence about patient outcomes for diagnostic technologies is typically lower in quantity and quality than evidence for pharmaceutical products'* and that *'different types of evidence are collected and a linked evidence approach taken'* in such situations. Whilst it appears the DAP process allows for a linked evidence approach, and recognises the complexity of assessing diagnostic technologies, this approach has not been fully considered during this assessment and instead strict thresholds have been placed on the level of certainty/uncertainty accepted by the committee.	Thank you for your comment which the committee considered. The committee considered the uncertainty in the model. It 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 (see section 5.12 of the second diagnostics consultation document).

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188	Roche Products Ltd UK		Specific comments on the results: Statistical analysis and bias may have been impacted by the study design, since patients with small tumours were often not included in the trials due to limited patient material to run the assay Response to chemo - many drugs trials include scans after ~3 cycles of chemo to assess patient response - it would be interesting to see if this was included as part of some of the retro trials what the statistical evidence was i.e did the test predict those patients who didn't respond? Was the assessment of follow up time in the trials, sufficient to gain the necessary evidence to prove the "recurrence prediction" that oncotype Dx reports?	Thank you for your comment which the committee considered. The EAG noted that most studies excluded tumour samples with insufficient tissue, and 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 (section 5.3 of the second consultation document). The EAG noted that the diagnostics assessment report focussed on long-term outcomes such as distant recurrence and survival. It included studies with a follow-up of at least 3 years for recurrence outcomes or 5 years for survival outcomes.

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Comment number	Name and organisation	Section number	Comment	NICE response
189	Macmillan Cancer Support		*Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* We note the summary of clinical utility and how the impact of chemotherapy takes all studies into account. However, we would observe that comparing these studies requires us to also look at the baseline adopted in terms of what point chemotherapy would normally be provided to a patient. To compare studies of different populations (e.g. North America and the UK), with different baseline practices, is not in our view the most useful analysis and the information provided from each study type should be considered as 'stand-alone' data. We also note that robust data based on Randomised Control Trials and longer-term survival are the ideal source for decision making. However, that does not negate the importance of other data. For example, a study that determines whether an additional test alters a clinician's judgement on the appropriateness of treatment is worthwhile data. Not routinely providing tumour profiling testing likely means we have no real means of	Thank you for your comment which the committee considered. The EAG noted that the diagnostics assessment report only included decision impact studies (with data on changes in chemotherapy use) conducted in the UK or Europe, and the modelling used chemotherapy rates from UK sources. Sensitivity analyses were undertaken using European studies where UK studies were lacking.

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			capturing data in future on the impact felt by patients of providing chemotherapy when it isn't needed. The decision would be a step away from modern developments in cancer treatment, especially when we note the growing importance of personalised treatment. The Oncotype Dx test is based on individuals' cancer cell activity and PREDICT, whilst a useful tool, is population based.	
190	NHS Professional		2) The suggestion of spectrum bias due to the exclusion of very small tumours is purely speculative. The tests only apply to ER positive HER2 negative tumours and patients in this group with tumours smaller than 1cm would be very unlikely to be offered chemotherapy.	Thank you for your comment which the committee considered. The EAG noted that there were concerns about patient spectrum bias in all studies reporting prognostic ability. 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 (section 5.3 of the second consultation document).

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191	NHS Professional	5.5	It is very difficult to say very much about the MINDACT study because of the extremely good 5-year outcomes and the presence of approximately 20% of patients in the randomised part of study who do not fall within the target population (10% “triple negative” breast cancer, 9.5% ER-positive, HER2-positive).	Thank you for your comment which the committee considered.
192	Royal College of Pathologists	2.1	In the justification for lack of benefits of Oncotype Dx, (In lymph node negative patients, using the test in clinical practice appeared to result in low rates of chemotherapy use in low-risk patients (2% to 12%; see table 14 in the overview in which low risk is around 24-54%), with acceptable outcomes), it seems that the proportion of low risk patients (2-12%) is underestimated and the figures needed for definition of acceptable outcome (96-99%) are overestimated.	Thank you for your comment which the committee considered.
193	NHS Professional		An interesting review that might inform is: Systematic review of the clinical and economic value of gene expression profiles for invasive early breast cancer available in Europe. Blok EJ, Bastiaannet E, van den Hout WB, Liefers GJ, Smit VTHBM, Kroep JR, van de Velde CJH. Cancer Treat Rev. 2018 Jan;62:74-90. doi: 10.1016/j.ctrv.2017.10.012. Epub 2017 Nov 6. Review.	Thank you for your comment which the committee considered. The EAG noted that the systematic review by Blok et al. 2018 was published after the submission of the diagnostics assessment

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<table>
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<tr><td></td><td></td><td></td><td></td><td>report, and that the conclusions of the Block et al. review are consistent with the EAG review.</td></tr>
<tr><td>194</td><td>Agendia N.V.</td><td>4.4.2 (page 185 of DAP37 evaluation report, Nov 2017),</td><td>‘Outcomes did not always match standardized definitions; several described analyses of distant metastases but were not clear whether all deaths and breast cancer deaths were counted as events or were censored, which makes it difficult to know whether the analyses were of DRFS or DRFI.53, 63, 64, 86, 126-128..’

Please find below clarifications on the definitions in outcomes for the studies mentioned in this section.

<table>
<tr><th>Ref DAR report</th><th>Outcome measures used</th><th>Outcomes defined as</th></tr>
<tr><td>53, van ‘t Veer</td><td>BCSS and DMFS</td><td>BCSS;
DMFS; The primary clinical endpoint used in data analysis was time to distant metastasis. Distant metastasis-free survival (DMFS) was defined as the time from diagnosis to first distant Local/regional recurrences before distant metastasis were censored at the time of</td></tr>
</table>
</td><td>Thank you for your comment which the committee considered.

This information was noted by the EAG, but it was not possible to add information to the diagnostics assessment report at this stage.</td></tr>
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					relapse. For analysis, data were censored at 15 years, as 490% of the distant metastatic events occurred before this time point. (Jerevall et al. 2011)metastasis.	
			63, Bueno-De-Mesquita 2009	DMFP; distant metastasis free percentage and OS	DMFP; Distant metastasis as first event and overall survival	
			64 Buyse		We analyzed three main endpoints: time from surgery to distant metastases, which was the endpoint used to identify the gene signature (5) (all other events were ignored for this endpoint);overall survival, which was defined as time from surgery to death from any cause; and disease-free survival, which was defined as time from surgery to any recurrence (local or regional), second breast primary, distant metastasis, or death from any cause. The Kaplan – Meier product-limit estimator was	

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<tr><td></td><td></td><td>used to display time to- event curves for these three endpoints.</td></tr>
<tr><td>86, Ishitobi 2010</td><td>DMFS</td><td>Distant metastasis and death.</td></tr>
<tr><td>126, Knauer 2010</td><td>BCSS and distant disease-free survival (DDFS)</td><td>(BCSS), defined as time from surgery to breast cancer-related death and distant disease-free survival (DDFS), defined as time from surgery to any distant metastasis. For both outcomes, follow-up was censored at 5 years, because firstly, most of the treatment effect of adjuvant CT is observed within 5 years</td></tr>
<tr><td>127, Bueno-de-Mesquita 2011</td><td>DMFS and OS</td><td>The two survival end points were time from surgery to distant metastasis as first event (DMFS), which was the end point used to identify the 70-gene signature [2], and OS, defined as time from surgery to death. In the analysis of distant metastasis, patients whose first failure was distant metastasis were counted as failures; all other patients were censored at the date of their last follow-up, death,</td></tr>
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<tr><td></td><td></td><td>contralateral breast cancer, other second primary or locoregional recurrence.</td></tr>
<tr><td>128, Beumer 2016</td><td>OS, DMFS, DMFI</td><td>Overall survival (OS) was defined as the time from surgery until death by any cause.17 Distant metastasis-free interval (DMFI) was defined as the time from surgery until the diagnosis of a distant recurrence. Distant metastasis-free survival (DMFS) was defined as the time from surgery until the diagnosis of a distant metastasis or death by any cause.</td></tr>
</table>
</td><td></td></tr>
<tr><td>195</td><td>Agendia N.V.</td><td>4.8.3 (Page 283 of DAR of DAP37 evaluation report, Nov 2017)</td><td>‘Out of the 4 in-scope tests, MammaPrint assigned the most patients to the low-risk category (table 14), but unlike the other 3 tests it does not have an intermediate category. When low and intermediate categories were treated as 1 category for the 3 tests that have 3 risk groups, Oncotype DX assigned the most to the low/intermediate category (82%), and MammaPrint the least (61).’

We disagree with the methodology of the EAG and the OPTIMA prelim study on this point, and do not believe treating low and intermediate categories as one category is scientifically sound. For the OPTIMA prelim study Oncotype DX RS was dichotomized around 25 which pools</td><td>Thank you for your comment which the committee considered.

The EAG noted that the diagnostics assessment report stated the RS cut point for OPTIMA prelim as RS<25, but also noted that it could have been clearer that the cut-point used was not in line with current cut-points for Oncotype DX in the UK.

The EAG noted that the diagnostics assessment report states that there is</td></tr>
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			a proportion of Oncotype DX intermediate risk patients into a low/intermediate risk pool. Firstly we believe, for transparency, it should be clearly stated in the DAR that the low/intermediate risk group Oncotype RS score threshold was set at 25 for the low risk/intermediate. In addition as described by Bartlett et al., *"No outcome data from OPTIMA prelim were available at the time of analysis. As the sample size is comparatively small, it is highly unlikely that it will prove possible to compare the ability of the tests studied here to predict patient outcome*." The final DAR should clearly state the limitations of the OPTIMA trial and that comparing genomic tests based on this study is highly uncertain. Secondly, as shown in Paik et al., 2004 in Figure 2 (inserted below), in Supplementary Figure 2B, and 2C (plus described in the main text of the paper), there is a statistically significant difference in distant recurrence, relapse free interval and overall survival between the RS low risk, intermediate risk and high risk groups (P<0.001).	uncertainty around how intermediate RS patients should be treated, and that the drawing together of low/intermediate patients was not intended to imply that intermediate patients should be treated as low risk patients. The EAG noted that Tsai 2016 was excluded from the diagnostics assessment report because it recruited only patients with RS18-30, which is not a population of direct relevance to the decision problem. It also gives no information on how Oncotype DX would perform in comparison to MammaPrint across the full spectrum of patients.

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			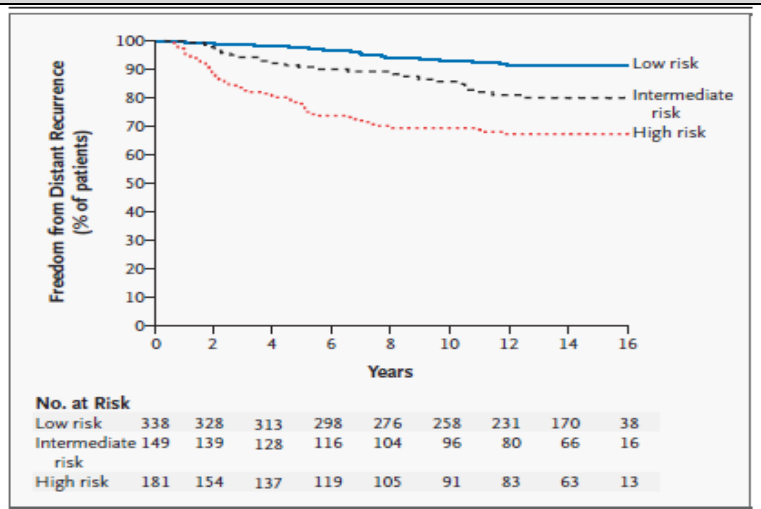 **No. at Risk** Low risk 338 328 313 298 276 258 231 170 38 Intermediate risk 149 139 128 116 104 96 80 66 16 High risk 181 154 137 119 105 91 83 63 13 **Figure 2. Likelihood of Distant Recurrence, According to Recurrence-Score Categories.** A low risk was defined as a recurrence score of less than 18, an intermediate risk as a score of 18 or higher but less than 31, and a high risk as a score of 31 or higher. There were 28 recurrences in the low-risk group, 25 in the intermediate-risk group, and 56 in the high-risk group. The difference among the groups is significant (P<0.001).	

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			In addition in Table 1 of Paik et al., 2004 the rate of distant recurrence at 10 years is 14.3% (95% CI 8.3-20.3). This is above the 10% threshold set for LOW-RISK in the MammaPrint test, and the below the generally accepted 90% DMFS for low risk patients.	

Table 1. Kaplan–Meier Estimates of the Rate of Distant Recurrence at 10 Years, According to Recurrence-Score Risk Categories.*

Risk Category	Percentage of Patients	Rate of Distant Recurrence at 10 Yr (95% CI)†
		percent
Low	51	6.8 (4.0–9.6)
Intermediate	22	14.3 (8.3–20.3)
High	27	30.5 (23.6–37.4)‡

* A low risk was defined as a recurrence score of less than 18, an intermediate risk as a score of 18 or higher but less than 31, and a high risk as a score of 31 or higher.
† CI denotes confidence interval.
‡ P<0.001 for the comparison with the low-risk category.

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			Thirdly, the Prospective Study of MammaPrint in Breast Cancer Patients with an Intermediate Recurrence Score (PROMIS) trial, recently published in JAMA Oncology (Tsai 2017) showed the impact of performing a MammaPrint test on 840 women who had early-stage breast cancer and an ODx intermediate recurrence score 18-30. Each woman had her sample re-tested with MammaPrint and treatment recommendations were recorded before and after receipt of the MammaPrint results. 45% of intermediate risk patients had a Low Risk result with MammaPrint and 55% had a High Risk result. This shows that using the whole intermediate risks into the low risk category is not justified and suggests that the intermediate RS results of the 21-gene assay have the potential to cause over- and under-treatment of patients.	
196	Agendia N.V.	Comment no. 17 page 39 of 212 (NICE	Comment no. 17 page 39 of 212 (NICE Addendum 2; 1.5) It is good to read that the EAG agree with the Albain et al analysis having low clinical relevance given that it reports only the 50-point difference.	Thank you for your comment which the committee considered. The EAG agreed that a 50-point difference is not clinically meaningful, but interpreted the analysis as done using RS as a continuous variable but scaled up to report the effect, in

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		Addendum 2; 1.5) Comment no. 30 page 63 of 212 (NICE Addendum 2; 1.5)	However, we would like to make EAG aware that it can seriously be doubted whether "the use of the 50-point difference in the adjusted analyses of prognostic performance indicate that RS is prognostic after adjusting for clinicopathological factors…" We would like to respond to the following EAG response concerning the reported 50-point differences: "….but disagree that the studies are irrelevant – the statistical significance of a 50-point differences, implies a statistically significant change for a 1 point differences, and therefore implies that there would be a statistically significant difference between risk groups, but does not indicate which cut points are optimal, or how clinically meaningful the difference would be." In order to understand how reporting 50-point differences is clinically meaningless, one should know how often patients have score exceeding a Recurrence Score of 50. The Oncotype Recurrence Score runs from zero to 100, but depicted on their result form and most publications the figures do not show Recurrence Scores over 50. In TAILORx only 2% of patients have a Recurrence Score over 50.	this case based on a 50-point difference. The EAG noted that the effect of RS on the continuous scale was statistically significant for a unit increase in RS. The EAG concluded therefore, that the test has prognostic value, but noted it is a matter of clinical judgement what constitutes a meaningful difference.

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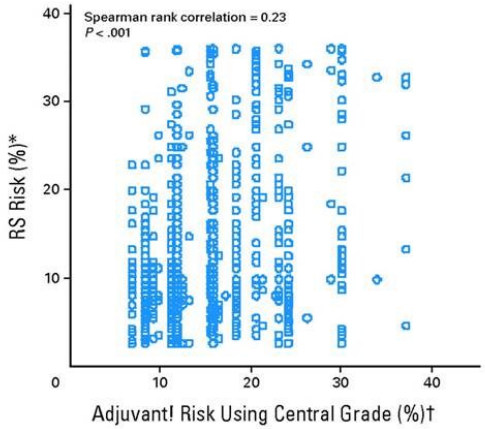
			Also in the TransATAC Study by Dowsett et al, hardly any patient occur with Recurrence Scores over 40:  Because more than half of all the patients in these studies have a Recurrence Score lower than 18, an analysis using a 10-point increase, or even better, a 1-point increase (a continuous score) would have been the optimal way of analyzing.	

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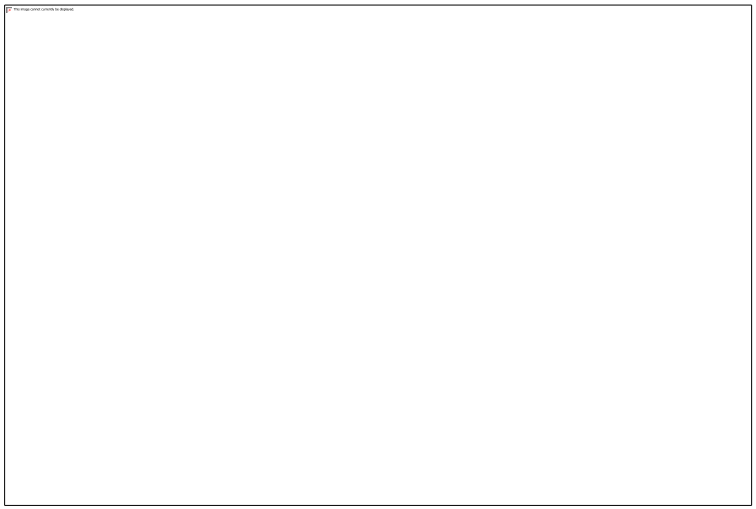
			The problem with analyzing the Onctotype test using the 50-point increment has also been clearly described by Thomas B. Newman & Michael A. Kohn in their book “Evidence-Based Diagnosis” (first published in 2009). See below the textbox that refers to the 50-point increment: 	

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			This is of special interest for the second study analyzing predictiveness (Albain et al, SWOG8814), because in this study 50-point difference in Recurrence Score is the only statistical result for the Recurrence Score.	

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THEME: EAG economic model

Comment number	Name and organisation	Section number	Comment	NICE response
197	NHS Professional	Document 2 (DAR) Section 2.4.2 ˜Cost effectiveness result", Page 18/510	Section ˜The EAG model is also subject to a number of limitations and uncertainties', Page 407/510 Table 128, Page 363/510 Section 6.6, Page The lower use of chemotherapy following Oncotype DX testing is cited as THE key driver of the reversal of the recommendation for the Oncotype DX test Comment: This is precisely what would be expected from Oncotype DX testing and is well supported by prevailing evidence demonstrating that low-RS patients can safely avoid chemotherapy and the associated side-effects - until differential relative risk reduction from chemotherapy across Recurrence Score groups is modelled in the analysis to reflect that low-Recurrence Score patients deriving negligible/no chemotherapy benefit, NHS success at advancing breast cancer care will be entirely misinterpreted.	Thank you for your comment which the committee considered. The EAG noted in the diagnostics assessment report that there is uncertainty regarding whether Oncotype DX is associated with predictive benefit, and that sensitivity analyses were done in which a predictive benefit is assumed for Oncotype DX. 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 5.4 of the second consultation document).
198	NHS Professional		2. We would like clarification of the assumptions within the EAG Markov model on several counts:	Thank you for your comment which the committee considered.

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Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 14 March 2018

THEME: EAG economic model

Comment number	Name and organisation	Section number	Comment	NICE response
			a. For the LN0 NPIâ‰¤3.4 and LN+ subgroups from the NCRAS bespoke data request, were these data cross checked to ensure none of the patients had undergone Oncotype DX testing in their decision making (NHS or Private)? Were such patients excluded from the analysis? b. We do not consider the opinions of 11 oncologists sufficiently robust data to base an analysis of this importance. At the very least we should be provided with data on experience level eg years of breast medical oncology service prior to survey response. Please also detail how the EAG ensured that it was indeed the oncologist and not their trainees that completed the survey eg was the survey password protected, confidential, did the introductory notes explain the importance of self-completion. What was the denominator for the questionnaire and why are 11 responses considered satisfactory?	The EAG explained that it asked for data from 2012 to 2015 in order to explore whether the probability of receiving chemotherapy may have been influenced by the introduction of Oncotype DX testing. The EAG did not see any obvious pattern in the data. The EAG noted that their model uses published data on the probability of receiving chemotherapy where these data exist; where published data were not available or were inadequate, the UKBCG survey estimates were used. Alternative sources of these probabilities were applied in sensitivity analyses. Responses were sent directly to the EAG lead. No instructions were given to demand self-completion by respondents; the EAG considered it unlikely that any other party completed the questionnaire other than the individual emailing

Comment number	Name and organisation	Section number	Comment	NICE response
				the response. The survey was not password protected.
199	NHS Professional	General	4. It is also worth noting that the chemotherapy used for cost analysis is 'FEC'. We most commonly use EC-Weekly paclitaxel, which is substantially more expensive than 6 cycles of FEC. Hence, avoiding chemotherapy in patients with a low risk as predicted by genomic tests will give a higher cost-saving than modelled for this review.	Thank you for your comment which the committee considered. The EAG noted that, based on expert advice, the model included 4 regimens: FEC100-T (3+3 cycles); TC (4 cycles); FEC75 (6 cycles), and FEC100-Pw (3+3 cycles). The diagnostics assessment report includes sensitivity analyses around the costs of chemotherapy.
200	Royal Marsden Hospital	4.5	It is unfortunate that the assessment has been made entirely on the base of risk categories when there is substantially more value in them as continuous scores. Discussion about the added value of chemotherapy with patients with risks of 2% vs 9% 10-year risk or with 11% vs 19% risk are very different despite being in the same respective risk category.	Thank you for your comment which the committee considered. The assessment was done according to the risk categories defined by the companies in the test instructions for use documents, or alternative

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Comment number	Name and organisation	Section number	Comment	NICE response
				documentation for tests without instructions for use.
201	Royal Marsden Hospital	4.47	It is stated that: *The model assumed that the risk of distant metastases between 10 and 15 years was halved, and after 15 years was zero.* This does not seem appropriate given the work by the Early Breast Cancer Collaborative Group showing near linear hazard plots out to 20 years for patients with ER+ disease.	Thank you for your comment which the committee considered. The EAG noted that there is some evidence which suggests that for some patients with particular disease subtypes, recurrence rates remain approximately constant between 5 and 20-years, But this is uncertain, hence constraining recurrence at 15-years reduces the likelihood of overestimating the benefit of chemotherapy. Sensitivity analyses in which the risk tapering assumption was removed were done.

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Comment number	Name and organisation	Section number	Comment	NICE response
202	Royal Marsden Hospital	4.56	It is very common nowadays for patients to be offered “open access” for follow-up during endocrine therapy rather than the annual visits allowed for. This reduces the frequency of visits markedly.	Thank you for your comment which the committee considered. The EAG noted that the population considered in the model is assumed to be ER+, therefore all patients are assumed to receive endocrine therapy in both the test and no test groups. The impact of alternative assumptions regarding endocrine therapy follow-up on the cost-effectiveness of the tests would be negligible.
203	NHS Professional	2.2, pages 33-34	In overview, costs of a course of adjuvant chemotherapy estimated to be Â£3145. In DAR document 5 cycles costed at Â£3901. Inconsistent between documents. There is no account of the use of growth factors which increase costs considerably. In local audit approximately 80% of adjuvant chemotherapy cycles included use of growth factors.	Thank you for your comment which the committee considered. The EAG noted that this is not an inconsistency: the Genomic Health model applied an estimated chemotherapy cost of £3,901; the EAG model applied an estimated chemotherapy cost of £3,145.

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Comment number	Name and organisation	Section number	Comment	NICE response
				The costs associated with adjuvant chemotherapy were taken from a previous costing analysis of the OPTIMA Prelim trial (Hall et al. 2017).
204	NHS Professional		1) Firstly the continued use of the Nottingham Prognostic Index for any decision or assessment. This is an outdated concept that does not take into account any of the receptors known to affect prognosis. It has not been used in Newcastle for many years	Thank you for your comment which the committee considered. The EAG noted that the NPI was included as one of several comparators in the clinical review, and was used to identify intermediate risk patients in the economic analysis due to the absence of data to do this using Adjuvant! Online or PREDICT. The EAG also noted that the comparator in the model is not NPI; this was used only as a means of subdividing LN negative patients into low or intermediate clinical risk. The comparator for Oncotype DX, Prosigna, IHC4+C and EndoPredict was usual clinical practice.

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Comment number	Name and organisation	Section number	Comment	NICE response
205	Agendia N.V.	EAG model: DAP37 FinalModelSent ToNICE_Redacted No ACIC	To appropriately compare the results of the corrected Agendia model with the updated EAG model, we noticed that the labelling of the deterministic results in the DAP37 FinalModelSentToNICE_Redacted No ACIC is incorrect and – based on where the cells refer to – the text should be as follows (please see copy of deterministic results and text in red below): **Determinstic results** Option / LYGs / QALYs / Costs / Inc/ LYGs / QALYs / Costs / ICER (per QALY gained) **MINDACT ITT population (should be NPI low risk?)** MammaPrint 16.218 13.489 £8,897.45 0.01 0.01 £1,756.49 **£134,052** No test 16.209 13.476 £7,140.96 **mAOL high-risk (should be NPI high risk?)** MammaPrint 15.46 12.82 £12,217.44 -0.07 -0.04 £1,380.02 **Dominated** No test 15.52 12.87 £10,837.41 **mAOL low-risk (should be node positive?)** MammaPrint 16.44 13.69 £7,594.67 0.01 0.01 £2,414.96 **£399,168** No test 16.43 13.68 £5,179.71	Thank you for your comment which the committee considered. The EAG agreed that some of the labelling within the model is incorrect for the MINDACT analysis. It also noted however, that the analyses for MINDACT shown in the results worksheet are correct, and that these relate to 3 groups: (1) the MINDACT ITT population; (2) the MINDACT mAOL high-risk subgroup, and (3) the MINDACT mAOL low-risk subgroup.

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Comment number	Name and organisation	Section number	Comment	NICE response
			We request that the correct cell numbers are used for the intended EAG labelling in black, referring to the MINDACT ITT population, mAOL high-risk and mAOL low-risk.	
206	Agendia N.V.	DAP37 FinalModelSent ToNICE_Redacted No ACIC	Minor comment: to allow appropriate comparison of the corrected Agendia model with the reported results in section 4.63 (page 32 of the DAP37 DG10 Update), we note that these do not exactly match the results of the 'DAP37 FinalModelSentToNICE_Redacted No ACIC' model when the test cost of £2326 (taken from Table 2, page 29 of the DAP37 DG10 Update) is entered in sheet 'Premodel', cell C266. The correct value for C266 should be £2326.	Thank you for your comment which the committee considered. The EAG noted that the difference seen is because the values cited in the diagnostics consultation documents were based on the probabilistic version of the model. The cost of the test was applied as £2,326.09.

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			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.	
207	Agendia N.V.	5.3.3 (Table 125 and page 411 of DAP37 evaluation report pdf, Nov 2017), EAG model: DAP37 FinalModelSe	*Probability of developing distant metastases (without chemotherapy) – MammaPrint* In the EAG model, and as shown in Table 125 of the DAR the AOLhigh/MP low patients that receive chemo have a 0.029 higher 10-year DMFS versus those who do not receive chemo (0.920 for chemo vs. 0.891 for no chemo [Premodel, K166:K167]. This corresponds to the reported absolute difference of ~1.5% per 5 year. Also in line with that paragraph on page 409 of DAP37, the AO low/MP high patients that receive chemo have a benefit of	Thank you for your comment which the committee considered. The EAG noted that the company's model assumed that chemotherapy does not offer any clinical benefit to any patient (even in the clinical high- MammaPrint high and clinical low-MammaPrint low groups). The EAG have provided more explanation in the third addendum to the diagnostics assessment report.

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		ntToNICE_Redacted No ACIC	0.015 in 10-year DMFS (0.918 for chemo versus 0.903). This corresponds to ~0.8% per five years. These differences, however, were not found to be a statistically significant, as reported in Cardoso et al. 2016. The EAG has acknowledged this in their reply to Agendia (e.g. comment #4 and #64 in the DAR comments table received by Agendia Jan 3rdth 2018) and the updated text, referring to these percentages as non-significant, accordingly in the Erratum to the DAR.	The EAG also advised that the errors referred to by the company are because the model PSA index needs to be reset to a value less than the maximum PSA iterations by the user.

Table 125: Calculation of 5-year DMFS probabilities by clinical/genomic risk group and chemotherapy use

Randomised group	Treatment	EAG group label	N randomised before genomic correction	N randomised after genomic correction	N in group*	Percent	5-year DMFS	5-year cumulative DMFS probability	Rate (year)	10- year DMFS probability for group	6-month recurrence probability for group
mAOL low,	Chemotherapy	A	2634	2745	37	0.55%	97.60%	2.40%	0.005	0.953	0.002
MMP low	No chemotherapy	B			2708	40.46%	97.60%	2.40%	0.005	0.953	0.002
mAOL high,	Chemotherapy	C	1497	1550	793	11.85%	95.90%	4.10%	0.008	0.920	0.004
MMP low	No chemotherapy	D			757	11.31%	94.40%	5.60%	0.012	0.891	0.006
mAOL low,	Chemotherapy	E	690	592	296	4.42%	95.80%	4.20%	0.009	0.918	0.004
MMP high	No chemotherapy	F			296	4.42%	95.00%	5.00%	0.010	0.900	0.005
mAOL high,	Chemotherapy	G	1873	1806	1735	25.92%	90.60%	9.40%	0.020	0.821	0.010
MMP high	No chemotherapy	H			71	1.06%	90.60%	9.40%	0.020	0.821†	0.010

* Based on Cardoso *et al*[214] supplementary material, Table S11
†Adjusted 10-year DMFS without chemotherapy estimated to be 0.766

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			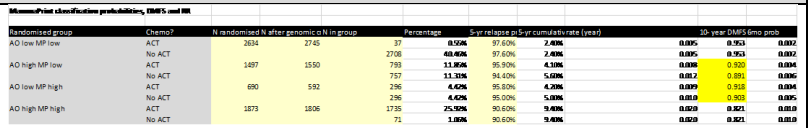 We are aware that it is standard practice in probabilistic modelling to use reported differences regardless of whether these are statistically significant, as long as the uncertainty surrounding the point estimate is taken into account. In such case, each model-run should randomly draw from a parameter distribution around the point estimate which, in the case of a non-significant difference should include zero in its range. However, in the EAG Model the +1,5% difference (and the +0.8%) are used as *fixed inputs*, not probabilistic. Given that the model parameter is fixed yet the difference is more likely to be noise instead of a signal (as these are non-statistically significant differences), it is best practice to model *no difference* in DMFS for chemo vs. no chemo in the AO high/MP low group. Doing so consistently in the updated EAG model for both the AO high/MP low group as well as the AO	

<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>low/MP high group (i.e. using 0,891 for chemo and no chemo in the AO high/MP low group; and using 0.903 for chemo and no chemo in the AO low/MP high group) gives an ICER <30k/QALY in the high risk group, see below (and see the attached amended EAG model “DAP37 model_Agendia”):

Determinstic results

<table>
<tr><th>Option</th><th>LYGs</th><th>QALYs</th><th>Costs</th><th>Inc/ LYGs</th><th>QALYs</th><th>Costs</th><th>ICER (per QA</th></tr>
<tr><td>MINDACT ITT population</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>MammaPrint</td><td>16.170</td><td>13.448</td><td>£9,077.72</td><td>0.01</td><td>0.02</td><td>£1,737.34</td><td>£100,473</td></tr>
<tr><td>No test</td><td>16.156</td><td>13.430</td><td>£7,340.38</td><td></td><td></td><td></td><td></td></tr>
<tr><td>mAOL high-risk</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>MammaPrint</td><td>15.49</td><td>12.85</td><td>£12,104.51</td><td>0.03</td><td>0.04</td><td>£1,027.33</td><td>£28,281</td></tr>
<tr><td>No test</td><td>15.46</td><td>12.81</td><td>£11,077.19</td><td></td><td></td><td></td><td></td></tr>
<tr><td>mAOL low-risk</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>MammaPrint</td><td>16.41</td><td>13.66</td><td>£7,760.34</td><td>0.00</td><td>-0.01</td><td>£2,527.85</td><td>Dominated</td></tr>
<tr><td>No test</td><td>16.42</td><td>13.67</td><td>£5,232.49</td><td></td><td></td><td></td><td></td></tr>
</table>

In the DAP37 DG10 Update DCD v8 to PM, the EAG, in discussion with the Committee, acknowledges that chemotherapy benefit is a fixed parameter in the model despite the uncertainty and that sensitivity analyses were done to test these parameter.</td><td></td></tr>
</table>

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			(See section 5.8, page 41 "The committee considered other assumptions used in the model such as the cost of chemotherapy, the fixed benefit of chemotherapy, and the probability of having chemotherapy. 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.") While sensitivity analyses may have been performed, the *results* of each of those are not included in the model that was sent, and *are not reported* separately in the DAP37 DG10 Update v8 to PM separately. Our sensitivity analysis shows that this particular parameter is so influential on the model outcomes that it leads to a different conclusion about the expected cost-effectiveness of MammaPrint in the high risk subgroup, i.e. MammaPrint is now cost-effective at a threshold of £30,000/QALY, and this would require an update of the statement in Section 4.74, page 36 "Modified Adjuvant! Online	

Comment number	Name and organisation	Section number	Comment	NICE response
			high-risk subgroup: MammaPrint was dominated by current practice across almost all scenarios." Probabilistic results: MammaPrint versus current practice (mAOL) *Central estimates of cost-effectiveness - (probabilistic) (page 395 of the DAR)* In addition, to rebut the conclusion drawn in section 5.3.6 (page 395 of the DAR, and Tables 149 and 150) we have attempted to include the DMFS parameter as a probabilistic one in the EAG model to appropriately account for the uncertainty around that parameter. Yet we found that the model as sent by NICE does not allow probabilistic subgroup analyses for the high risk and node positive groups. We also note that the majority of parameters pertaining to chemotherapy use and effect are not appropriately assigned a parameter distribution. See the parameter input sheet in Appendix A showing mainly #N/A or "0" inputs for the EAG model in probabilistic mode. Hence, it is entirely unclear on what basis the Committee reached its conclusion about the validity and/or robustness of model results in subgroups (shown in Table	

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			149, and 150 on page 395 of the DAR) as based on this non-transparent and possibly flawed model. We would like to see DAR correct and update the EAG model using the corrected probabilistic analysis.	

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208	NHS Professional	Section 5.2, page 346	The Diagnostic Review spent some time reviewing the economic analysis of this study, performed by the University of York Centre for Health Economics, and then dismisses this work as "The EAG did not receive a model for EndoPredict and therefore cannot comment fully on the reliability of the results presented". The authors are happy to share academic information relating to the model and strongly suggest that the committee request this. Their evaluation is incomplete without this.	Thank you for your comment which the committee considered. The EAG noted that it critiqued the model, based on the draft paper describing the model, however it was not possible to determine whether the model is free from programming errors without access to the model files. Scrutiny of this model would not add any further information to the critique presented in the diagnostics assessment report.
209	Agendia N.V.	Section 5.2 Page 346, DAP 37 evaluation report, Nov 2017; Page 323 DAP 37 evaluation	Given that the EAG states that *the "The Agendia model for MammaPrint includes correctable errors;"* we corrected the identified errors in the model (as described on page 323 DAP 37 evaluation report, Nov 2017). We agree there were some errors in the model presented and have adjusted the model accordingly. In the comments below (2 to 14) we present each correction made and the corresponding results. Given the limitations in the EAG model as acknowledged by the EAG (section 6.2.2 pages 411-412) and the fact that the Agendia model makes optimal use of the only high-quality randomised control trial data available (see reply to comment	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report. Data from MINDACT were used in

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		report, Nov 2017	6 in the DAR-comments published by NICE 10th Jan) on genomic testing in this patient group, which pertain specifically to MammaPrint as no other manufacturer performed such a study, we strongly believe that the DAP should inform its decision using this model and these data. If, however, the EAG retains the position that the updated EAG model should be used, we also present the results of the updated EAG model with corrected usage of available MammaPrint data in those instances where we strongly disagree with the chosen inputs in the current model (see comment 17 [205] and provided model document: DAP37 model_Agendia.xls).	the EAG's model for the MammaPrint analyses.
210	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: The cost-effectiveness was calculated based on the MINDACT findings that for the clinical-high/genomic-low patients, chemotherapy can be safely omitted, as it does not provide clinically significant benefit. Based on this finding, St Gallen, ASCO amongst others have included this in their guideline recommendations.	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.

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Comment number	Name and organisation	Section number	Comment	NICE response
			To reflect this in the cost effectiveness calculation based on the MINDACT data, we omitted the Clinical-high/MP-low group who were randomized to chemotherapy (this was already done in the former model), but now, we duplicated the group clinical-high/MP-low who were randomized to no chemotherapy (and duplicated the group clinical-low/MP-high who were randomized to CT in case of the total population strategy), and vice versa for the clinical assessment arm. In this way the cost-effectiveness calculation reflects the clinical practice situation (reflecting the actual proportions of risk groups) when MammaPrint would be implemented to test high clinical risk patients for the purpose of addressing who can forego chemotherapy. In the MINDACT paper [Cardoso, NEJM, 2016], this strategy was also applied to estimate the survival when using the one or the other strategy (Supplementary material, figure S1). The results below are the results of the base case analysis, (keeping (non-)compliance to MammaPrint recommendation into account), which shows that MammaPrint is dominating AOL in the clinical high risk group and cost effective in the clinical high risk, ER+/Her2- group.	

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			Results (deterministic) discounted *MINDACT-EORTC database-MP versus MAOL* Diagnostic instrument / Life Years / QALY's / Costs in Pounds / incremental LY / incremental QALY / incremental COSTS / ICER LY / ICER QALY / preferred strategy Strategy 1: Total population 1 Genomic (MP) 9,9389 6,6857 £9.674 -0,0029 0,0089 £631 -£220.470 £71.021 MAOL 2 Clinical (MAOL) 9,9418 6,6768 £9.043 Strategy 2: Clinical high risk 1 Genomic (MP) 9,9153 6,6296 £11.382 -0,0049 0,0300 -£352 £71.523 -£11.739 MP 2 Clinical (MAOL) 9,9202 6,5996 £11.734 Strategy 3: Clinical high risk Er+/Her2- 1 Genomic (MP) 9,9275 6,6374 £10.358 -0,0041 0,0308 £125 -£30.799 £4.049 MP 2 Clinical (MAOL) 9,9316 6,6066 £10.233	
211	Agendia N.V.	Page 323 DAP 37 evaluation report, Nov 2017	The EAG noted that the calculation of transition probabilities for all analyses was incorrect. We corrected the calculation as follows: We have submitted an updated version of the Agendia cost-effectiveness (CE) 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: VRetel_MINDACT_180131_NICE.xls).	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.
212	Agendia N.V.	Page 323 DAP 37	The EAG noted that the Agendia model used a "*Questionable assumption that risk exclusively determines whether patients receive*	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
		evaluation report, Nov 2017	*adjuvant chemotherapy*". To clarify, the model submitted by Agendia does *not* assume that risk is the sole determinant of whether patients receive adjuvant chemotherapy. 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. This data can be found in the "model" sheet of the Agendia model (document name: VRetel_MINDACT_180131_NICE.xls, see attached), 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 AOL in the clinical high risk group and cost effective in the clinical high risk, ER+/Her2- group, as shown in the figure below. Base case (using Bloomfield and Stein adherence):	The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.

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Comment number	Name and organisation	Section number	Comment	NICE response
			Results (deterministic) discounted *MINDACT-EORTC database-MP versus MAOL* Diagnostic instrument / Life Years / QALY's / Costs in Pounds / incremental LY / incremental QALY / incremental COSTS / ICER LY / ICER QALY / preferred strategy Strategy 1: Total population 1 Genomic (MP) 9,9389 6,6857 £9.674 -0,0029 0,0089 £631 -£220.470 £71.021 MAOL 2 Clinical (MAOL) 9,9418 6,6768 £9.043 Strategy 2: Clinical high risk 1 Genomic (MP) 9,9153 6,6296 £11.382 -0,0049 0,0300 -£352 £71.523 -£11.739 MP 2 Clinical (MAOL) 9,9202 6,5996 £11.734 Strategy 3: Clinical high risk Er+/Her2- 1 Genomic (MP) 9,9275 6,6374 £10.358 -0,0041 0,0308 £125 -£30.799 £4.049 MP 2 Clinical (MAOL) 9,9316 6,6066 £10.233 Sensitivity Analysis (using Cusumano and Stein adherence): Results (deterministic) discounted *MINDACT-EORTC database-MP versus MAOL* Diagnostic instrument / Life Years / QALY's / Costs in Pounds / incremental LY / incremental QALY / incremental COSTS / ICER LY / ICER QALY / preferred strategy Strategy 1: Total population 1 Genomic (MP) 9,9388 6,6837 £9.783 -0,0030 0,0070 £741 -£248.054 £106.480 MAOL 2 Clinical (MAOL) 9,9418 6,6768 £9.043 Strategy 2: Clinical high risk 1 Genomic (MP) 9,9153 6,6296 £11.382 -0,0049 0,0300 -£352 £71.523 -£11.739 MP 2 Clinical (MAOL) 9,9202 6,5996 £11.734 Strategy 3: Clinical high risk Er+/Her2- 1 Genomic (MP) 9,9275 6,6374 £10.358 -0,0041 0,0308 £125 -£30.799 £4.049 MP 2 Clinical (MAOL) 9,9316 6,6066 £10.233	
213	Agendia N.V.	Page 323 DAP 37 evaluation	The EAG noted the use of *potentially outdated cost estimates in the Agendia model*. The corrected model now includes the same cost estimates as the EAG model (see Sheet "parameters", Cells range D490-D505, and sheet "cost countries", range D1-D19.	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect, because of errors

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Comment number	Name and organisation	Section number	Comment	NICE response
		report, Nov 2017	As the strategy of the Agendia model differed from the EAG model (we took into account the total population, and the clinical high risk population), we have incorporated in the updated model a third analysis set: The ER+/Her2- subgroup (only in the clinical high risk population), because this group resembles best the perspective of the EAG model. (e.g. excluding Trastuzumab). The addition of the third analysis set did not change the overall conclusion of the Agendia model, as the ICER for the ER+/Her2- clinical high risk group yielded £4,049/QALY (see results figure in comment 2).	in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.
214	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* 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	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
			removed these analyses from the Agendia model. If NICE would like to see these analyses as well, we can offer this data separately.	
215	Agendia N.V.	Page 323 DAP 37 evaluation report, Nov 2017	*The EAG noted that the time horizon of the Agendia model was short (5 years).* We extended the time horizon to 10 years using three different extrapolation approaches: Time-to- DMFS and time-to-death were derived from a Weibull, Gompertz and exponential distribution. The time between events was modelled by randomly sampling values from parametric survival distributions either exponential, Gompertz or Weibull. The exponential variant was chosen for the base case analysis, as it is comparable to the EAG model approach. The results for the Weibull and Gompertz extrapolation can be found in the sheet "sensitivity analyses", cells A45-S88, and are shown in the figures below. Gompertz	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect, because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.

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Comment number	Name and organisation	Section number	Comment	NICE response
			Results (deterministic) discounted *MINDACT-EORTC database-MP versus MAOL* Diagnostic instrument / Life Years / QALY's / Costs in Pounds / incremental LY / incremental QALY / incremental COSTS / ICER LY / ICER QALY / preferred strategy Strategy 1: Total population 1 Genomic (MP) 9,8019 6,5875 £11.644 -0,0091 0,0048 £656 -£72.468 £135.453 MAOL 2 Clinical (MAOL) 9,8109 6,5827 £10.987 Strategy 2: Clinical high risk 1 Genomic (MP) 9,7269 6,4915 £14.584 -0,0147 0,0230 -£263 £17.872 -£11.432 MP 2 Clinical (MAOL) 9,7416 6,4684 £14.848 Strategy 3: Clinical high risk Er+/Her2- 1 Genomic (MP) 9,7483 6,5016 £13.903 -0,0127 0,0244 £225 -£17.685 £9.237 MP 2 Clinical (MAOL) 9,7611 6,4772 £13.678 Weibull Results (deterministic) discounted *MINDACT-EORTC database-MP versus MAOL* Diagnostic instrument / Life Years / QALY's / Costs in Pounds / incremental LY / incremental QALY / incremental COSTS / ICER LY / ICER QALY / preferred strategy Strategy 1: Total population 1 Genomic (MP) 9,9038 6,6599 £10.245 -0,0044 0,0078 £638 -£144.501 £81.510 MAOL 2 Clinical (MAOL) 9,9083 6,6521 £9.607 Strategy 2: Clinical high risk 1 Genomic (MP) 9,8669 6,5932 £12.317 -0,0074 0,0281 -£327 £44.448 -£11.623 MP 2 Clinical (MAOL) 9,8743 6,5651 £12.644 Strategy 3: Clinical high risk Er+/Her2- 1 Genomic (MP) 9,8878 6,6068 £11.199 -0,0059 0,0293 £148 -£25.034 £5.053 MP 2 Clinical (MAOL) 9,8937 6,5775 £11.051 As shown in the figure in comment 2 and in figures above, the addition of the 10yrs extrapolation did not change the overall conclusion that MammaPrint is dominating AOL in the clinical high	

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			risk group and cost effective in the clinical high risk, ER+/Her2- group.	
216	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 "Agendia model" sheet. (Document name: VRetel_MINDACT_180131_NICE.xls, see attached). The change of the chemotherapy utility did not change the overall conclusion of the model (please see results in comment 2).	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.
217	Agendia N.V.	Former suggestion using MINDACT "test- "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. Please find explanation on how these EQ-5D values were derived more specifically, in the attached PDF document named: VRetel_CEA_MINDACT_180131_NICE. We again suggest to use these values (they could be found in the first Cost-effectiveness	Thank you for your comment which the committee considered. The EAG noted that it is unclear how the EQ-5D scores have been generated, as it does not appear that the EQ-5D was included in the MINDACT trial.

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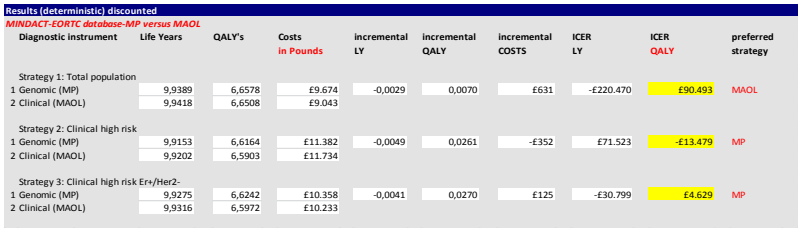
			report, table 1, but also in the updated report, table 1, and in the updated Agendia model, sheet "parameters", Cells D472-D477.	
218	Agendia N.V.	Updated Agendia model - Sensitivity analysis: using MINDACT utilities	In the updated Agendia model we have included a sensitivity analysis without using the test values: See sheet "sensitivity analyses", cells A23-S44. Excluding these particular "test" utilities did not change the conclusion, see below.  Results (deterministic) discounted *MINDACT-EORTC database-MP versus MAOL* Diagnostic instrument / Life Years / QALY's / Costs in Pounds / incremental LY / incremental QALY / incremental COSTS / ICER LY / ICER QALY / preferred strategy Strategy 1: Total population 1 Genomic (MP) 9,9389 6,6578 £9.674 -0,0029 0,0070 £631 -£220.470 £90.493 MAOL 2 Clinical (MAOL) 9,9418 6,6508 £9.043 Strategy 2: Clinical high risk 1 Genomic (MP) 9,9153 6,6164 £11.382 -0,0049 0,0261 -£352 £71.523 -£13.479 MP 2 Clinical (MAOL) 9,9202 6,5903 £11.734 Strategy 3: Clinical high risk Er+/Her2- 1 Genomic (MP) 9,9275 6,6242 £10.358 -0,0041 0,0270 £125 -£30.799 £4.629 MP 2 Clinical (MAOL) 9,9316 6,5972 £10.233	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.
219	Agendia N.V.	Page 323 DAP 37 evaluation report, Nov 2017	*The EAG noted that there is uncertainty surrounding UK clinical high risk analysis.* We agree with this and have removed this analysis (referred to as Analysis 8 in the DAR) from the updated Agendia model. (See both attached documents named: VRetel_CEA_MINDACT_180131_NICE	Thank you for your comment which the committee considered.

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			(PDF) for further explanation on the model and the model itself in: VRetel_MINDACT_180131_NICE (XLS).	
220	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.* 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 (please see results in comment 2).	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.
221	Agendia N.V.	Updated Agendia model: Additional sensitivity analysis (SA5)	In this sensitivity analysis, all corrections were incorporated in the analyses where there was no duplication used for the discordant groups. See "sensitivity analyses" sheet, Cells A111-S132. This also did not change the overall conclusion.	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.

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			Results (deterministic) discounted *MINDACT-EORTC database-MP versus MAOL* Diagnostic instrument / Life Years / QALY's / Costs in Pounds / incremental LY / incremental QALY / incremental COSTS / ICER LY / ICER QALY / preferred strategy Strategy 1: Total population 1 Genomic (MP) 9,9377 6,6826 £9.775 -0,0017 0,0053 £845 -£493.721 £159.113 MAOL 2 Clinical (MAOL) 9,9394 6,6773 £8.930 Strategy 2: Clinical high risk 1 Genomic (MP) 9,9061 6,6067 £12.289 -0,0032 0,0193 £190 -£59.917 £9.845 MP 2 Clinical (MAOL) 9,9093 6,5874 £12.100 Strategy 3: Clinical high risk Er+/Her2- 1 Genomic (MP) 9,9214 6,6164 £11.018 -0,0026 0,0198 £496 -£190.098 £25.014 MP 2 Clinical (MAOL) 9,9240 6,5965 £10.522	
222	Agendia N.V.	Summary of updated Agendia CE model	To summarise current updated Agendia model: Using the duplicated subgroups, exponential extrapolation, Bloomfield and Stein chemotherapy use probabilities, half cycle correction, conditional survival, updated UK costs as a base case, our conclusion is: Using the MammaPrint for the clinical high risk population is dominating AOL, and in the ER+/Her2- population, MammaPrint is cost-effective compared to AOL (ICER £4,049/QALY) (please see results of the base case in comment 2 and the attached document named; VRetel_CEA_MINDACT_180131_NICE (PDF) for further explanation on the model adaptations and sensitivity analyses performed.	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.

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Comment number	Name and organisation	Section number	Comment	NICE response
223	Agendia N.V.	108 (p 327) of the 'DAP37 evaluation report 301117'	Paragraph '*Corrected results for the Agendia MammaPrint model'* Results of Table 108 shows the result of the corrected model of Agendia. The use of MammaPrint in the clinical High risk subgroup and high clinical risk ER+/HER2- subgroup is dominating Adjuvant Online. This result does however not match with the overall conclusion drawn concerning the cost effectiveness in the use of MammaPrint on Page 395 of the 'DAP37 evaluation report 301117' and needs to be adjusted to correlate with the conclusion that can be drawn from the adjusted table.	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.
224	Agendia N.V.	Attached documents in email to DAR	An overview and more detailed information of the model of Agendia and the cost effectiveness (sensitivity) analyses for MammaPrint based on this model can be found in the attached PDF document named: VRetel_CEA_MINDACT_180131_NICE. Appendix A	Thank you for your comment which the committee considered. The EAG considers Agendia's updated analyses to be incorrect because of errors in the model's programming. The EAG have provided more explanation in the third addendum to the diagnostics assessment report.

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			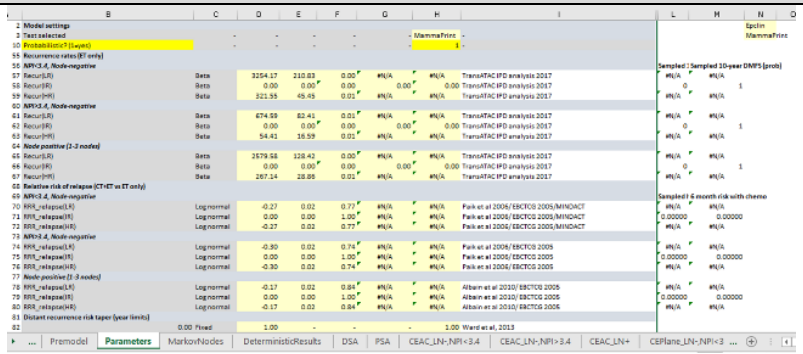	

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THEME: Intrinsic subtypes

Comment number	Name and organisation	Section number	Comment	NICE response
225	NanoString	4.13, pages 15-16	The intrinsic subtype test output provided by Prosigna, which is provided along with the Risk of Recurrence Score, has been demonstrated to be associated with response to different therapies in various settings and patient populations. The intrinsic subtypes are included in both retrospective and prospective studies in breast cancer worldwide. We expect that emerging evidence will further demonstrate the ability of Prosigna to impact treatment decisions more broadly than the scope of the current review. Ongoing Prospective Studies: EXPERT: ClinicalTrials.gov Identifier NCT02889874 PRECISION: ClinicalTrials.gov Identifier NCT02653755 ECOG EA1131: ClinicalTrials.gov Identifier NCT02445391 Retrospective Studies: Cheang MC, Voduc KD, Tu D, et al. Responsiveness of intrinsic subtypes to adjuvant anthracycline substitution in the NCIC.CTG MA.5 randomized trial. Clin. Cancer Res. Apr 15 2012;18(8):2402-2412. Martin M, Prat A, Rodriguez-Lescure A, et al. PAM50 proliferation	Thank you for your comment which the committee considered. It was not within the scope of the assessment to look at intrinsic subtypes.

			score as a predictor of weekly paclitaxel benefit in breast cancer. Breast Cancer Res. Treat. Apr 2013;138(2):457-466. Tutt A, Ellis P, Kilburn L, Gilett C, et a. TNT: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). San Antonio Breast Cancer Symposium. 2014. Prat A, Bianchini G, Thomas M, et al. Research-based PAM50 subtype predictor identifies higher responses and improved survival outcomes in HER2-positive breast cancer in the NOAH study. Clin. Cancer Res. Jan 15 2014;20(2):511-521 Jorgensen CL, Nielsen TO, Bjerre KD, et al. PAM50 breast cancer intrinsic subtypes and effect of gemcitabine in advanced breast cancer patients. Acta Oncol. Jun 2014;53(6):776-787. Chia SK, Bramwell VH, Tu D, et al. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. Clin. Cancer Res. Aug 15 2012;18(16):4465-4472.	

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THEME: Incorporating clinical factors

Comment number	Name and organisation	Section number	Comment	NICE response
226	Royal Marsden Hospital	3.15	While the RSPC has not been subjected to independent validation it is critical that clinicians should integrate clinical and pathologic factors into their calculations of risk for those molecular tests that do not already do this. IHC4+C, Prosigna and EndoPredict each do this to include at last nodal status and tumour size but Oncotype does not do this. The alternatives if not using RSPC are (i) to not adjust at all, which will be markedly suboptimal: we believe that clinicians should be actively made aware of the need to adjust or (ii) to adjust in an informal manner using so-called clinical judgement; the RSPC is most unlikely to provide a poorer adjustment than by informal measures of that type. NB, IHC4+C and RSPC both include an adjustment for use of an aromatase inhibitor as opposed to tamoxifen while the other tests use a single measure. Where a test that is calibrated to tamoxifen is used there is a relative overestimate of risk between 15 and 20%.	Thank you for your comment which the committee considered.

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THEME: Comments on IHC4+C

Comment number	Name and organisation	Section number	Comment	NICE response
227	Royal Marsden Hospital	3.21	It is stated that: *ER and HER2 markers are commonly measured in NHS laboratories, but PR and Ki67 markers are not.* Ki67 is measured in most NHS laboratories although not necessarily on breast cancer (NEQAS estimate >85% of labs). Staining methodology is therefore readily available.	Thank you for your comment which the committee considered. The EAG noted that in the diagnostics assessment report evidence on Ki67 was limited to studies relating to breast cancer. These studies suggest that analytical validity of IHC4 remains uncertain..
228	Royal Marsden Hospital	5.7	*'The committee discussed the analytical validity of IHC4+C. The EAG explained that evidence has developed since diagnostics guidance 10 was published. The committee noted that the data showed good correlation between different centres on scoring and staining when assessed separately for measurement of the Ki67 marker, which had been achieved with training.'* This is in reference to our 2016 International Working group publication (scoring) and our J Clin Pathol paper (staining), which is appropriate and acceptable statement. *'But it also noted that when studies looked at staining and scoring combined, the correlation decreased substantially. The committee*	Thank you for your comment which the committee considered. The committee heard from the EAG that in Polley *et al*. 2013, ICC for scoring alone (intra-laboratory) was very high for Ki67 (ICC=0.94, 95% CI = 0.93 to 0.97), whereas inter-laboratory ICC from the same study, where labs used their own methods of staining and scoring were much lower (central staining: ICC = 0.71, 95% CI = 0.47 to 0.78; local staining: ICC = 0.59, 95% CI = 0.37 to 0.68). However, this study did not include

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THEME: Comments on IHC4+C

Comment number	Name and organisation	Section number	Comment	NICE response
			concluded that because of these issues with Ki67, the reproducibility of IHC4+C is poor.' It is not clear to which studies reference is made here. In our J Clin Path paper (Dodson et al, 2016, 69:128-35) we compared the staining methods from the three main analytical platforms used in the UK with that used in the Royal Marsden. The correlations between the estimated risks of distant recurrence ranged from 0.972-0.984, which would be deemed excellent. *'It also heard that different methods of assessing ER and PR receptors may be needed for the IHC4+C method compared with those already used routinely, which may introduce additional complexity. The committee concluded that if this test were to be developed further there would need to be substantial investments in staff training and a quality assurance scheme would need to be set up.'* While not currently used always in routine practise the methods of scoring ER and PR are well known and easy to implement for staff trained in interpreting IHC analyses: H-Score is a well-known and established scoring method for ER, and as such would not require 'introduction'; the %-positivity assessment for PR is already	any experimental training or methodological improvements. The EAG noted that they are not aware of any data relating to the analytical validity of the use of IHC4+C in PRIMETIME. The committee considered the evidence on analytical validity further and heard from a clinical expert 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 available studies are not directly comparable. This is noted in section 5.7 of the second consultation document.

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THEME: Comments on IHC4+C

Comment number	Name and organisation	Section number	Comment	NICE response
			frequently used. There are already quality assessment schemes set up to assess all the components of IHC4 including Ki67 (which has been assessed on 12 separate assessment runs by UK NEQAS ICC & ISH over the last 5 years). In addition positive discussions with UK NEQAS have already taken place with regard to the feasibility of setting-up an IHC4 specific scheme (NB One of us [AD] is Deputy Director of UK NEQAS ICC & ISH). Also of note, a UK-wide prospective randomised control trial which requires risk of recurrence on endocrine therapy to be assessed (PRIMETIME) chose IHC4+C as its method of risk assessment has demonstrated the feasibility of disseminating the use of IHC4 beyond RMH initially to 2 other centres (Addenbrookes, Cambridge and NHS Lothian Hospitals, Scotland) but with the prospect of extending to all recruiting centres (currently 23 open centres).	
229	Royal Marsden Hospital	5.12	*'It also noted that the ICERs for IHC4+C were low or dominating in all subgroups. But the committee noted its earlier conclusion on the analytical validity of IHC4+C (see section 5.7) and felt that the test cost had been underestimated because it did not include any costs for training or for setting up a quality assurance scheme. The*	Thank you for your comment which the committee considered. The committee decided to make it clearer throughout the document the reasons why particular tests were not recommended. A new paragraph was added to specifically discuss the

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THEME: Comments on IHC4+C

Comment number	Name and organisation	Section number	Comment	NICE response
			committee concluded that the cost effectiveness of all tumour profiling tests was highly uncertain.' Given "*that the ICERs for IHC4+C were low or dominating in all subgroups"* the comment that the cost effectiveness of all tumour profiling tests was highly uncertain is unfounded. While there are costs involved in training and in conducting a QA scheme for IHC4+C these are estimated to be very modest as illustrated as follows: EQA scheme set-up costs of £50K, running costs of £80K per annum (equating to an annual subscription cost per centre of £1000); even gross inaccuracy in these estimates would still leave the IHC4+C as a highly cost-effective approach. It would be more appropriate to recommend that the IHC4+C be recommended but only with standardisation of methodology and the setting up of a QA scheme. An alternative recommendation would be that one or more centres be identified to provide centralised service(s). Our estimate of the cost of conducting tests in those circumstances would be to around £200 per case from the time of receiving either a block for sectioning and staining or sections for staining and therefore similar to the costs used in this assessment.	considerations on the cost-effectiveness of IHC4+C (section 5.19 of the second consultation document). The committee reiterated that although IHC4+C may be cost effective, it has ongoing concerns about the reproducibility of the test in practice.

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THEME: Comments on IHC4+C

Comment number	Name and organisation	Section number	Comment	NICE response
			This cost excludes HER2 testing, which is routinely locally performed and assessed to a very high standard. Please note that while we are listed for the purpose of this assessment as manufacturers, the ethos of our approach has been to deliver a test that can be delivered across the UK at low-cost and with no financial benefit to ourselves.	
230	NHS Professional	General	General comment Histopathological reporting has poor concordance particularly for Ki67 (PLoS One. 2012; 7(5): e37379. In spite of repeated attempts to standardise Ki67 there remains no consistency between labs. Routine histology is not suitable for stratifying patients to treatments in itself. This is in contradistinction to RTPCR methods which are highly repeatable. Even different blocks or different tumours in multifocal disease return consistent results. This histopathological variability is likely to be responsible for the lack of concordance between any of the tests which include any element of such data. The UKBSP confidential audit on histopathological reporting by specialist pathologist working in the UK screening programme clearly demonstrates the variability. I am sure the committee could request to see these results in confidence. You have rejected my previous evidence on variability in histopathology reporting as being a major factor in the discordance between gene	Thank you for your comment which the committee considered. The committee concluded the reproducibility of IHC4+C is poor. It also concluded that if IHC4+C 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. The committee decided to add more detail to the section on IHC4+C analytical validity, which is described in section 5.7 of the second diagnostics consultation document.

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THEME: Comments on IHC4+C

Comment number	Name and organisation	Section number	Comment	NICE response
			expression and Bayesian predictions of prognosis but this position needs to be justified. I believe that it is up to the committee to demonstrate statistically that the inconsistency of histological reporting is NOT contributing to significant misallocation of patients within prognostic groups rather than simply accepting the historical view.	
231	Agendia N.V.	Comment no. 15 page 52 of 212 (NICE Addendum IHC4 analytical validity rapid review)	(NICE Addendum IHC4 analytical validity rapid review) We would like to respond to the conclusions drawn by EAG concerning the analytical validity of IHC4. The conclusion that “excellent levels of agreement appear achievable” is an exaggeration of the analyzed data. We strongly suggest to start the conclusive remarks with stating that the evidence base for the analytical validity of IHC4 is not complete (yet) and should first be provided before definite conclusions can be made. We would like to underscore the small number of samples in the first 2 analyzed studies: The Dodson et al study analyzed 28 samples;	Thank you for your comment which the committee considered. The EAG noted that the study with the best results out of several that tested and improved methods, reported high inter-laboratory reproducibility following web-based training in scoring (Intra-class correlation 0.94, 95% credible interval 0.90, 0.97; Polley et al. 2015). However, overall the committee concluded the reproducibility of IHC4+C is poor. It also concluded that if IHC4+C 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. The committee

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THEME: Comments on IHC4+C

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			the Engelberg study included 32 samples. These numbers are not nearly sufficient to make any statement about agreement. Borowsky et al did not provide agreement results for Ki67, and is therefore not a clinical validity study of IHC4. Especially since Ki67 reproducibility issues are clearly show by Dowsett et al. and Polley et al with an interlaboratory reproducibility of 0.59 for locally stained samples. Leung et al showed that Ki67 reproducibility increased following web-based training, but only for central staining, and only for n=30. The conclusions drawn in the Addendum are in our view not representative of the reviewed data. For clinical use, tests should adhere to analytical validity requirements, and from the addendum, the only conclusion that can be drawn is that IHC4 has not provided this data yet.	decided to add more detail to the section on IHC4+C analytical validity, which is described in section 5.7 of the second diagnostics consultation document.
232	Royal College of Pathologists	2.1	In the evidence on decision impact (Page 21), it was stated that: The review of decision impact focused on studies done in the UK or the rest of Europe. This indicated one study on IHC4 (IHC4+C: 1 UK study and 0 other European studies) but the final recommendation is biased toward IHC4+C results which may seem a biased analysis	Thank you for your comment which the committee considered.

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THEME: PREDICT tool, NPI and Adjuvant! Online

Comment number	Name and organisation	Section number	Comment	NICE response
233	NHS Professional		-I have some concerns that the Predict prognostic database is being used as some sort of 'Gold Standard'. This itself is a model and I'm not sure how well it would fare if it were subjected to NICE-level scrutiny. One of the main feeders of the score is tumour grade, for which it is well-known that there is inter-observer variability. To my mind, an entirely reproducible score such as Oncotype can only be a positive step forward.	Thank you for your comment which the committee considered. The committee noted that the PREDICT tool was provisionally recommended in the NICE draft guideline on early and locally advanced breast cancer (update), which is due to publish in July 2018.
234	NHS Professional	6.1, page 44	Your summary states: 1.2 Further research is recommended on the effect (â€¦) on long-term patient outcomes such as distant recurrence, and on pre and post-test adjuvant chemotherapy decisions compared with the PREDICT tool. And further the Diagnostics Consultation Document states: 6.1 Further research is recommended comparing the tumour profiling tests (EndoPredict, Oncotype DX, MammaPrint and Prosigna) with the PREDICT tool. The results should record both pre- and post-test adjuvant chemotherapy decisions.	Thank you for your comment which the committee considered. The EAG noted that it does not have access to the publication in press, but assumed that the study referred to is Bloomfield 2017, which is included in the diagnostics assessment report. This study does not show the effect of the test on long-term patient outcomes.

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Comment number	Name and organisation	Section number	Comment	NICE response
			We have successfully conducted just such a study designed by senior UK breast oncology clinicians and psycho-social researchers to address the issues faced in NHS clinics daily in the UK. The particular strength of the design was that the additional Endopredict test was used after face to face discussion between the patient and the treating oncologist to facilitate a decision on whether or not to have chemotherapy. The pre and post-test decisions were recorded. A paper describing this study has been accepted by the peer reviewed journal Psycho-Oncology and is in press: The study was conducted in NHS Cancer Units by 14 oncologists working in 7 different multidisciplinary breast cancer teams - This represents pragmatic UK clinical practice. The Predict tool was the online tool available in clinic. And led to these experienced clinicians judging there to be an equivocal indication for chemotherapy in the patients enrolled into the study	The committee considered the data on pre- and post-test chemotherapy decisions used in the model. It concluded that there was much more uncertainty around chemotherapy decision-making for the 2-level tests than for the 3-level tests. This consideration is described in more detail in section 5.9 of the second diagnostics consultation document.

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Comment number	Name and organisation	Section number	Comment	NICE response
			The change in decisions (as published in ASCO abstract) show that nearly half of these initial decisions made between clinician and patient based on standard prognostic variables were opposite to that which the test would indicate. These demonstrates that clinicians are using the PREDICT tool to identify a group of patients where there is genuine uncertainty around chemotherapy or not. There was no reduction in overall chemotherapy given, but nearly half the patients potentially avoided chemotherapy and nearly half were recommended chemotherapy with the potential to improve survival according to the Oxford Overview of adjuvant chemotherapy. We do not need clinical trial data to show that not having chemotherapy will improve quality of life in the patients receiving it. Omitting chemotherapy is not a situation that requires formal trials, rather it constitutes a â€˜parachute testâ€™ where the outcome on quality of life is so obvious that it is unethical.	

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Comment number	Name and organisation	Section number	Comment	NICE response
235	Royal Marsden Hospital	1.2	The PREDICT tool includes values for Ki67 if available. There is no discussion of the impact that any inaccuracy in Ki67 might have on this despite this being the comparator. In contrast the document's strongest critique of IHC4+C is based around perceived inaccuracies in Ki67 analyses (section 5.7; see further comments on that section below).	Thank you for your comment which the committee considered. It was noted that PREDICT can be used without a Ki67 test result, and so the impact of this test on PREDICT is less relevant than for IHC4+C.
236	Royal Marsden Hospital	2.11	It is noted that *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.* Given the importance of using this as a comparator, greater evidence than "expert advice suggests" should be gathered to support this. In our own major institution this tool is not used.	Thank you for your comment which the committee considered. The committee noted that the PREDICT tool was provisionally recommended in the NICE draft guideline on early and locally advanced breast cancer (update), which is due to be published in July 2018. The EAG noted that the inclusion criteria for the review stated "the comparator for the assessment is standard UK practice for

Comment number	Name and organisation	Section number	Comment	NICE response
				chemotherapy decision-making". When relevant data were available, the EAG included comparisons to the major tools used in the UK (such as PREDICT, the NPI and Adjuvant! Online). Tools less frequently used in the UK (such as St Gallen criteria and the National Comprehensive Cancer Network guidelines) were excluded when a study was available that reported comparisons to PREDICT, NPI or AOL, but were included otherwise. The Clinical Treatment Score (CTS) was included as a comparator even though it is not commonly used in practice as a tool, because it is used in a number of key studies and includes a set of variables which are used in practice.
237	Royal Marsden Hospital	3.24	It is stated that:	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
			The comparator is current decision-making for adjuvant chemotherapy prescribing, which is based on clinical and pathological features or the results of tools used to assess risk. Current practise is affected by the widespread availability of Oncotype.	The decision was made during scoping to include Oncotype DX as an index test rather than a comparator.
238	Genomic Health UK Ltd.	Diagnostic Consultation Document Section 1 'Draft recommendations', Page 2/48 Section 5.1	*One of the draft recommendations was for further research "on pre- and post-test adjuvant chemotherapy decisions compared with the PREDICT tool". However, this data is already available for Oncotype DX, from the NHS dataset, as decision tools were recorded as part of the data collection* *Based on our preliminary analysis, a similarly large impact of Oncotype DX testing on chemotherapy treatment decisions was shown vs. PREDICT in the NHS audit, as per the broader dataset.* *Our preliminary analysis indicates that in ~40% of all cases where PREDICT was used, clinicians recorded an 'Unsure – no leaning either way' decision with regards to recommending chemotherapy to the*	Thank you for your comment which the committee considered. The EAG confirmed that the Genomic Health Access Scheme Dataset is comprised of pre-test decisions based on PREDICT, NPI, AOL, local guidelines. The PREDICT tool was provisionally recommended in the NICE draft guideline on early and locally advanced breast cancer (update), which is due to be published in July 2018.

Comment number	Name and organisation	Section number	Comment	NICE response
		'Committee discussion' Page 36/48	*patient. This alone indicates that Oncotype DX can provide important additional information to help guide chemotherapy treatment decisions.* *The validity of PREDICT being positioned as the benchmark in this analysis is also questionable, given that this population-based prognostic tool has not undergone a rigorous assessment by NICE and is supported by substantially less evidence versus Oncotype DX.* *The Committee also concluded that "the PREDICT tool is now used rather than Adjuvant! Online or the Nottingham Prognostic Index (NPI)". This is a factual error. The NHS audit data showed 60% NPI use (19% for PREDICT). Whilst the proportional use of these tools may have changed, it is understood from the clinical community that NPI is still used, so NICE should not assume that PREDICT is the only tool used.*	
239	Myriad Genetics	5.1	The committee concluded that future research on tumour profiling tests should include comparisons with PREDICT. Notably, a recent UK study published data showing a comparison in the performance of EndoPredict versus PREDICT in 120 patients with ER+, HER2- breast	Thank you for your comment which the committee considered. The EAG noted that Mokbel 2017 was not published when the diagnostics assessment

Comment number	Name and organisation	Section number	Comment	NICE response
			cancer (6). Data from this study have not been considered by the EAG, as the study was not published at the time of the systematic review stage of the DAP process. Mokbel and colleagues concluded that computational algorithms such as PREDICT may not accurately predict the need for chemotherapy leading to over-treatment, under-treatment or anxiety in a significant proportion of patients (6). This study provides recent data, in a UK-specific population, comparing EndoPredict with PREDICT. 6. Mokbel K, et al. A Comparison of the Performance of EndoPredict Clinical and NHS PREDICT in 120 Patients Treated for ER-positive Breast Cancer. Anticancer Res. 2017 Dec; 37(12):6863-6869.	report was written. It also noted that this is a study of concordance rather than decision impact and it would not meet the inclusion criteria for the EAG review.
240	NHS Professional	2.11	Issue of fact. PREDICT is used throughout the UK and is arguably the current most used risk calculation tool worldwide	Thank you for your comment which the committee considered.

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				The EAG noted that it was unable to use PREDICT in the analysis due to the limitations of the data available.
241	Agendia N.V.	Whole report – limitations of NPI as a decision making tool	*Limitations of NPI as a decision making tool* Nottingham Prognostic Index (NPI) is widely used by clinicians in the United Kingdom to help inform the selection of women with early breast cancer. NPI, as any tool, has limitations, with clinicians using this tool only enabling them to calculate a patient's index score and then to reference the relevant life table survival curve from a series of prognostic groups constructed by the author of the original publication. With the hazard function from the model not ever having been reported, it is not possible to use the NPI in conjunction with estimates of treatment efficacy to generate prognoses for individual patients both before and after any proposed therapy.	Thank you for your comment which the committee considered. The EAG agreed that there are limitations with NPI, but noted that it is the only risk tool for which data were available to stratify patients according to clinical risk in the economic modelling.
242	Agendia N.V.	DAR comments	Agendia comment: "*AOL is currently being updated and has been temporarily disabled*."	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
		(comment #90), section: Comparator	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 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." EAG response: "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." 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 Plus have not. This argument can also not be used to discount the usefulness of the	The diagnostics assessment report cannot be updated at this stage in the assessment. The EAG noted that it does not think that the statement made is erroneous or misleading. The committee noted that the economic analyses done for Mammaprint used adjuvant online to stratify patients according to clinical risk.

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			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.	

Table S 13: Classification of patients according to clinical risk assessment by the modified version of Adjuvant!Online

ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
			1-3 positive nodes	≤ 2 cm	C-low
				2.1-5 cm	C-high
		moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
ER negative	HER2 negative	well differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		moderately differentiated OR poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	well differentiated OR moderately differentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	Any	Any size	C-high

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Comment number	Name and organisation	Section number	Comment	NICE response
243	Agendia N.V.	Comment on Chapter 6 of the NICE diagnostic consultation document on page 44 of 48	Draft recommendations for further research suggests that tumor profiling tests should be compared with the PREDICT tool. We urge EAG to seriously question whether PREDICT is really a reasonable comparator. PREDICT is based on a cancer registry database of 5694 patients in the UK. The quality of the cancer registry data has been questioned by Joishy et al, J Cancer Educ. 1989 and Brewster et al, Br J Cancer. 1994. Wong et al, Medicine, 2015 found that PREDICT substantially overestimates survival in very young patients with breast cancer and those receiving chemotherapy. One can question whether PREDICT has provided substantial proof of analytical validity to be considered the true comparator. Most breast cancer tests have provided the proof that was defined by stakeholders in the oncology community, with the MINDACT study evaluated as having the highest level of evidence achievable for such tests. Oncologists, patients, investors, researchers, companies have all	Thank you for your comment which the committee considered. The committee noted that the PREDICT tool was provisionally recommended in the NICE draft guideline on early and locally advanced breast cancer (update), which is due to be published in July 2018

Comment number	Name and organisation	Section number	Comment	NICE response
			contributed to the stringent requests that were needed to provide the highest level of evidence for clinical use of these tests. We find it disconcerting that these validated tests are to be compared with PREDICT, that has not provided this type of analytical and clinical validity and utility data.	
244	Private sector professional		We have recently assessed the impact of the use of Endopredict Clinical score and the use of chemotherapy in our centre using a cohort of 120 patients, with ER positive breast cancer. We used two widely used algorithms initially to assess the potential need for adjuvant chemotherapy (NHS Predict and NPI). The first paper has been reviewed in a peer-reviewed journal (Anti-Cancer Research) and I have attached a copy of this paper for your information. https://www.ncbi.nlm.nih.gov/pubmed/29187466/ We have observed that the NHS Predict does not accurately predict the genomic profiling score and, overall, the number of chemotherapy prescriptions were reduced by approximately 50% when Endopredict	Thank you for your comment which the committee considered. The EAG noted that Mokbel 2017 was not published when the diagnostics assessment report was written. It also noted that this is a study of concordance rather than decision impact and it would not meet the inclusion criteria for the EAG review.

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Comment number	Name and organisation	Section number	Comment	NICE response
			Clinical was applied. We have obtained similar results when using the Nottingham Prognostic Index.	

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THEME: Conflicts of interest

Comment number	Name and organisation	Section number	Comment	NICE response
245	NHS Professional		The ethical issue with the report relates to the fact that one of the Breast Cancer Clinical Advisors is the CI of the OPTIMA trial, and is in receipt of several million pounds of funding from the HTA. He has a clear conflict of interest as this trial will not report until 2025 and any positive NICE recommendations in node positive patients would jeopardize recruitment to the OPTIMA study. The clinical adviser on the NICE panel is another coinvestigator and Manchester PI of the OPTIMA trial and also has a conflict of interest. It is disappointing that only Medical Oncologists provided advice to the group as the interpretation of much of the data and clinical findings is therefore subject to the prejudices of Medical Oncologists, which might not have the same for Clinical Oncologists or Surgeons, who are equally a part of the MDT determining chemotherapy use. The use of OncotypeDx RS to decide chemotherapy has reduced oncologists private practice income from chemotherapy. Moreover, the opinion across medical oncology is split between those who believe strongly Oestrogen and Progesterone receptor positive HER2 negative tumours benefit from endocrine therapy only and not from chemotherapy and those who offer chemotherapy to all patients	Thank you for your comment which the committee considered. Conflicts of interests are considered very carefully by NICE. Both NICE and the EAG (ScHARR) followed their respective policies on conflicts of interest during this assessment. Specialist committee members on this evaluation are listed in section 8 of the second consultation document, and included a clinical oncologist, a medical oncologist and a breast surgeon.

Comment number	Name and organisation	Section number	Comment	NICE response
			and over treat. Oncological advice from both sides of the debate should have been obtained but was not. "	
246	Genomic Health UK Ltd.	Diagnostic Assessment Report "Authors" and "Acknowledgements", Pages 1-2	As set out in our letter of 3 November 2017, authors of and contributors to the DAR have conflicts of interest. We are concerned that NICE have not ensured that processes meant to ensure the impartiality of the assessment have been followed. One of the reference authors of the DAR is the author of a report which reached conclusions on the cost-effectiveness of three of the assessed tests in this project (Oncotype DX, MammaPrint, and Prosigna) and was previously removed from the NICE Specialist Committee due to this acknowledged conflict of interest. One of the commentators on the report, acknowledged by the DAR, is also a co-author of the above-mentioned report and thus in the same conflicted position. No declaration of conflicts of interest has been made in the DAR in respect of this commentator. In addition, the 'transATAC team', acknowledged in the DAR for its 'bespoke analyses and data to inform this assessment', includes: (i) the co-authors of a study of EndoPredict's prognostic ability along with four authors from Sividon Diagnostics GmbH, EndoPredict's manufacturer;	Thank you for your comment which the committee considered. Conflicts of interests are considered very carefully by NICE. Both NICE and the EAG (ScHARR) followed their respective policies on conflicts of interest during this assessment. All conflicts judged to be relevant are declared in the report.

Comment number	Name and organisation	Section number	Comment	NICE response
			and (ii) one of the developers of the IHC4 test included in this NICE assessment. Which members of the 'transATAC team' contributed to the DAR is not disclosed but if these individuals were involved, this represents a conflict of interest. Again, no conflicts of interest have been declared.	
247	NHS Professional	General	General comment: There has to be a concern that this report is subject to a conflict of interest. The chairman was asked to stand down because of his involvement in the OPTIMA trial. This occurred at a late stage when the report must have been largely complete.	Thank you for your comment which the committee considered. Conflicts of interests are considered very carefully by NICE. Both NICE and the EAG (ScHARR) followed their respective policies on conflicts of interest during this assessment. The Chair of the diagnostics advisory committee is named in section 8 of the second diagnostics consultation document. As Chair of the independent advisory committee they have had no involvement with the production of the assessment report, or the OPTIMA study.

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THEME: Wording of recommendations and other editorial comments

Comment number	Name and organisation	Section number	Comment	NICE response
248	Royal Marsden Hospital	1.1	We do not agree with the information conveyed in last sentence of section 1.1 being applied to all the tests under consideration. '*Their cost effectiveness compared with current practice is highly uncertain.*' is true for the more costly molecular-based tests, but doesn't tally with your findings for IHC4+C. In particular in section 4.61 it is stated that: '*ICH4 (sic) +C was dominant over current practice (that is, it was less expensive and more effective)*.' While there would be some extra costs for the QA of IHC4 if done locally this would be minimal. Also see comment 14 below.	Thank you for your comment which the committee considered. The EAG noted that its report on Ki67 was limited to studies relating to breast cancer, as it was given to understand that methodologies differ across cancer types. The EAG noted that the studies suggested that analytical validity of IHC4 remains under-evidenced. The committee decided to revise section 1.1 in the second diagnostics consultation document.
249	Myriad Genetics	1.1	The DCD reports that for all tests assessed '*the cost effectiveness compared with current practice is highly uncertain'.* Myriad Genetics considers it is inappropriate for the DCD to group all five tests assessed together in this statement. The incremental cost-effectiveness ratios (ICERs) reported for EndoPredict were significantly lower than some of	Thank you for your comment which the committee considered. The committee decided to separate out its considerations on the economic model

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THEME: Wording of recommendations and other editorial comments

Comment number	Name and organisation	Section number	Comment	NICE response
			the other tests evaluated. Indeed, under the evidence assessment group (EAG) base case assumptions ([redacted] the ICER for the lymph node positive (LN+, 1-3 nodes) cohort is £21,458 per QALY gained, which falls well below the £30,000 per quality adjusted life year (QALY) willingness to pay threshold.	results from each of the tests. These are detailed in sections 5.16 to 5.19 of the second consultation document.
250	NHS Professional	Page 30	With reference to our trial: "It is unlikely to accurately represent the use of chemotherapy in node-positive disease". Page 30 Evidence Overview We disagree with this statement “of the 149 patients, 99 were node negative, 21 had micrometastases alone and 29 macrometastases”	Thank you for your comment which the committee considered.
251	Myriad Genetics	5.12	In the context of the ICERs reported for EndoPredict, and other tests, the DCD reports that ‘*the committee considered these ICERs to be highly uncertain because of the available clinical data’.* This statement is ambiguous, and it is not clear to the reader what part of the clinical data	Thank you for your comment which the committee considered.

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THEME: Wording of recommendations and other editorial comments

Comment number	Name and organisation	Section number	Comment	NICE response
			the committee are referring to as being the root cause of the committee's *'uncertainty*'. This statement also contradicts earlier statements in the DCD, during which the committee recognises the long-term (10 years) prognostic ability of EndoPredict, for example: '*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'*.	The uncertainties in the inputs and assumptions used in the model were considered by the committee and are described in sections 5.8 to 5.12 of the second consultation document.
252	Royal College of Pathologists	2.2	Table 16: there is a typo: Second line; MINDACT Adjuvant! Online clinical high-risk subgroup (n=3,324): This should be low-risk subgroup	Thank you for your comment which the committee considered.

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THEME: Access proposals

Comment number	Name and organisation	Section number	Comment	NICE response
253	Genomic Health UK Ltd.	Diagnostic Consultation Document	[redacted]	Thank you for your comment which the committee considered.
254	Myriad Genetics	4.53	In the base case analysis, the cost of an EndoPredict assay completed under centralised testing is assumed to be £1,500. [redacted]	Thank you for your comment which the committee considered.
255	Myriad Genetics		Myriad Genetics is committed to further advancement in the disease state of breast cancer as well as to gene expression testing – specifically EndoPredict. [redacted]	Thank you for your comment which the committee considered.

NICE National Institute for Health and Care Excellence

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THEME: Access proposals

Comment number	Name and organisation	Section number	Comment	NICE response
			Appendix A – [redacted] Appendix B – [redacted]	

1. National Institute for Health and Care Excellence. Tumour profiling tests to guide adjuvant chemotherapy decisions in people with breast cancer (update of DG10) - final scope. London, 2017:1-25.
2. Holt S, Bertelli G, Humphreys I, et al. A decision impact, decision conflict and economic assessment of routine Oncotype DX testing of 146 women with node-negative or pNImi, ER-positive breast cancer in the U.K. *British Journal of Cancer* 2013;108(11):2250-58. doi: https://dx.doi.org/10.1038/bjc.2013.207
3. Bloomfield DJ, Arbon A, Cox J, et al. Patient/oncologist decisions about adjuvant chemotherapy in ER+ve, HER2-ve early breast cancer following EndoPredict testing. *American Society of Clinical Oncology (ASCO) conference* 2017