**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**
**DIAGNOSTICS ASSESSMENT PROGRAMME**

**Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat**

**<u>Second</u> Diagnostics Consultation Document – comments and responses**

| Comment number | Name and organisation | Section number | Comment | Response |
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| 1 | Consultee 15: Royal College of Physicians - (Health Professional Organisation) | 1 | The NCRI/RCP/RCR/ACP/JCCO is grateful for the opportunity to comment. We welcome the NICE Diagnostics Consultation Document and support the conclusion that more research into the 4 technologies evaluated is required. We note that the Committee believed that the evidence that the evidence that Oncotype DX is able to predict differential chemosensitivity amongst ER +ve breast cancer independently of other prognostic factors is not robust (section 6.2). Our experts believe that the existing evidence is highly suggestive that Oncotype DX does predict a differential sensitivity to chemotherapy and that this is likely to extend to all of the evaluated technologies as argued in our response to the previous (February 2012) Diagnostics Consultation Document. We believe that this is a key research question that should be included as a recommendation for further research. | Thank you for your comment.<br><br>Following consideration of the range of evidence available on chemotherapy prediction for Oncotype DX, the Committee considered that the data on the ability of Oncotype DX to predict chemotherapy benefit to be insufficient at this time and have recommended further research. Further details can be found in sections 6 and 7 of the guidance.<br><br>The Committee has recommended further research on the ability to predict chemotherapy benefit for all tests. See section 7 of the guidance. |
| 2 | Consultee 13: (NHS Professional) | 1 | We have been very disappointed to see that NICE has not recommended the routine use of Oncotype DX Breast Cancer test for eligible patients.<br><br>In an era when we are discussing the benefits | Thank you for your comment.<br><br>The Committee found that Oncotype DX was a clinically effective (based on its ability to predict prognosis but not chemotherapy |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | versus harm of all our medical interventions, surely we should be looking towards personalising patients? treatment, and offering chemotherapy only to those patients that will gain benefit from it.<br><br>In the Newcastle region we are very keen to be able to offer our patients this test and provide a personalised treatment plan. This will improve quality of care and increase physicians' and patients' confidence in and satisfaction with their treatment decision.<br><br>A recent 6 month audit (Sept 2011 to March 2012) of early breast Cancer patients was performed at the Queen Elizabeth Hospital, Gateshead. This showed that 81 out of 181 newly diagnosed patients discussed at our MDT were referred for adjuvant chemotherapy based on local guidelines (taking into account ER status, HER2 Status, tumour size/grade, patients age and nodal status.)<br><br>Twenty two out of eighty one patients referred for adjuvant chemotherapy were in the 'clear' Oncotype DX test group: ER+, HER2-, N0 and either >2cm or Grade 3. These are patients who are fit for chemotherapy and according to local guidelines, are prescribed chemotherapy, but there is some doubt as to its benefit<br><br>Nineteen out of eighty one patients referred for adjuvant chemotherapy were in the 'potential' Oncotype DX test group: ER+, HER2-,N0 and 1- | benefit) and cost-effective (at the revised confidential price used in the access proposal) use of NHS resources in patients deemed to be at intermediate risk of distant recurrence. Therefore, the technology has been recommended for adoption in this patient group – please refer to section 1 of the guidance. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | 2cm, Grade 2 .These are patients who are fit for chemotherapy and according to local guideline, are not prescribed chemotherapy, but a small number will have a high recurrence score and likely to benefit from chemotherapy.<br><br>By utilizing the Oncotype DX test we believe that we will be able to reduce the amount of unnecessary chemotherapy given in this group of selected patients. This will improve patients' quality of life as they will not have to suffer the sometimes devastating effects of chemotherapy. These effects can be both physical such as sickness, hair loss, potential fatal infections, and social such as inability to work and loss of earnings.<br><br>Reducing the number of patients receiving chemotherapy will also free up chemotherapy slots for those patients who do need chemotherapy and thus enable us to deliver chemotherapy in a timely manner.<br><br>This test is available in other countries, and is endorsed by many leading international breast cancer treatment guidelines including ASCO (2007), NCCN (2008), ESMO (2010) and St. Gallen (2011). We feel it will be very regrettable if we are unable to offer this choice to our patients.<br><br>Your review has admitted that Oncotype Dx is the 'furthest along the validation pathway by previous systematic reviews', with evidence that the Oncotype | |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | DX recurrence score significantly correlated with disease free survival and overall survival. You have made reference to the IHC4 test, but state that 'No studies in the analytical validity of IHC4 were identified', and there is 'no published evidence on the clinical utility of IHC4'.<br><br>It will take several years to gain such evidence, and in the interim we have a clinically validated test that should be available for use on selected patients.<br><br>We would urge you to reconsider your position on the use of this test. | |
| 3 | Consultee 2: (NHS Professional) | 1 | impact studies suggest that chemo can be avoided in some which if confirmed is a major step forward and wider use will follow | Thank you for your comment. |
| 4 | Consultee 3: (Health Professional Europe) | 1 | I would like suggest the committee to consider the prognostic effects of the different tests. The first step in the decision to advise a given patient with primary breast cancer to have adjuvant systemic treatments, is the prognostic features of the cancer. If the prognosis ie potential capacity of the primary cancer to produce 'effective' dissemination is so low that the effect of adjuvant systemic therapy -in particular chemotherapy- to reduce the appearance -ultimately fatal- distant relapse is equal or lower as the risk of causing serious harms/late effects by chemotherapy in long term (serious congestive heart failure, AML), being around an absolute 1-2%, the administration of chemotherapy has to be questioned seriously. Since the Oxford/Peto overview show an relative reduction of relapse by chemotherapy of around 25% across | Thank you for your comment.<br><br>The Committee has reviewed the evidence base available for each test. The Committee considered that the uncertainty in the clinical-effectiveness evidence (including clinical validity – ability to predict prognosis) for MammaPrint limited the validity of the economic analysis.<br>The Committee concluded that the uncertainty in the clinical effectiveness, in particular the clinical validity and clinical utility of the test, was too high to recommend the adoption of MammaPrint for general use in the NHS at this time and recommended the test for research only. Further details can be found in sections 6 |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | all subgroups, the threshold of advising adjuvant chemotherapy should be around 5% 5 year distant relapse free survival. One test has repeatedly shown to be able to predict such a low risk/good survival estimate in an important proportion of so called early breast cancer patients (the 70-gene amsterdam - mammaprint- test). | and 7 of the guidance. |
| 5 | Consultee 4: (Sponsor - Agendia) | 1 | GENERAL COMMENT: This document lacks proper referencing, making it hard to go back and judge some of the statements.<br><br>1.1: Agendia disagrees with the statement that there is too much uncertainty in the evidence of clinical effectiveness leading to uncertainty about the cost effectiveness. An additional important piece of evidence (first ever prospective data on patients treated according to multi-gene assay) had been sent to you under confidentiality previously for your consideration. | Thank you for your comment.<br><br>Detailed referencing is included in the Diagnostics Assessment Report produced by the External Assessment Group.<br><br>RASTER study – see appendix 1 for the External Assessment Group analysis of the RASTER study. Committee considerations of the study can be found in section 6 of the guidance.<br><br>The Committee concluded that, despite these data, the uncertainty in the clinical effectiveness data for MammaPrint remained which limited the validity of the economic analysis. |
| 6 | Consultee 5: (University Faculty) | 1 | It is true that the evaluation of cost effectiveness is usually based on the assumption of the clinical utility of the assays. If some critical data are overlooked, the subsequent cost-effective analysis is meaningless. | Thank you for your comment.<br><br>The External Assessment Group believes that the cost effectiveness analysis is fit for purpose and adheres to NICE principles. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| 7 | Consultee 1: (Sponsor - Genomic Health) | 1.1 | Genomic Health Inc. disagrees with the provisional recommendations from the diagnostic assessment committee. In light of the limited evidence supporting current clinical practice and the other tests included in this assessment, Onco*type* DX remains the best and most validated option to inform individual treatment decisions in the eligible UK patients for whom the benefit of chemotherapy remains unclear. The UK department of health's strategy is to allow access for NHS patients to stratified/ personalised medicine which is made possible through well validated molecular diagnostics such as Onco*type* DX. Sir David Nicholson recently stated "*There is a revolution in genome sequencing to monitor cancer and deliver personalised treatments; and to transform the detection, diagnosis and treatment of infectious diseases, the NHS must harness and lead this*" (Foreword to the NHS document "Innovation, Health and Wealth", 5 December 2011). It is therefore concerning that the provisional recommendations from NICE don't support this priority. Along with many physicians in the UK, we believe that Onco*type* DX will be cost-effective if used in the appropriate group of patients and would like to have a dialogue with NICE to discuss patient access schemes to make Onco*type* DX available for those patients who need it the most.<br><br>We would like to highlight that many of the comments provided below were already provided on the first draft consultation document and the | Thank you for your comment.<br><br>The Committee found that Oncotype DX was a clinically effective (based on its ability to predict prognosis but not chemotherapy benefit) and cost-effective (at the revised confidential price used in the access proposal) use of NHS resources in patients deemed to be at intermediate risk of distant recurrence. Therefore, the technology has been recommended for adoption in this patient group – please refer to section 1 of the guidance. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | diagnostic assessment report.<br><br>The current diagnostic consultation document fails to highlight the lack of predictive evidence and limited prognostic evidence supporting the current standard clinical practice in the UK (i.e. AOL and NPI). This limited evidence regarding existing measures should have been taken into account in the assessment to allow an objective evaluation of the incremental data supporting the Onco*type* DX test. We would therefore like the diagnostic assessment committee to respond to the following question : "should we continue to inform chemotherapy decisions with existing clinical practice knowing that it is supported by limited prognostic evidence and no predictive evidence or, should we use a test supported by both strong prognostic evidence (including in the UK) and predictive evidence, knowing that this evidence led numerous independent committees in multiple countries to include this test in all major breast cancer guidelines?"<br><br>While NICE acknowledges in several sections of the document (sections 5.14 and 6.1) that "the highest quality evidence was reported for Onco*type* DX", this fact is not reflected in the provisional recommendation stating that all tests are not recommended "because of the uncertainty about their overall clinical benefit". Not only does the provisional recommendation not differentiate Onco*type* DX and its acknowledged highest quality evidence from the other tests, but it is misleading by | Reviewing current practice is outside the scope for this assessment (and in NICE Diagnostics Assessment Programme assessments in general). The External Assessment Group's role was to review the new technologies.<br><br>The Committee agrees that there are potential limitations with tools currently used in the NHS, the suggested imperfect nature of such tools is captured in paragraph 3.13 of the guidance document.<br><br>Following consideration of the range of evidence available on this outcome, the Committee considered that the data on the ability of Oncotype DX to predict chemotherapy benefit to be insufficient at this time and have recommended further research. Further details can be found in sections 6 and 7 of the guidance. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | stating that there is uncertainty about the "*overall* clinical benefit".<br><br>Genomic Health also disputes the statement from the diagnostic assessment committee on the uncertainty of evidence regarding clinical effectiveness for Onco*type* DX. Throughout the document the studies regarding prediction of chemotherapy are incorrectly referred to as retrospectively designed studies. In fact, these studies are prospectively-designed and performed using archival specimens from previously conducted prospective randomized trials with long term follow-up (so called "prospective-retrospective" trials). Prospectively-designed studies of archival materials from previously conducted prospective controlled trials can generate level 1-evidence; this is a concept that is well established in the scientific community (Simon et al 2009). In addition, NICE has previously accepted such prospective-retrospective study data in making a positive recommendation for KRAS testing in colon cancer. Prediction of relative chemotherapy benefit, with significant benefit seen in patients with high Recurrence Scores and minimal, if any, benefit in patients with low Recurrence Scores has been demonstrated consistently in the NSABP B-20 (Paik et al, JCO 2006) and SWOG 8814 (Albain et al. Lancet Oncology 2010) clinical validation studies. It should be pointed out that the probability that the results from both of these well-known studies are chance findings is extremely low. In addition, there are published supportive data from | Section 5.8 of the guidance has been updated to include studies that are prospectively designed to analyse archival specimens.<br><br>Although the concept of undertaking a prospective analysis of retrospective clinical data (i.e. use of archival samples from a previously conducted RCTs) is well established (Simon et al., 2009), its scientific validity remains controversial (Wang et al. 2006, 2008; Ahern & Hankinson, 2011) e.g. confounding and biases related to the completeness of ascertaining biological specimens (including quality, missing data, diagnostic criteria etc.), possibility that iterative discovery from a retrospective source might necessitate correction for multiple testing, data from well conducted, high quality RCTs should be available particularly for a large number of patients to avoid selection bias, and analysis should be pre-defined.<br><br>References<br>Ahern TP, Hankinson SE. Re: Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2011 Oct 19;103(20):1558-9;<br><br>Simon RM, Paik S, Hayes DF. Use of archived |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | the neo-adjuvant setting where pathological complete responses have only been reported in patients with Recurrence Scores of 25 and above (Gianni L, et al. *J Clin Oncol.* 2005;23(29):7265, Yardley et al. SABCS 2011) and similar data have been reported for clinical complete response (Chang JC, et al. *Breast Cancer Res Treat*. 2008;108(2):233). The body of evidence in support of the Recurrence Score's ability to predict chemotherapy benefit is therefore compelling. These data have led to the inclusion of Onco*type* DX as a test predictive of chemotherapy benefit in the guidelines of the ASCO in 2007, NCCN in 2008, ESMO in 2010 and St Gallen in 2011. In addition, it should be noted that the level of evidence for Onco*type* DX as a marker upon which to base treatment decisions regarding chemotherapy or not in this patient population far exceeds that of currently used markers; no other test nor the current clinical practice in the UK has demonstrated prediction of chemotherapy benefit in even a single randomized clinical trial.<br><br>In drawing its conclusion the recommendation states that the uncertainty about the overall clinical benefit "is leading to uncertainty about their cost-effectiveness". As detailed below, any "uncertainty" behind the cost-effectiveness of Onco*type* DX appears to have been introduced by the modellers who made scientifically unjustified and potentially skewed assumptions on the Onco*type* DX | specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2009 Nov 4;101(21):1446-52. Epub 2009 Oct 8.<br><br>Wang SJ, Cohen N, Katz DA, et al. Retrospective validation of genomic biomarkers—what are the questions, challenges and strategies for developing useful relationships to clinical outcomes—workshop summary. Pharmacogenomics J 2006;6:82–8.<br><br>Wang SJ. Utility of adaptive strategy and adaptive design for biomarker-facilitated patient selection in pharmacogenomic or pharmacogenetic clinical development program. J Formos Med Assoc. 2008 Dec;107(12 Suppl):19-27.<br><br>The External Assessment Group disagrees with this comment and does not believe that any errors have been introduced in the modelling. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | Recurrence Scores which were not transparently applied to the modelled population.<br><br>For the sake of transparency, NICE should identify the committee members who have been involved in the development and or study of any of the four assays and describe their roles and activities in the assessment and specifically whether they recused themselves from any portion of the assessment or recommendation. | NICE operates a transparent policy on declaring and dealing with conflicts of interest known as 'A Code of practice for Declaring and Dealing with Conflicts of Interest' (published on the NICE website). Members of the Committee who were not deemed to be conflicted and who have participated in this evaluation can be found in section 11 of the guidance. |
| 8 | Consultee 2: (NHS Professional) | 2 | only experience with oncotype | Thank you for your comment. |
| 9 | Consultee 6: (Patient Representative) | 2 | No comment | Thank you for your comment. |
| 10 | Consultee 1: (Sponsor - Genomic Health) | 2.1 | We are advised that NICE cannot issue recommendations for products which are not CE marked or have not received a CE mark within 12 months of the start of the evaluation. It is not clear whether IHC4 has received a CE mark within 12 months of the start of the evaluation. | Thank you for your comment.<br><br>The sponsor of IHC4 confirms that the test is available to the NHS and, therefore, qualifies for NICE guidance.<br><br>The programme manual states '*If a diagnostic technology requires CE marking*, the Programme can only carry out an evaluation of that technology if the CE mark is received by |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | | the time any documents are issued for public consultation.' |
| 11 | Consultee 9: Royal College of Pathologists (Health Professional Organisation) | 3 | This is a thorough review of the evidence. I am not sure about the validity of the rationale in regarding evidence from overseas centres as less valid then from UK centres. | Thank you for your comment.<br><br>Although the evidence is reviewed on merit, it is possible that evidence generated outside of England may not be applicable. For example, cost effectiveness analyses from other countries are typically not generalisable to the UK due to variations in a range of factors including baseline levels of chemotherapy and the cost of chemotherapy. The same may be true for studies of clinical decision-making. |
| 12 | Consultee 10: (NHS Professional) | 3 | I was surprised to see that the specialist committee does not consist of any practising medical or clinical oncologists, or indeed nurse clinicians, that sit on a multidisciplinary team making decisions on breast cancer patient management. This seems to be a serious deficiency and an explanation as to why this is the case would be useful. | Thank you for your comment.<br><br>The Diagnostics Assessment Programme (DAP) recognises the importance and value of experts in the field. As such, the programme recruits Specialist Committee Members (SCMs) from a range of backgrounds in the NHS to support the guidance production process for each guidance topic – SCM positions are advertised on the NICE website. We continue to encourage people with the appropriate expertise to engage with the DAP. In addition, the independent external assessment group (The School of Health and Related Research, University of Sheffield) also seeks input from its own team of experts throughout the evaluation. |
| 13 | Consultee 2: | 3 | current standard assessment of current prognostic | Thank you for your comment. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | (NHS Professional) | | variables are certainly imperfect | The potential limitation of tools used in current practice is captured in paragraph 3.13 of the guidance document. |
| 14 | Consultee 3: (Health Professional Europe) | 3 | Current guidelines, including NPI, are mainly based on 3 factors: size of primary cancer, grade of the cancer, and nodal status (presence, size and number of cancer containing nodes).<br><br>Size is measurable, but strongly correlated to the biology of the cancer. Grade is a subjective measurement, particularly grade 2 cancers: the kappa correlation coefficient between experienced pathologist in published series is between 0.5-0.6, thus clinically not practicable. Further the prognostic value of lymphnode metastases is recently under debate. Still we use these week and subjective prognosticators in every's daily practice. A -far- more objective estimation of the metastatic potential is urgently needed, and moreover far more objective and reproducible (well validated) parameters are available. | Thank you for your comment.<br><br>The potential limitation of tools used in current practice is captured in paragraph 3.13 of the guidance document.<br><br>The Committee found that Oncotype DX was a clinically effective (based on its ability to predict prognosis but not chemotherapy benefit) and cost-effective (at the revised confidential price used in the access proposal) use of NHS resources in patients deemed to be at intermediate risk of distant recurrence. Therefore, the technology has been recommended for adoption in this patient group – please refer to section 1 of the guidance. |
| 15 | Consultee 6: (Patient Representative) | 3 | Currently it is difficult for clinicians to decide whether individual patients with ER+ breast cancer will gain benefit from chemotherapy or not. There are a significant number of woman who receive chemotherapy and do not gain any benefit as their risk of recurrence is low, so do not require this treatment. Therefore, if this population of patients can be identified they can be spared the side effects of these drugs. Although there are tools that take into account clinical characteristics of a woman's | Thank you for your comment.<br><br>The potential limitation of tools used in current practice is captured in paragraph 3.13 of the guidance document. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | tumour these have several limitations. There is therefore a need for reproducible and effective tests that can identify those women who will benefit from chemotherapy and those who will not. These four tests aim to do this, by categorising women into low or high risk groups, by measuring either the activity of certain genes or levels of a number of proteins. | |
| 16 | Consultee 7: (NHS Professional) | 3 | The appraisal does not mention or deal with the significant emotional and psychological strain placed on the patient during the discussion of adjuvant therapy. This is an important omission. Oncologists accept uncertainty and know that the absolute benefit of chemotherapy quoted will have wide confidence intervals. That uncertainty is shared with the patient as part of shared decision making and a need to respect the autonomy of the patient. For some patients a decision to have (or not have) chemotherapy causes great distress and an increasing level of certainty around the likely absolute benefit can be particularly helpful to those women who seek reassurance that not having treatment is a sensible strategy. There is a wide literature on decision-regret and psychological impact but a relevant recent publication is: Women's interest in gene expression analysis for breast cancer recurrence risk by O'Neill et al J Clin Oncol. 2007 Oct 10;25(29):4628-34. | Thank you for your comment.<br><br>The Committee understands and agrees that patients can face significant emotional and psychological strain when considering treatment decisions. Section 3.1 and 6.2 of the guidance has been updated to reflect this. |
| 17 | Consultee 1: (Sponsor - Genomic Health) | 3.1 | In order to assess the incremental value of Onco*type* DX and the other tests assessed, NICE should have conducted a systematic review of the evidence supporting tools currently used in standard clinical practice (i.e. NPI and AOL) to inform chemotherapy | Thank you for your comment.<br><br>Reviewing current practice is outside the scope for this assessment (and in NICE Diagnostics Assessment Programme assessments in |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | decisions. Genomic Health has conducted a systematic review of the evidence supporting existing measures which first draft is attached hereto (see annex I). This review shows that the evidence supporting the prognostic ability of NPI and AOL is quite weak. Indeed, all the studies validating these tools are observational and were conducted in mixed populations (including ER-and HER2+ patients for most of them). There are no studies showing that these tools are predictive of chemotherapy benefit even in populations broader than that of the consultation document (ER+, LN-, HER2-).<br><br>The lack of predictive evidence and limited prognostic evidence supporting tools such as AOL and NPI should be highlighted in the draft consultation and should be taken into account when comparing the evidence supporting the clinical value of the Recurrence Score to current clinical practice. Indeed, when such a balanced comparison is made, the need for well validated tests such as Onco*type* DX becomes clearly evident given the absence of strong data supporting decision making in current clinical practice. As highlighted in a survey of treatment protocols across the UK (HTA 2006; Vol10 (34)), UK physicians currently use very different protocols using (or not) NPI and AOL to decide on the use of adjuvant chemotherapy. Onco*type* DX could help in standardising chemotherapy decision making in the eligible population across the UK and therefore enhance equity of access to chemotherapy across the NHS. | general). The External Assessment Group's role was to review the new technologies.<br><br>The Committee agrees that there are potential limitations with tools currently used in the NHS, the suggested imperfect nature of such tools is captured in paragraph 3.13 of the guidance document. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | It is stated that "all four tests ***may*** be predictive of chemotherapy benefit". However, the only assay for which a formal interaction with chemotherapy treatment has been demonstrated is the Onco*type* DX assay (in the NSABP B-20 and SWOG 8814 prospective-retrospective trials). Importantly, Mammostrat failed to predict benefit from chemotherapy in the very same study in which Onco*type* DX was predictive (NSABP B-20); showing equal relative benefit in the Mammostrat "high risk" as well as "low risk" tumours and no benefit in patients with intermediate risk (Ross et al. Clin Cancer Res. 2008; 14(20):6602-9). There is also no data demonstrating that IHC4 would be predictive of chemotherapy benefit and the correlation of IHC4 with the Recurrence Score in the transATAC study was only modest (0.7), insufficient to enable prediction of chemotherapy benefit to be extrapolated from its modest association with the Recurrence Score. Without data to support prediction it is scientifically, medically and health economically appropriate to conclude only that IHC4 ***may or may not*** be predictive. | Section 3 of the guidance document outlines the clinical need and current practice associated with this assessment and suggests that the technologies evaluated may be able to predict the benefit of chemotherapy. This section does not include an assessment of the evidence-base for the prediction of chemotherapy benefit of the four tests. Such evidence, as highlighted in the evaluation, is presented in section 5 of the guidance. Committee considerations of the data are captured in section 6 of the guidance.<br><br>However, we agree that the suggested amend is appropriate – this has been accepted and the guidance updated. |
| 18 | Consultee 2: (NHS Professional) | 4 | good summary | Thank you for your comment. |
| 19 | Consultee 5: (University Faculty) | 4 | Tumour grade is subject to misclassification but heavily involved in some guidelines | Thank you for your comment.<br><br>The potential limitation of tools used in current practice is captured in paragraph 3.13 of the guidance document. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 20 | Consultee 10: (NHS Professional) | 4 | No mention here of the UK derived PREDICT programme which is now commonly used, UK specific and includes assessment of HER2. | Thank you for your comment.<br><br>As PREDICT has only recently become available and is not yet widely used in the UK, and has not been used as a comparator in any of the GEP/IHC studies, this would have been inappropriate to use for the present review although the Committee accepts that this holds promise. Section 3.6 of the guidance has been updated to include information on the availability of PREDICT to the NHS. |
| 21 | Consultee 7: (NHS Professional) | 4 | Increasingly UK oncologists are using the PREDICT model (www.predict.nhs.uk) . This has two clear advantages over Adjuvant!; firstly it uses UK data on competing mortality rather than US SEER data and secondly it includes Her 2 status in the assumptions on relative benefit. It also distinguishes between screen and non screen detected cancers. This is an important advance and helps refine risk profile (a little) for UK patients. | Thank you for your comment.<br><br>As PREDICT has only recently become available and is not yet widely used in the UK, and has not been used as a comparator in any of the GEP/IHC studies, this would have been inappropriate to use for the present review although the Committee accepts that this holds promise. Section 3.6 of the guidance has been updated to include information on the availability of PREDICT to the NHS. |
| 22 | Consultee 8: (NHS Professional) | 4 | PREDICT which is based on NHS patients should be considered as an alternative to Adjuvant on line | Thank you for your comment.<br><br>As PREDICT has only recently become available and is not yet widely used in the UK, and has not been used as a comparator in any of the GEP/IHC studies, this would have been inappropriate to use for the present review although the Committee accepts that this holds promise. Section 3.6 of the guidance has been updated to include information on the |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | | availability of PREDICT to the NHS. |
| 23 | Consultee 6: (Patient Representative) | 4 | There are a few omissions to the descriptions of these technologies which could be added to improve the accuracy and completeness of this document:<br>Mammaprint (point 4.5) can estimate risk of distant recurrence independent of ER status in early breast cancer, which is not mentioned.<br>Oncotype Dx and IHC4 predict likelihood of 10 year recurrence, which is not mentioned (4.5 and 4.7).<br>Mammostrat stratifies ER+ patients, which is not mentioned (4.7).<br>Point 4.8 ? It would be useful if there were statistics or estimates of the frequency these tools are currently used in clinical practice, as these are the main comparator for these tests.<br>In 4.10, the Nottingham Prognostic Index is described as involving time-dependent factors and aspects of tumour aggressiveness. The tumour's characteristic components are discussed, but the time-dependent factors are not. Â It would be helpful to include this information. | Thank you for your comment.<br><br>There are a range of data on the types of breast cancer patients stratified (for example, ER- and LN+) by each of the tests and the output of the test (for example, predicting the likelihood of recurrence at 5 years and 10 years). Given the variety of data it was felt the current descriptions were appropriate. We hope to have summarised the relevant evidence for each test in section 5 of the guidance. In addition, a more complete description of the tests and the relevant evidence is available in the diagnostics assessment report.<br>The Committee agrees it would be useful to have information on the frequency these tools (NPI and Adjuvant! Online) are currently used in clinical practice, however, such data, although sought, were not identified during the assessment.<br><br>Tumour size and lymph node status/score can be viewed as time-dependent factors. |
| 24 | Consultee 11: (NHS Professional) | 4 | My interpretation of the test and supporting data is that Oncotype DX predicts not only recurrence risk but also the proportion of overall benefit contributed by endocrine therapy and chemotherapy. When the test returns a low RS then all, or almost all, of the adjuvant benefit is derived from endocrine therapy | Thank you for your comment.<br><br>Following consideration of the range of evidence available on this outcome, the Committee considered that the data on the ability of Oncotype DX to predict chemotherapy |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | alone (such that at the very low end of the scale chemotherapy increases risk to the patient). At the other end of the scale the major benefit comes from chemotherapy with little contribution from endocrine therapy. I do not concur with the view that, "equal benefit of chemotherapy should be assumed across all Oncotype DX risk groups". This does not make sense from a biological view point when we know that more active tumours with more deregulated pathways are generally much more susceptible to chemotherapy and, conversely, tumours with more conserved metabolisms are more likely to be controlled with single pathway interference, such as targeted endocrine therapy. The recurrence score, by the way it is calculated, is a reflection of the degree to which the cellular control mechanisms are deregulated. | benefit to be insufficient at this time and have recommended further research. Further details can be found in sections 6 and 7 of the guidance. |
| 25 | Consultee 9: Royal College of Pathologists (Health Professional Organisation) | 4 | As the document admits, the data on IHC4 are premature - for example, it notes that this is a local laboratory test (page 9), but all the results which are published as based on central testing.<br><br>Para 4.6 p10 'Her-2 testing is not carried out by all UK labs' it is centralised in some areas | Thank you for your comment.<br><br>Noted. The Committee agrees and has recommended further research on IHC4, including research on the reliability and reproducibility of IHC4 when performed in local laboratories.<br><br>Noted. The word 'all' has beeen removed from the sentence in the guidance document. |
| 26 | Consultee 1: (Sponsor - Genomic Health) | 4.2 | It is stated that 3 of the tests require that the sample be sent to a central laboratory. The fourth test which is highlighted as not requiring central laboratory performance is importantly not commercially available (and potentially not even CE marked). | Thank you for your comment.<br><br>The sponsor of IHC4 confirms that the test is available to the NHS and, therefore, qualifies for NICE guidance. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | Further there is no data supporting accuracy and reproducibility if the test was to be performed in local laboratories. It must therefore at this point be assumed that if ICH4 ever would become commercially available it is likely to be performed in one or perhaps a small number of central laboratories. Finally, the turn-around time for IHC4 is also reported as less than a week but this estimate is purely based on speculation because the test is not available commercially and no central laboratory which is able to handle the expected volume of UK samples with a validated quality-assured process yet exists. | The programme manual states '*If a diagnostic technology requires CE marking*, the Programme can only carry out an evaluation of that technology if the CE mark is received by the time any documents are issued for public consultation.'<br><br>The estimated turnaround time was provided by the sponsor and accepted by the Committee.<br><br>The Committee agrees that research is needed on IHC4 before it can be considered for widespread adoption. Recommendations include research into the performance of the IHC4 test in local laboratories (see section 7 of the guidance document). |
| 27 | Consultee 1: (Sponsor - Genomic Health) | 4.5 | It is stated that Mammaprint can be used in both fresh frozen and formalin fixed paraffin imbedded tissue samples. However, all development and validation studies for Mammaprint were performed using only fresh frozen samples and no bridging study comparing results from fresh frozen and formalin fixed paraffin embedded samples have been reported. | Thank you for your comment.<br><br>This issue has been captured in section 5.13 of the guidance. In addition, the Committee understands, from the manufacturer, that MammaPrint on formalin-fixed paraffin-embedded samples has been CE marked and that the manufacturer had submitted data to the FDA to demonstrate that the performance of MammaPrint in formalin-fixed paraffin-embedded samples is equivalent to that of fresh samples – this is captured in section 6.2 of the guidance. |
| 28 | Consultee 1: | 4.8 | In light of the recently published *audit of screen-* | Thank you for your comment. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | (Sponsor - Genomic Health) | | *detected breast cancers for the year of screening April 2010 to March 2011* by the NHS Breast Cancer Screening Program and the Association of Breast Surgery, May 2012 which reports that the use of adjuvant chemotherapy was recorded for 27% of women with screen detected tumours, we believe that the registry data used by NICE which indicates significantly lower chemotherapy treatment rates, is subject to question. It would be reasonable to believe that chemotherapy use in the overall breast cancer population will be at least as high as in the screen detected tumours. Importantly, the figures presented in the recent NHSBSP and ABS audit are more consistent with the Onco*type* DX decision impact study data (Holt et al, 2011). | The External Assessment Group used data from 2 cancer registries (WMCIU and ECRIC) which form 2 out of the 9 cancer registries involved in the screening audit mentioned by the commentator.<br><br>These data indicate that 14.42% of women with ER+, LN-, HER2- currently receive chemotherapy. The proportion from the screening audit is higher at 27% for the following reasons:<br><br>- This includes women with ER- early breast cancer (who are more likely to receive chemo compared with those with ER+ early breast cancer)<br><br>- This includes women with LN+ (who are more likely to receive chemo compared with LN-)<br><br>- This includes women with HER2+ (more likely to receive chemo compared with HER2-)<br><br>- The audit only includes screened women, that is, women who are detected earlier, therefore at younger age. It is known that the probability of receiving chemotherapy decreases with age. |
| 29 | Consultee 2: (NHS Professional) | 5 | nil to add | Thank you for your comment. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| 30 | Consultee 5: (University Faculty) | 5 | It is true that data from the B-20 tamoxifen-only-treated patients were used in the development of the Oncotype DX Recurrence Score and it could theoretically compromise the verification of the prospectively specified hypothesis on the predictive utility of RS for the B-20 study published on JCO in 2006. However, the validation data reported on the New England Journal of Medicine showed consistency, qualitatively and quantitatively, among similar patient population with the same treatment in the NSABP B-14. Looking at the Kaplan-Meier curves in those two papers, any oncologist or statistician cannot just simply cast them away as "not robust evidence". They should read more or ask more about the data if they care. | Thank you for your comment.<br><br>Following consideration of the range of evidence available on this outcome, the Committee considered that the data on the ability of Oncotype DX to predict chemotherapy benefit to be insufficient at this time and have recommended further research. Further details can be found in sections 6 and 7 of the guidance. |
| 31 | Consultee 3: (Health Professional Europe) | 5 | The External Assessment group should omit the Paik et al 2006 study because it has severe flaws with major implications for the outcome of this study. It used 233 samples from the B20 tamoxifen treated arm for training, and used these same samples again in a comparative analysis for the chemotherapy prediction. The re-use of training samples is a methodological flaw and specially in this comparison where the re-use of this arm provides a selective advantage. | Thank you for your comment.<br><br>The purpose of the systematic review in the diagnostics assessment report (DAR) was to undertake a narrative approach to the synthesis of evidence. The report, therefore, provides a summary of the body of evidence including the author's conclusions. The limitations of the study, as considered by the Committee, are described in paragraph 6.5 of the guidance document.<br><br>It is understood that data for the tamoxifen treated patients of the B20 study were used in both the training and validation of Oncotype DX, whereas, data from the B20 tamoxifen plus chemotherapy–treated patients were not |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | | used in the training set. |
| 32 | Consultee 4: (Sponsor - Agendia) | 5 | 5.12: If the committee decides to omit the Knauer data because of the data being pooled, it should also omit the Paik et al data, because of this study being flawed (Symmans, 2012, Oncology; Ioannidis, The Oncologist 2007).<br><br>5.13: The MammaPrint test for formalin-fixed paraffin embedded samples is substantially equivalent to the fresh test; the FDA clearance process is ongoing. Equivalence data in a technical summarizing report can be shared with the committee under confidentiality pending the FDA process.<br><br>5.14: the Paik et al. 2006 should be omitted from the review because of the essential flaw, preferentially influencing the study outcome. | Thank you for your comment.<br><br>The Knauer study was based on pooled analyses of existing studies. The exclusion of pooled studies was done to avoid double counting of studies within the systematic review, that is, Knauer included studies that were already included in the review, not on the basis that there were flaws in the trial design.<br><br>The Committee notes that such data have been submitted to the FDA in section 6.12 of the guidance.<br><br>The purpose of the systematic review in the diagnostics assessment report was to undertake a narrative approach to the synthesis of evidence. The report, therefore, provides a summary of the body of evidence including the author's conclusions. The limitations of the study, as considered by the Committee, are described in paragraph 6.5 of the guidance document.<br><br>It is understood that data for the tamoxifen treated patients of the B20 study were used in both the training and validation of Oncotype |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | | DX, whereas, data from the B20 tamoxifen plus chemotherapy–treated patients were not used in the training set. |
| | | | 5.15: For the one "large-scale UK trial" cited for Oncotype supportive evidence, we would like to point out that a significant association for a 50-point increment is NOT clinically meaningful. Proper Oncotype evidence would only be a significant difference in outcome between the low risk and the intermediate/high patient group (Ioannidis, The Oncologist 2007). | Noted. The clinical significance of Oncotype DX has been explored beyond the 50 point increment using the model which utilised risk classification and risk of distant recurrence data from a re-analysis of the ATAC trial. |
| 33 | Consultee 11: (NHS Professional) | 5 | The UK paper on Oncotype DX usage in the UK is available academic in confidence. In summary: Oncotype DX® testing resulted in changes in chemotherapy decision in 38 of 142 (26.8%) women, with 26 of 57 (45.6%) spared chemotherapy and 12 of 85 (14.1%) requiring chemotherapy when not initially recommended. Decision conflict analysis showed that Oncotype DX® testing increased patients confidence in treatment decision-making. Economic analysis showed that routine Oncotype DX® testing costs £6,232 per quality-adjusted life year gained.<br><br>The trial inclusions were: Women with excised ER positive (Allred score < or = 3/8 by immunohistochemistry IHC) and node negative (pN0 or pN0i+) invasive breast cancer, or with minimal node involvement (pN1mic) were identified at the multidisciplinary team (MDT) meetings as being | Thank you for your comment.<br><br>At the time of the systematic review conducted by the External Assessment group, only the original poster/abstract of the interim results of the Holt study was available which included 106 patients. The subsequent abstract referred to 142 patients. For the economic model, the full dataset (142 patients) was available and used. The guidance has been updated to reflect this. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | suitable for testing even if initial assessment suggested they were at very low risk of recurrence. Please contact simon.holt@wales.nhs.uk for the full text. | |
| 34 | Consultee 10: (NHS Professional) | 5 | 5.16 "3 of the 4 individual tests that make up IHC4 (ER, PR and HER2) are commonly used in the NHS." - this is factually incorrect as PR is now not performed as not recommended by NICE. ER testing in IHC4 requires H-score, this is not performed in the vast majority of pathology labs and takes significantly more pathologist time to perform than Allred score or % score. The performance of an H-score needs to be factored into the financial analysis.<br><br>5.24 I have serious concerns with the methodology of testing IHC4 using assumptions from ODX. If the data do not exist for IHC4 independently then that is the end of the story and no further testing should be done. It is not at all clear why the chemotherapy usage figures are so disparate between ODX and IHC 4 when you have used one to inform on the other! All clinical utility studies have shown less | Thank you for your comment.<br><br>Accepted. The guidance has been updated.<br><br>It is acknowledged within the diagnostics assessment report that there is a lack of robust estimates on the additional cost associated with performing IHC4 (quantitative assessment of ER, PR and Ki67). The developer of IHC4 was contacted and an estimate of £100-£200 was given to cover the additional cost associated with IHC4 compared with tests currently used in clinical practice. A cost of £150 was used in the model and accepted by the Committee (it thought the cost was likely to be lower). An additional cost of £400 was used in the sensitivity analysis for the model.<br><br>For the IHC4 analysis, patients are first classified according to the Oncotype DX test, then within each OncotypeDX risk groups (low, intermediate, high), patients are further classified using the IHC4 test into low, intermediate and high. Given that we have some information about the prognosis profile of patients within the broader group category (according to Oncotype DX), we assumed that |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | chemo use with ODX, explain why you see more. | patients within a pre-defined Oncotype DX risk group (low, intermediate, high) would have the same prognosis whether classified at low, intermediate or high with IHC4.<br><br>Therefore, data from OncotypeDX have not been directly used to inform the IHC4 analysis (except for the probability of receiving chemo depending on the results of the test) but used indirectly.<br><br>Furthermore, because patients are classified differently with Oncotype DX and IHC4 (that is, within the low risk group with OncotypeDX some patients may be classified at high risk with IHC4 for instance), the proportion of patients receiving chemotherapy is expected to be different between the 2 tests.<br><br>Whilst most clinical studies showed a reduction in the number of patients receiving chemotherapy with OncotypeDX, most of these studies assumed a higher baseline level of chemotherapy within clinical practice compared with what was observed in cancer registries in the UK. |
| | | | Using a NPI of 3.4 but limiting to LN-ve patients is flawed. This excludes all G3 T1 tumours and only includes G2 tumours >7 cms. A true intermediate risk group consists of G3 T1 and G2 T2 but excludes | The focus of the External Assessment Group analysis was in the ER+ve, LN-ve population. NPI> 3.4 was used as a proxy for intermediate risk in this LN-ve population. The aim of this subgroup analysis was to explore whether |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | all G1 and G2 T1. NPI is not helpful if you leave out 1 of the 3 constituent parts. | using the test in a particular subgroup of patients may be more cost-effective. The limitation of using NPI>3.4 is acknowledged in the diagnostics assessment report. The role of these tests in other populations, including patients with LN +ve early breast cancer is an important question and should be the subject of future research. A health economic evaluation is planned as part of the OPTIMA trial (J Clin Oncol 30, 2012 (suppl; abstr TPS665). The current evaluation does not preclude a NICE evaluation in the future concerning people with LN+ breast cancer. |
| 35 | Consultee 9: Royal College of Pathologists (Health Professional Organisation) | 5 | There have been no validations of local testing/application of Ki67 (as identified on page 21). | Thank you for your comment. |
| | | | There are currently no universally accepted cut-offs for Ki-67 evaluation. Validation of local testing/application of Ki-67 is the step that is obviously most urgently needed and perhaps ought to be one of the recommendations of this document. | Noted. The Committee agrees and has recommended further research on IHC4, including research on the reliability and reproducibility of IHC4 when performed in local laboratories. The Committee understands that a UK NEQAS is being investigated for the Ki 67 marker. |
| | | | On page 24 is suggests that PR is undertaken routinely (and therefore not included in costs) - the NICE Early Cancer Guidelines contradict this and do not suggest testing for PR. | Accepted. The guidance has been updated. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | On page 32, there is an assumption that there are not additional NHS costs for the use of fresh tissue samples. This is naive and fresh tissue sampling is actually very expensive. | A cost of £250 was included in the economic analysis for dealing with a fresh tissue sample. This is detailed in section 5.5.5.3 and Table 43 of the diagnostics assessment report. |
| 36 | Consultee 12: (Sponsor - Clarient) | 5 | According to the EAG (pg 225 EAG report), changing the chemotherapy treatment decision following Mammostrat varied the ICER, particularly for the chemotherapy treatment decision following a Medium Risk result. The base case values assumed for the chemotherapy treatment decision are not clear in the EAG?s analysis so we cannot determine whether Mammostrat was evaluated appropriately. Considering the ICER's sensitivity to this input, additional clarity is required. | Thank you for your comment.<br><br>Data on chemotherapy treatment decision are crucial. The External Assessment Group used data from the Holt study in the basecase (submitted to NICE as academic in confidence) as this was the best UK data available on chemotherapy treatment decision based on a GEP/expanded IHC test.<br><br>The External Assessment Group implicitly assumed that results of any GEP test would be interpreted the same way (that is, the probability of receiving chemotherapy if classified as high risk would be same whether classified with OncotypeDX or Mammostrat).<br><br>As data from the Holt study were submitted academic in confidence, it was not possible to provide a description of the values used for the basecase. However, a sensitivity analysis was conducted assuming 0% for low, 50% for intermediate and 100% for high.<br>These data have since been published and are now released in the diagnostics assessment report. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | In the EAG analysis, risk of recurrence for Mammostrat was derived from a subset of patients from Ring et al (2006) and personal communication on the ATAC trial which was submitted as Commercial-in-Confidence. Combining these data may not produce an accurate reflection of Mammostrat's prognostic ability; using an alternate published source of data for this input may improve robustness of the analysis. | The External Assessment group agrees that combining data from different sources may generate biases. However, alternative robust data were not identified. |
| 37 | Consultee 14: (Sponsor - Clarient) | 5 | Due to gaps in the currently available clinical evidence for Mammostrat the External Assessment Group was only able to complete an 'exploratory' cost-effectiveness analysis using a number of assumptions which may have undervalued the clinical utility of Mammostrat. NICE's draft recommendations support GE/Clarient's on-going clinical validation programme for Mammostrat to establish the health benefits which accrue to breast cancer patients following testing with Mammostrat.<br><br>Assumptions were made in the EAG analysis for clinical inputs which impact the cost-effectiveness of Mammostrat, which may have caused the clinical utility of Mammostrat to be undervalued. A recurrence-free survival benefit was not given for the Mammostrat Medium Risk group in the EAG model. In the B20 NSABP cohort (Ross et al, 2008), Low Risk patients experienced a 5% absolute increase in distant recurrence-free survival by adding cytotoxic | Thank you for your comment.<br><br>The External Assessment Group disagrees with this comment. The benefit of chemotherapy was taken from the Ross study which showed a benefit for patients classified at low (HR: 0.4) and high risk (HR: 0.4) with Mammostrat. It was reported that no statistical significant benefit was observed for patients at intermediate risk and the HR was not reported.<br><br>The External Assessment Group assumed no benefit (or disbenefit) for chemo for this subgroup of patients. The External Assessment Group agrees that additional study of the benefits and risks of chemotherapy in these intermediate risk patients is needed. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | chemotherapy and High Risk patients were observed to experience an absolute increase of 21%. The additional benefit of chemotherapy for Medium Risk patients was inconclusive due to under-powering of the sample. Uncertainty for the Intermediate Risk Group using Oncotype was also observed in the B20 NSABP cohort (Paik et al, 2006): 'for women with intermediate RSs, it is uncertain that the benefits of chemotherapy exceed the risks. Additional study of the benefits and risks of chemotherapy in this middle range of patients is needed.' Although the benefit of chemotherapy benefit in the Intermediate Risk group has been generally questioned only in the Mammostrat analysis was this benefit excluded from the base case. This creates bias against Mammostrat and undervalues its benefit to clinical decision-making. | |
| 38 | Consultee 4: (Sponsor – Agendia) | 5 | BECAUSE LACK OF SPACE UNDER 5:<br><br>5.5 Agendia submitted data for evidence on cost effectiveness in the previous round; why has this not been taken into account?<br><br>We would like to know what studies are being referred to in the following sentence in order to properly judge this information (for we disagree with it and would urge the committee to review this data):<br><br>5.10 A range of studies provided evidence on the | Thank you for your comment.<br><br>This evidence has been considered previously by the External Assessment group and the Committee. However, the lack of detailed methodology did not allow a clear assessment of the quality of the evaluation. Section 6.13 of the guidance has been updated to reflect this.<br><br>The studies being referred to have been |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | prognostic ability of MammaPrint in heterogeneous populations. However, the previous systematic reviews indicated that evidence relating to the clinical validity of MammaPrint was not always conclusive nor supported the prognostic value of the test.<br><br>Also, the next sentence mentions a retrospective study demonstrating impact on clinical decision making. This actually is a prospective study on MammaPrint for clinical decision making, the first ever to have been presented with 5 year outcome data at EBCC this year. And the increase of number of patients receiving adjuvant treatment is merely what would have been expected provided the extremely stringent Dutch recommendations for adjuvant treatment at that time. | summarised in section 4.2.4 of the diagnostics assessment report (in particular, prognostic ability refers to data on clinical validity). The sentence “The evidence relating to the clinical validity of MammaPrint® was not always conclusive nor supported the prognostic value of the test.” was taken from a previous systematic review by Smartt (2009) – p63, paragraph 5.<br><br>Agreed – this sentence will be amended to indicate that this is a prospective study, as outlined in section 4.2.1 of the diagnostics assessment report.<br><br>The Committee are satisfied with the External Assessment Group’s review of the data as summarised in section 5 of the guidance.<br><br>RASTER study – see appendix 1 for the External Assessment Group analysis of the RASTER study. Committee considerations of the study can be found in section 6 of the guidance. |
| 39 | Consultee 4: (Sponsor – Agendia) | 5 | 5.11: A preferential disliking for MammaPrint can be read from unnecessary additions like "did not identify any prospective studies": none of the tests have this.<br><br>Also, MammaPrint has many studies with overall survival, no preferential difference should be made with Oncotype. | Thank you for your comment.<br><br>The External Assessment Group did not identify prospective studies on the impact of the tests on long term outcomes. The sentence ‘The External Assessment Group did not identify any prospective studies of the impact |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | | of Mammostrat on long-term outcomes such as overall survival.' Has been used in the clinical effectiveness sections for all four tests.<br><br>The data have been judged on individual merit but described, in places, in comparison to other tests. |
| | | | We disagree that "most of the MammaPrint evidence relates to outcome at 5 years": most relates to 10 years or more. | Noted. The guidance document has been amended to 'A mix of evidence exists for outcomes at 5 and 10 years.' |
| | | | Also, the most important study on clinical utility of MammaPrint (RASTER) is not cited under 5.11. | The original reference to the RASTER study was included in the previous systematic review by Smartt. Section 5 of the guidance document has been updated to reflect this.<br><br>RASTER study – see appendix 1 for the External Assessment Group analysis of the RASTER study. Committee considerations of the study can be found in section 6 of the guidance. |
| | | | 5.15: Preferential review can also be inferred from how 'four studies present further evidence on clinical decision-making'. As if it is the number of studies that determine these; one would hope that number of patients and study design are more important. Another example is the mentioning of 4 recent | The purpose of the systematic review in the diagnostics assessment report was to undertake a narrative approach to the synthesis of evidence. The report, therefore, provides a summary of the body of evidence |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | publications on benefit from chemotherapy, whereas 3 of the 4 have used previous samples. The committee should omit these studies from this document.<br><br>So we disagree with 'a broad evidence base for Oncotype (5.15)' versus 'robust evidence of clinical utility for MammaPrint not available (5.13)'. | including the author's conclusions. The diagnostics assessment report and guidance highlight that of the four citations, three use the same trial data.<br><br>Section 5.15 of the guidance document has been amended to '. . .Oncotype DX is considered to have the most robust evidence base, of the tests reviewed in this guidance, with data on . . .'. |
| 40 | Consultee 4: (Sponsor – Agendia) | 5 | Please note that the MammaPrint platform also reports out ER, PR and HER2 status (TargetPrint), as well as Molecular Subtyping (BluePrint).<br><br>Also please note that Oncotype uses 5 of the 21 genes for normalization. MammaPrint is a 70-gene profile with hundreds of normalization genes.<br><br>BECAUSE LACK OF SPACE UNDER 5:<br><br>5.28: Where are the percentages coming from? | Thank you for your comment.<br><br>We understand that these tests (TargetPrint and BluePrint) are separate to MammaPrint. All of these tests are part of the Symphony range offered by Agendia.<br><br>Comment noted.<br><br>This is an output from the External |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | 19.11% of patients receiving chemotherapy with Oncotype does not seem representative of their test, which stratifies 50% of patients as intermediate/high risk. Cost effectiveness is relatively easy to achieve with such a low base line % of CT receiving patients. | Assessment Group economic model after combining evidence on risk reclassification and likelihood of receiving chemotherapy according to the risk group.<br><br>The economic model was constructed to specifically address the decision problem for this evaluation. |
| 41 | Consultee 8: (NHS Professional) | 5 | UHNS experience is small. Where AOL or Predict show a definite indication for chemotherapy, there is no perceived need for further investigations. For patients with slightly less potential benefit, extra information may affect management. 13 patients have been tested with Oncotype DX. None were in the high recurrence score, 5 were intermediate (one patient chose to have chemotherapy) 8 were in the low recurrence score group. 92% of this selected group avoided chemotherapy. I do not have figures for the numbers (substantial) where the MDT would have liked Oncotype DX before recommending chemotherapy. We strongly support use of Oncotype DX for selected groups of node negative ER+ve patients. | Thank you for your comment.<br><br>The Committee found that Oncotype DX was a clinically effective (based on its ability to predict prognosis but not chemotherapy benefit) and cost-effective (at the revised confidential price used in the access proposal) use of NHS resources in patients deemed to be at intermediate risk of distant recurrence. Therefore, the technology has been recommended for adoption in this patient group – please refer to section 1 of the guidance. |
| 42 | Consultee 6: (Patient Representative) | 5 | In the second analysis, the patient population was restricted to those that had a NPI of 3.4 or greater. If this criteria was to be implemented the available evidence would need to ensure that this did not exclude any patients that may benefit from any of these tests. This could be particularly important for a test that reallocates more women to chemotherapy compared to standard practice, as the NPI>3.4 criteria may exclude some women who are thought | Thank you for your comment.<br><br>The Committee has considered this issue when formulating their recommendations.<br><br>The Committee found that Oncotype DX was both clinically and cost effective in patients deemed to be at intermediate risk only and, therefore, was only able to recommend the test |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | to have a very low risk of recurrence, who may actually gain benefit from chemotherapy. | for this particular population. |
| 43 | Consultee 1: (Sponsor - Genomic Health) | 5.15 | The recommendation mistakenly states that the UK decision impact study by Holt et al. included 106 patients. The correct number is 142.<br><br>It is also incorrectly stated that there were limitations due to study design and that the generalisabilty was limited because it lacked a description of how treatment decisions were made. We previously submitted (and attach again in Annex II) the complete study protocol which was approved by the Ethics Committee and R&D committees at the study sites and which makes clear how treatment decisions were made. It would therefore be helpful if NICE could explain what exactly is meant by "limitations in relation to the study design were identified by the Committee". | Thank you for your comment.<br><br>At the time of the systematic review conducted by the External Assessment Group, only the original poster/abstract of the interim results of the Holt study was available which included 106 patients. The subsequent abstract referred to 142 patients. For the economic model, the full dataset (142 patients) was available and used. The guidance has been updated to reflect this.<br><br>The section of the sentence …. " because it lacked a description of how treatment decisions were made" has been deleted in section 5.15 of the guidance.<br>The External Assessment Group had concerns that patients may not be representative of patients seen in clinical practice in England. In section 5.5.5.4 of the diagnostics assessment report, the NPI distribution of patients included in the Holt study (2011) was compared with the NPI distribution of patients from two registries (ECRIC and WMCIU) and showed that patients included in the Holt study were more severe – with larger tumours and a higher proportion of grade 2 and 3 tumours (analysis conducted by External Assessment Group). In addition the proportion of patients that are recommended |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | | for chemotherapy in the Holt study appears to be high compared with the proportion of patients that are offered chemotherapy based on data from two cancer registries in England and Wales (section 5.5.5.4 of the diagnostics assessment report). |
| | | | Furthermore, it's incorrectly stated that the majority of the Onco*type* DX studies were small and retrospective. It would be fair to point out that 5 validation studies with between 367 and 1231 patients have been performed with Onco*type* DX. Importantly, they have all reached their primary endpoint with statistical significance, which demonstrates that the studies were of sufficient size (see 5.9). The studies have consistently been prospectively designed with pre-specified statistical analysis plans and the assays have been performed completely blinded to the clinical data (see 5.8). | Whilst the majority of the clinical validation studies (that used archival samples from previously conducted RCTs – TransATAC [Dowsett et al., 2010], and subgroups from the NSABP B-14, and NSABP-20 trials [Mamounas et al., 2010; Tang et al., 2011]) analysed relatively large cohorts (sample size >1000 participants), a large proportion of the other Oncotype DX studies had small sample sizes for assessing analytical validity and clinical utility.<br><br>Section 5.8 of the guidance has been updated to include studies that are prospectively designed to analyse archival specimens.<br><br>Although the concept of undertaking a prospective analysis of retrospective clinical data (i.e. use of archival samples from a previously conducted RCTs) is well established (Simon et al., 2009), its scientific validity remains controversial (Wang et al. 2006, 2008; Ahern & Hankinson, 2011) e.g. confounding |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | | and biases related to the completeness of ascertaining biological specimens (including quality, missing data, diagnostic criteria etc.), possibility that iterative discovery from a retrospective source might necessitate correction for multiple testing, data from well conducted, high quality RCTs should be available particularly for a large number of patients to avoid selection bias, and analysis should be pre-defined.<br><br>References<br>Ahern TP, Hankinson SE. Re: Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2011 Oct 19;103(20):1558-9;<br><br>Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2009 Nov 4;101(21):1446-52. Epub 2009 Oct 8.<br><br>Wang SJ, Cohen N, Katz DA, et al. Retrospective validation of genomic biomarkers—what are the questions, challenges and strategies for developing useful relationships to clinical outcomes—workshop summary. Pharmacogenomics J 2006;6:82–8.<br><br>Wang SJ. Utility of adaptive strategy and adaptive design for biomarker-facilitated patient selection in pharmacogenomic or |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | | pharmacogenetic clinical development program. J Formos Med Assoc. 2008 Dec;107(12 Suppl):19-27. |
| | | | NICE does not conclude, as it does for the other tests, on the type of evidence needed for Onco*type* DX. NICE should clearly state what evidence (if any) is needed for Onco*type* DX. Many UK physicians have commented that they could not participate in additional research in the node negative patient population due to ethical concerns regarding the appropriateness of conducting such research given the sufficiency of the body of evidence validating the Onco*type* DX test in this specific group. It would therefore be important to specify, as was done for the other tests, what additional research should be conducted. | Please refer to section 7 (Research recommendations) of the guidance. Considerations leading to the research recommendations are captured in section 6 of the guidance. |
| 44 | Consultee 1: (Sponsor - Genomic Health) | 5.16 | With regard to IHC4, it should be pointed out that the same study material (transATAC) was used for both development and validation of the assay. Therefore the need for a representative external validation cohort is of high importance. In fact, more than 50% of the patients in the external validation cohort did not receive 5 years of endocrine treatment (Cuzick et al, J Clin Oncol 2011); such patients are not representative of the target patient population. It should also be pointed out that another external validation study has now been reported in the large TEAM study and the risk of recurrence at 8 years for low risk (lower quartile) by IHC4 was quite high (12%)(Christiansen et. Al. J Clinical Oncology 30, | Thank you for your comment.<br><br>These points are noted. Committee considerations of IHC4 in sections 6.9 and 6.10 of the guidance have been updated following Committee discussion. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | 2012 (suppl; abstr517)), and very different in the TEAM study compared to transATAC and this is a great concern. Two different methodologies for IHC4 assessment were also tested and importantly the correlation between these methods was modest (0.65) (Christiansen et al. J Clin Oncol 30, 2012 (suppl; abstr 517) – see figures below). In contrast, Onco*type* DX in the node negative setting has consistently identified approximately 50% of patients (twice as many as those in the lowest quartile) as having an extremely low risk of recurrence and the 10-year risks of distant recurrence in these studies have consistently been in the range of 3-7% (NSABP B-14, transATAC, Kaiser Permanente (reported only breast cancer specific mortality (3.3%)). | |
| 45 | Consultee 1: (Sponsor - Genomic Health) | 5.24 | With regard to cost effectiveness, in the last sentence of paragraph 5.24, it is stated that the cost effectiveness model for IHC4 is based on "various assumptions that, due to the absence of data for IHC4," are based on data for the Recurrence Score. Importantly, the pairwise correlation of IHC4 and the Recurrence Score was only 0.7, which is insufficient for extrapolating results for the Recurrence Score to IHC4. For a decision as important as that of whether to treat or not with chemotherapy a much higher correlation is needed in order to extrapolate data from one test to another. Simply assuming that the IHC4 is reproducible is not based on evidence since no study has shown that the test was validated analytically and could be reproduced in different laboratories and therefore the conclusion lacks any | Thank you for your comment.<br><br>The Committee has recommended further research on IHC4, including research on the reliability and reproducibility of IHC4 when performed in local laboratories. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | evidentiary support. | |
| 46 | Consultee 1: (Sponsor - Genomic Health) | 5.28 | From the perspective of the health economic analysis, it is noteworthy that the Onco*type* DX assay is supported by substantially more data (including UK-specific data) than any of the other tests under assessment. This fact is acknowledged in the consultation document (Sections 5.14 and 6.1). However, the approach to the independent modeling analysis introduced much uncertainty by making assumptions on the Onco*type* DX Recurrence Scores (low, intermediate or high) to be applied to the modeled population (i.e. ECRIC registry population). The evaluation group did not perform any sensitivity analyses on these assumptions directly, but noted that when UK-specific data was introduced from the Holt *et al*. study then the cost-effectiveness of Onco*type* DX improved substantially versus current clinical practice.<br><br>In the modeling analysis, it was assumed that the same percentages of patients would have low, intermediate and high Recurrence Scores as observed in the population of the ATAC study. This raises a number of concerns:<br>• ATAC represents a selected population that could be considered at low risk of distant recurrence (this has the potential to bias against the diagnostic tests) by classical | Thank you for your comment.<br><br>The External Assessment Group had concerns with the generalisability of the Holt study. Additionally the External Assessment Group used data from the ATAC trial as this provided data on both the risk reclassification and risk of recurrence from the same source (as these 2 parameters are correlated).<br>No sensitivity analysis was directly conducted varying the risk reclassification on its own, as there is a correlation between the risk reclassification and risk of recurrence; therefore the External Assessment Group believes that performing such analysis (varying the risk reclassification on its own) may be misleading.<br>These comments are however noted by the External Assessment Group.<br><br>This limitation is acknowledged by the External Assessment Group.<br>An alternative source for the risk of recurrence associated with endocrine therapy was the Paik et al. (2006) NSABP B-20 study of Oncotype DX was considered. However this study also has limitations. The population in the Paik study differs from the population in the External Assessment Group model and is higher risk - it is a younger population (44% |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | clinical and pathological parameters because patients participating in this study did not receive chemotherapy. | were less than 50yrs) and includes HER2+ patients. In addition all patients received tamoxifen rather than other hormonal therapies such as aromatase inhibitors. |
| | | | • The assumption that the distribution of Recurrence Scores would be the same in the modeled population, based on comparable characteristics in the ATAC and model populations, is fundamentally flawed and has no evidence to support it. The model is highly sensitive to changes in this assumption (e.g. 10% changes in patients allocated low, intermediate or high Recurrence Score can dramatically alter the ICER for Onco*type* DX versus current practice in the MS Excel model), yet no sensitivity analysis to investigate this point has been performed by the evaluation group. | No sensitivity analysis was directly conducted varying the risk reclassification on its own, as there is a correlation between the risk reclassification and risk of recurrence; therefore the External Assessment Group believes that performing such analysis (varying the risk reclassification on its own) may be misleading |
| | | | • As a result of this approach (using ATAC data), the modeling analysis based the 10-year risk of recurrence on very small numbers of ATAC patients (**fewer than 10 in several cases** as highlighted in Tables 51 & 52 of the assessment report) due to the divisions in the population by NPI score, Onco*type* DX Recurrence Score and ICH4 | This limitation is acknowledged in the diagnostics assessment report. The External Assessment Group also conducted an analysis excluding the split by NPI subgroup and excluding IHC4 which provided larger sample sizes, which showed limited impact on the results. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | risk. Again, the model is highly sensitive to these assumptions.<br><br>Sensitivity analysis has shown that a 20% relative increase in the risk of recurrence (for all risk groups) can reduce the ICER for Onco*type* DX versus current practice by approximately £4,500 per QALY gained.<br><br>The technology assessment report describes the registry data used to define the population for the modeling analysis. The population is selected as women with ER+, LN−, HER2− early stage breast cancer (stage I or II) aged less than 75 years at diagnosis. The decision to use registry data, thereby selecting a population for whom there were no Onco*type* DX test results (or IHC4 test results), raises some critical questions:<br><br>1. Why was the population limited to LN− patients (and stage I or II patients) for the cost-effectiveness evaluation of Onco*type* DX versus clinical practice? There is data on Onco*type* DX testing in broader patient populations (e.g. the data reported by Holt *et al.* from ER+, pN0 or pN1(mic) early breast cancer patients who have no contraindications for adjuvant chemotherapy) and UK physicians use the test in patients for whom the benefit of chemotherapy remains unclear with traditional criteria (see comment | The External Assessment Group agrees that this is an uncertainty and explored this in sensitivity analysis. It should be noted that these data were not available from the Holt study.<br><br>This subgroup was selected to be the focus of the economic analysis after review of the evidence available, the indications of the tests and discussion with clinical experts. Patients with HER2 + early breast cancer or with positive nodes were not considered in this assessment, due to time and resource constraints. Evidence for this population is developing and should be the subject of future research. The current assessment does not preclude a NICE assessment in patients with HER2+ or LN+ disease in the future. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | on paragraph 6.3) | |
| | | | 2. Why was an age limit applied to the population rather than selecting patients who did not have contraindications to chemotherapy? | An age limit was applied as a proxy for contraindications to chemotherapy. The External Assessment Group acknowledges the limitation with this approach. The proportion of patients receiving chemotherapy over the age of 75 is much lower than in younger age groups. Decisions in this older patient group will take account of more complex factors than just risk of recurrence alone. The scope for the Oncotype DX test to change patient management may therefore be more limited in this population. |
| | | | 3. Why were the 800 patients with unknown HER2 status from the ECRIC registry included (rather than excluded on this basis)? | The majority of these patients were expected to be HER2 negative. |
| | | | Points 1 and 2 (above) have the potential to create a selection bias in the population towards a particularly low risk subset explaining the very low usage of chemotherapy in this registry population (see comment on section 4.8). A cost-effectiveness evaluation in an artificially low risk population will be biased against the tests under evaluation. As indicated in paragraph 1.1, Onco*type* DX will be most cost-effective in the UK if used in the appropriate group of patients. The modeled population from the registry certainly doesn't reflect | The Committee found that Oncotype DX was a clinically effective (based on its ability to predict prognosis but not chemotherapy benefit) and cost-effective (at the revised confidential price used in the access proposal) use of NHS resources in patients deemed to be at intermediate risk of distant recurrence. Therefore, the technology has been recommended for adoption in this patient group – please refer to section 1 of the |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | this population where Onco*type* DX is most cost-effective. We would like to re-open the discussion with NICE regarding patient access schemes to make Onco*type* DX available for those patients who need it the most. | guidance. |
| 47 | Consultee 1: (Sponsor - Genomic Health) | 5.29 | The modelling analysis assumes equivalent 'effectiveness' (in modelling terms) for the IHC4 test as with Onco*type* DX despite there being little or no evidence to support this approach. NICE should identify the facts and basis upon which the cost effectiveness for IHC4 is stated. As highlighted earlier (see paragraph 5.24), the level and weight of evidence supporting these tests are very different and can't justify such an assumption. | Thank you for your comment.<br><br>The External Assessment Group does not assume equivalent effectiveness.<br><br>For clarity, IHC4 does not have evidence on its predictive ability. In the External Assessment Group's economic model the Oncotype DX risk group and the IHC4 risk group allocated to each patient is known. In the IHC4 analysis the benefit of chemotherapy is applied according to the Oncotype DX classification. So, in the IHC4 analysis, the IHC4 test result was used to determine if the patient will receive chemotherapy or not, but the Oncotype DX test result to determine their response to chemotherapy. This means that each patient is assumed to derive the same benefit of chemotherapy whether identified by Oncotype DX or IHC4, (but the different tests may categorise them differently in terms of risk and will therefore influence whether or not they receive chemotherapy in the first place). A sensitivity analysis assuming no predictive ability was undertaken and IHC4 remained cost saving. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | Given that a cost-effectiveness analysis is simply a method of balancing costs and effects for a given intervention, and the estimated cost of the IHC4 test is £100-200, then the outcome of the analysis between these two tests is a foregone conclusion. From the perspective of a cost-effectiveness evaluation (which can be considered an evaluation of the balance between costs and effectiveness), the assumption of "equivalent effectiveness" for IHC4 in relation to Onco*type* DX (particularly with regard to predicting chemotherapy benefit) is not supported by the data (see below). The nature of the analysis linking the performance of Onco*type* DX and IHC4 is far from clear in the technology assessment report and remains largely unpublished, but it is noteworthy that these assumptions have a huge bearing on the relative outcomes of the cost-effectiveness analysis. Indeed:<br>• The evidence relating the performance of IHC4 to Onco*type* DX is based on the ATAC trial, which as well as being from a selected population, is unpublished, is not described in the ScHARR report (on page 186 of the technology assessment report: *An overview of this evidence was presented in Cuzick et al. 2011.[75] However, the specific evidence used in the economic model for IHC4 was unpublished and was made available to the EAG for the purpose of this assessment [Personal Communication, September 2011, Professor Jack Cuzick, Queen Mary* | Limitations of using the ATAC study are highlighted in the diagnostics assessment report, but this was considered to the best source of data available, as this provided data on both risk reclassification and risk of recurrence from a UK source.<br><br>This limitation of small numbers is acknowledged in the diagnostics assessment report. The External Assessment Group also conducted an analysis excluding splitting the population by NPI and excluding IHC4 which provided a larger sample size, and showed |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | *University of London])*and is often based on very small numbers of patients (**fewer than 10 in several cases** as highlighted in Tables 51 & 52 of the assessment report). There is no way to assess whether the assumptions applied in the modeling analysis relating the performance of IHC4 to Onco*type* DX are reasonable when it is known that the pairwise correlation between both tests is only moderate (see comment on paragraph 5.24). Is it reasonable to evaluate the cost-effectiveness of IHC4 (and how it relates to Onco*type* DX) on this basis? | limited impact on the results. |
| | | | • Onco*type* DX is the only test in the assessment that has evidence of the ability to predict the magnitude of chemotherapy benefit (in patients with low, intermediate and high Recurrence Scores) as acknowledged on page 193 of the technology assessment report. It was assumed by the modelers that, in the absence of any evidence on prediction, that IHC4 would predict the magnitude of chemotherapy benefit in same way as Onco*type* DX (page 193). The modelers concede that "*it is not possible to ascertain the potential bias of such assumption*" but also speculate that it will be conservative. This is a bold assumption, with no basis in clinical evidence that is not properly investigated in sensitivity analyses. Given | Please see comments above.<br><br>A sensitivity analysis assuming no predictive ability was undertaken and IHC4 remained cost saving compared with current clinical practice. Therefore, the External Assessment Group does not believe this is a 'serious limitation' in the modelling analysis. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | that this is a key feature in the comparison of Onco*type* DX and IHC4, we contend that this represents a serious limitation in the modeling analysis. | |
| 48 | Consultee 1: (Sponsor - Genomic Health) | 5.32 | Analysis of the PSA results indicates that by introducing sampling from distributions into the analysis, the modellers have introduced some form of skew into the distribution of the cost-effectiveness results. This is evident in the base case analysis, but perhaps more so in the sub-group analysis of patients with NPI >3.4.<br>• In the PSA on the NPI >3.4 sub-group, the mean ICER reported is £9,774 per QALY gained. It is reasonable to expect that this value would be close to the median in a distribution of ICER values (and as a result, we could expect perhaps 40-60% of iterations to fall below a willingness to pay threshold of £10,000 per QALY gained). The modeler's report that at a higher willingness to pay of £20,000 per QALY gained, only 18.6% of iterations were below the threshold. This represents a significant skew in cost-effectiveness results for Onco*type* DX versus routine care that has not been addressed in the report by the modelers.<br><br>The distributions used in the PSA (particularly the | Thank you for your comment.<br><br>The External Assessment Group disagrees with this comment. From the diagnostics assessment report:<br>"The incremental cost for treatment guided using OncotypeDX was £9,774 per QALY gained compared with current clinical practice and £31,125 compared with IHC4 ….."<br>" The probability for treatment guided using OncotypeDX to be cost effective at a £20,000 threshold was 18.60% when compared in the incremental analysis and 91.56% when compared with current clinical practice alone."<br><br>It is clear from this text that the 18.6% probability referred to the analysis against IHC4 (not clinical practice) where the mean ICER was £31,125 (hence a low probability of being cost-effective at a threshold of £20K. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | Dirichlet distributions, which are generated by VBA code to assign patients to low, intermediate and high risk groups) have not been adequately defined in the modelling report, so it is difficult to understand what might be driving this apparent skew. Additional information on these distributions should be provided. | |
| 49 | Consultee 1: (Sponsor - Genomic Health) | 5.8 | It is stated that potential issues remain with prospective analysis of retrospective archived tissues; including "the effect of confounding and the possible incompleteness of some biological specimens." Prospectively-designed studies of archival materials from previously conducted prospective controlled trials can generate level 1-evidence - this is a concept that is well established in the scientific community (Simon RM et al, JNCI 2009) and also a concept that NICE has previously accepted in making a positive recommendation for KRAS testing in colon cancer. The studies have consistently been prospectively designed with pre-specified statistical analysis plans and the assays were performed completely blinded to the clinical data. The archival samples studied in the majority of the validation studies were from prospective randomized trials with long term follow up. This approach is very different from a traditional retrospective analysis which is exploratory and subject to numerous biases. A scientifically correct terminology for the type of study designs that have been used for the validation of Onco*type* DX would be: prospectively designed studies using archival specimens. | Thank you for your comment.<br><br>Section 5.8 of the guidance has been updated to include studies that are prospectively designed to analyse archival specimens.<br><br>Although the concept of undertaking a prospective analysis of retrospective clinical data (i.e. use of archival samples from a previously conducted RCTs) is well established (Simon et al., 2009), its scientific validity remains controversial (Wang et al. 2006, 2008; Ahern & Hankinson, 2011) e.g. confounding and biases related to the completeness of ascertaining biological specimens (including quality, missing data, diagnostic criteria etc.), possibility that iterative discovery from a retrospective source might necessitate correction for multiple testing, data from well conducted, high quality RCTs should be available particularly for a large number of patients to avoid selection bias, and analysis |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | | should be pre-defined.<br><br>References<br><br>Ahern TP, Hankinson SE. Re: Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2011 Oct 19;103(20):1558-9;<br><br>Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2009 Nov 4;101(21):1446-52. Epub 2009 Oct 8.<br><br>Wang SJ, Cohen N, Katz DA, et al. Retrospective validation of genomic biomarkers—what are the questions, challenges and strategies for developing useful relationships to clinical outcomes—workshop summary. Pharmacogenomics J 2006;6:82–8.<br><br>Wang SJ. Utility of adaptive strategy and adaptive design for biomarker-facilitated patient selection in pharmacogenomic or pharmacogenetic clinical development program. J Formos Med Assoc. 2008 Dec;107(12 Suppl):19-27. |
| 50 | Consultee 1: (Sponsor - Genomic Health) | 5.9 | It is stated that some studies supporting the Recurrence Score were of smaller sample size. It would be fair to point out that 5 validation studies with between 367 and 1231 patients each have been | Thank you for your comment.<br><br>Whilst the majority of the clinical validation studies (that used archival samples from |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | performed with Onco*type* DX. Importantly**, <u>they have all yielded statistically significant results</u>,** thereby demonstrating that these studies were of sufficient size. | previously conducted RCTs – TransATAC [Dowsett et al., 2010], and subgroups from the NSABP B-14, and NSABP-20 trials [Mamounas et al., 2010; Tang et al., 2011]) analysed relatively large cohorts (sample size >1000 participants), a large proportion of the other Oncotype DX studies had small sample sizes for assessing analytical validity and clinical utility. |
| 51 | Consultee 6: (Patient Representative) | 6 | No comment | Thank you for your comment. |
| 52 | Consultee 10: (NHS Professional) | 6 | It is very difficult to see where you derive the assertion that the Relative Risk Reduction with chemo is the same in the different recurrence score cohorts. Albain study clearly shows no benefit, and indeed potential harm in the low RS group. The absolute and relative benefits are confined to intermediate and high RS groups. The same is true for B14 and B20 studies but the issues with validation and test sets are accepted. NSABP B28 study shows no benefit for addition of taxane in the low RS group also and 2 studies show no pCR in RS<24. This test has predictive value. | Thank you for your comment.<br><br>Following consideration of the range of evidence available on this outcome, the Committee considered that the data on the ability of Oncotype DX to predict chemotherapy benefit to be insufficient at this time and have recommended further research. Further details can be found in sections 6 and 7 of the guidance. |
| 53 | Consultee 5: (University Faculty) | 6 | As reported in my publications, I concluded then and continue to believe based on the additional evidence that has been developed over the past 5 years that the Oncotype DX Recurrence Score is both prognostic of distant recurrence and predictive of chemotherapy benefit in node negative, ER+ breast cancer. | Thank you for your comment.<br><br>Following consideration of the range of evidence available on this outcome, the Committee considered that the data on the ability of Oncotype DX to predict chemotherapy benefit to be insufficient at this time and have recommended further research. Further details |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | | can be found in sections 6 and 7 of the guidance. |
| 54 | Consultee 4: (Sponsor – Agendia) | 6 | 6.2: Again, I would like to point out that the evidence on differential relative benefit according to Oncotype from the Paik et al 2006 study should be omitted from this document. Not only is the data not robust, the data is flawed. It doesn't use 'some results from the training set', but as can be read from the supplementary information- uses the exact same 233 LN-/ER+ patients from the NSABP-B20 study as were used for development of the Oncotype test: we weighted the NSABP B-20 study results most heavily in selecting the final gene list and algorithm for validation (Paik et al, NEJM 2006, suppl). This flaw has been noted several times in the literature ( for example Symmans, 2012, Oncology; Ioannidis, The Oncologist 2007).<br><br>6.6: see comment under 5.13. | Thank you for your comment.<br><br>The purpose of the systematic review in the diagnostics assessment report was to undertake a narrative approach to the synthesis of evidence. The report, therefore, provides a summary of the body of evidence including the author's conclusions. The limitations of the study, as considered by the Committee, are described in paragraph 6.5 of the guidance document.<br><br>It is understood that data for the tamoxifen treated patients of the B20 study were used in both the training and validation of Oncotype DX, whereas, data from the B20 tamoxifen plus chemotherapy–treated patients were not used in the training set. Therefore, the use of 'some samples' is felt appropriate. |
| 55 | Consultee 11: (NHS Professional) | 6 | The UK trial cost analysis of the use of Oncotype DX in the UK concludes, "A number of cost-effectiveness analyses of the Oncotype DXÂ® assay for other settings including the Unites States, Canadian, Japanese and Israeli have been published (Lamond et al¸ 2012, Kondo et al, 2011, Klang et al, 2010, Hornberger et al, 2005, Lyman et al, 2007). These previous analyses have shown that use of the Oncotype DX® assay is cost-effective (or cost-saving in the United States) from the | Thank you for your comment.<br><br>At the time of the systematic review conducted by the External Assessment Group, only the original poster/abstract of the interim results of the Holt study was available which included 106 patients. The subsequent abstract referred to 142 patients. For the economic model, the full dataset (142 patients) was available and used. The guidance has been updated to |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | perspective of a third party payer, with clinical benefits being primarily driven by the sparing of chemotherapy. The results of the current analysis concur and suggest that the Oncotype DX® assay can be considered to be cost-effective in the UK setting in comparison with current clinical practice." The full method and results are available, academic in confidence, from the main author simon.holt@wales.nhs.uk | reflect this.<br><br>Cost effectiveness analyses from other countries are typically not generalisable to the UK due to variations in a range of factors including baseline levels of chemotherapy and the cost of chemotherapy.<br><br>Paragraph 5.18 of the guidance document highlights the limitations of existing economic analyses identified by the systematic review and, therefore, the need for a de novo economic analysis. |
| 56 | Consultee 12: (Sponsor - Clarient) | 6 | We would like to emphasize a couple of general points in regards to appropriate use of these tests, highlight the recent publication of the validation of Mammostrat using samples from the European TEAM trial, and assert potentially important differences between Mammostrat and the other tests.<br><br>1. Mammostrat is independent of traditional risk factors and does not rely on quantitative measurement of ER, PR, her2 and proliferation status of tumours for risk stratification. Mammostrat is distinguished by measuring a collection of phenotypes not directly related to hormone or growth factor receptor status, nor proliferation. Therefore, the unique potential in using Mammostrat as compared to competing products, is to offer a measure of the aggressiveness of a patient's tumour completely independent of traditional biomarkers and | Thank you for your comment.<br><br>These points are noted.<br><br>With regards to the TEAM study, this provides additional supportive data for a large UK population on the prognostic ability of the test and expands the evidence base to patients treated with aromatase inhibitors, rather than tamoxifen. However the study does not provide any further evidence on the identified data gaps in the External Assessment Group economic analysis, particularly in terms of:<br><br>- lack of reclassification data of patients – reclassifying risk of patients current practice v Mammostrat risk group<br><br>- lack of evidence on impact of the test on |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | risk factors.<br><br>2. Mammostrat has substantial published validation data under-recognized by the NICE summary document.<br><br>We would like to bring to your attention, the recent publication of the successful testing of Mammostrat in a sixth independent cohort, and third major cooperative group clinical study (NSABP B14 and B20 being the first two), the European TEAM trial. This leaves no doubt as to the prognostic association of this test and affirms its utility in aromatase treated patients as well as tamoxifen treated patients.<br><br>We believe the statement in section 5.8, Almost all the clinical evidence was related to the Oncotype DX and MammaPrint tests because these tests are much further along the validation pathway than IHC4 and Mammostrat. is inaccurate. Due to requirement of fresh tissue for Mammaprint, only prospective institutional studies have been published. IHC4 evidence to date relies upon split training and validation in the trans-ATAC clinical trial with supporting evidence from a large institutional cohort (Nottingham). In the latter, cut-points for KI67 staining were adjusted due to the use of a different antibody reagent underscoring the early stage of standardization of this assay. Clearly OncotypeDX, which has been afforded early access to a number of | treatment decision making<br><br>- lack of robust evidence on the predictive ability of the test , particularly in terms of the moderate risk group<br><br>Key areas of uncertainty in the economic modelling therefore remain.<br><br>Noted. This sentence has been amended to 'Much of the clinical evidence . . .' in section 5.8 of the guidance. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | clinical studies, has the greatest amount of supportive information, but we believe published evidence in support of Mammostrat far exceeds either Mammaprint or IHC4.<br><br>3. Mammostrat has superior technical and analytic features compared to IHC4.<br><br>Mammostrat shares with IHC4, interpretation of biomarker expression by a pathologist in situ ensuring that the most aggressive part of a heterogenous tumour is evaluated, and avoiding errors due to expression of biomarkers in non-tumour tissue as can happen with tests that grind an entire sample into a pool for biomarker (RNA) measurement. The five Mammostrat antibodies were selected in a thorough screen of over 600 candidate antibody reagents in part with the criteria that they could be scored in a 'binary' fashion. In contrast, IHC4 antibodies are scored using pathologist subjective quantitative assessment. The reliance of the IHC4 algorithm upon quantitative measurements places a much higher burden on the technical consistency of staining and concordance with the original study where the algorithm was trained. Mammostrat antibodies are standardized, and since they are scored in a binary and simple fashion (stained or not stained at a greater than 10% level*), the burden upon precise, quantitative technical concordance with the training set is lower. In all published studies, concordance between independent stains for all five antibodies have been | |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | between 89-96% using the limited tissue available on tissue array cores.<br><br>*The NDRG1 antibody requires the pathologist subjective determination of whether the staining is homogenous or a hypoxic like pattern as part of the binary call.<br><br>The challenge facing clinicians and patients in assessing risk in an early stage is limited to those patients where traditional markers are unclear. A significant fraction of early stage cancers are strongly ER staining, her2 negative and without significant proliferation either assessed by mitotic index or KI67 staining. Conversely, a large fraction of cases are ER or PR weak, and strongly proliferative. In either of these cases, additional diagnostic testing is not needed. Prognostic biomarker testing can be helpful when for either technical or biologic reasons, interpretation of these traditional markers are unclear. IHC4, OncotypeDX and Mammaprint all convert these same traditional markers to a quantitative scale and estimate likelihood of recurrence. For the RNA-based technologies, an intermixing of normal, benign proliferative, or heterogeneous tumour tissue that can cause incorrect interpretation in some cases and confound interpretation. Mammostrat is the only test that uses biologic markers independent of traditional markers, interpreted by a Pathologist in situ, and therefore the only test to give independent, validated biomarker information. It can be interpreted in the context of all | |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| | | | other available information including hormone receptor, growth factor and proliferation status. We believe this incremental independent information will prove more valuable than quantitative conversion of ER, PR, her2 and proliferation. | |
| 57 | Consultee 14: (Sponsor - Clarient) | 6 | the recent publication of the TEAM trial results and an editorial from the Journal of Clinical; Oncology highlighting the distinct advantages of the immunohistochemistry determinations to predict tumour response over other tests. | Thank you for your comment.<br><br>With regards to the TEAM study, this provides additional supportive data for a large UK population on the prognostic ability of the test and expands the evidence base to patients treated with aromatase inhibitors, rather than tamoxifen. However the study does not provide any further evidence on the identified data gaps in the External Assessment Group economic analysis, particularly in terms of:<br><br>- lack of reclassification data of patients – reclassifying risk of patients current practice v Mammostrat risk group<br><br>- lack of evidence on impact of the test on treatment decision making<br><br>- lack of robust evidence on the predictive ability of the test , particularly in terms of the moderate risk group<br><br>Key areas of uncertainty in the economic modelling therefore remain. |

| Comment number | Name and organisation | Section number | Comment | Response |
|---|---|---|---|---|
| 58 | Consultee 14: (Sponsor - Clarient) | 6 | The recent publication of the TEAM trial results and an editorial from the Journal of Clinical; Oncology highlighting the distinct advantages of the immunohistochemistry determinations to predict tumour response over other tests. | Thank you for your comment.<br><br>With regards to the TEAM study, this provides additional supportive data for a large UK population on the prognostic ability of the test and expands the evidence base to patients treated with aromatase inhibitors, rather than tamoxifen. However the study does not provide any further evidence on the identified data gaps in the External Assessment Group economic analysis, particularly in terms of:<br><br>- lack of reclassification data of patients – reclassifying risk of patients current practice v Mammostrat risk group<br><br>- lack of evidence on impact of the test on treatment decision making<br><br>- lack of robust evidence on the predictive ability of the test , particularly in terms of the moderate risk group<br><br>Key areas of uncertainty in the economic modelling therefore remain. |
| 59 | Consultee 1: (Sponsor - Genomic Health) | 6.2 | It is stated that the most recent Oxford overview (2011) shows a benefit from chemotherapy across all subgroups based on historic assessment of traditional parameters. The conclusion from this can only be that existing tools (and any combination of them) for choosing patients for chemotherapy in this | Thank you for your comment.<br><br>Following consideration of the range of evidence available on this outcome, the Committee considered that the data on the ability of Oncotype DX to predict chemotherapy |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | patient population are not sufficient. Importantly, even in the abstract of the Oxford overview they state that gene expression analysis was not included in the analysis. Just as the overview shows that there is a benefit from chemotherapy in all subgroups of traditional parameters there is a distribution of Recurrence Scores in all subgroups of traditional parameters with high Recurrence Score tumours also in tumours with classical features that would indicate “low risk” such as grade I. The Recurrence Score assesses the underlying biology regardless of whether the patient has small or large, node negative or node positive disease (or any other traditional parameter) and the data shows that it’s the patients with the same underlying tumour biology (i.e., high Recurrence Scores) who have significant benefit from chemotherapy. Tumour size or node positivity per se is not predictive of chemotherapy benefit as has been shown in the Oxford overview. Finally, it is important to note that these data from the Oxford meta-analysis are consistent with the NSABP B20 Study (Paik et al, 2006). Indeed, in both studies, the overall absolute benefit of chemotherapy in these populations ranges between 4-6%.<br><br>Furthermore the predictive ability of Onco*type* DX is questioned and an equal relative benefit from chemotherapy is assumed across all Recurrence Score risk categories. This assumption is not scientifically supported. Onco*type* DX has proved predictive with a formal interaction in both the NSABP B-20 study (Paik et al, J Clin Oncol, 2006) | benefit to be insufficient at this time and have recommended further research. Further details can be found in sections 6 and 7 of the guidance.<br><br>Reviewing current practice is outside the scope for this assessment (and in NICE Diagnostics Assessment Programme assessments in general). The External Assessment Group’s role was to review the new technologies.<br><br>The Committee agrees that there are potential limitations with tools currently used in the NHS, the suggested imperfect nature of such tools is captured in paragraph 3.13 of the guidance document. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | and in the SWOG 8814 study (Albain et al, Lancet Oncology, 2009). In addition, there are supportive data from the neoadjuvant setting where pathological complete responses have only been reported in patients with Recurrence Scores of 25 and above (Gianni L, et al. *J Clin Oncol.* 2005;23(29):7265, Yardley et al. SABCS 2011) and similar data have been reported for clinical complete response (Chang JC, et al. *Breast Cancer Res Treat*. 2008;108(2):233), thus corroborating that patients with high Recurrence Scores are more likely to benefit from chemotherapy than those with low Recurrence Scores. The body of evidence in support of the Recurrence Score's ability to predict chemotherapy benefit is therefore compelling. NICE should explicitly state the basis for its assumption in 6.2 with regard to the predictive ability of Onco*type* DX.<br><br>Importantly, the wealth of data supporting Onco*type* DX as a prognosticator with consistent results from multiple studies and as a predictor of chemotherapy benefit in the NSABP B-20 and SWOG 8814 studies has to be seen in the context of the level of evidence supporting currently used markers. Neither NPI nor Adjuvant Online! have proved predictive of chemotherapy benefit. | |
| 60 | Consultee 1: (Sponsor - Genomic Health) | 6.3 | Genomic Health contends that the model has not been built based on the best available data. It appears that the population, structure and model were decided first (likely based on clinical opinion) and then populated with the only available data that | Thank you for your comment.<br><br>The External Assessment Group disagrees with this statement and considers that the best data available were used to populate and |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | fit (much of which had to be generated, remains unpublished and is not fully elucidated in the technology assessment report). Conversely, if the model had been designed around the best available data from the systematic literature review described in the report, there may have been less uncertainty in the modeling outcomes and it is likely that the cost-effectiveness results would have been notably different.<br><br>The potential implications of using different data are explored Section 5.7.1 of the technology assessment report, whereby data from the Genomic Health cost-effectiveness evaluation of Onco*type* DX versus current practice were integrated stepwise into the independent model. There are some noteworthy points raised by the analysis, which should be considered in terms of revising the modeling analysis:<br><br>• The estimated 10-year risks of recurrence in the model are fraught and have not been published: estimates are based on very small patient numbers (**less than 10 patients in several cases** as highlighted in Tables 51 & 52 of the diagnostic assessment report). Using the 10-year risk of recurrence estimates data from the Paik et al, 2006 study have been shown to significantly reduce the ICER for Onco*type* DX versus current practice. The estimates from ATAC should be considered for the sensitivity | construct the model.<br><br>All potential data sources had strengths and weaknesses. The model was not built around data from the Holt study given the limitations highlighted in the diagnostics assessment report. Data from the ATAC study were used instead as this provided data on the risk reclassification and risk of recurrence from a single UK source. The Holt study did not provide data on the risk of recurrence.<br><br>This limitation is acknowledged in the diagnostics assessment report. The External Assessment Group also conducted an analysis excluding the split by NPI subgroup and excluding IHC4 from the analysis which provided larger sample size, which showed limited impact on the results. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | analyses but not for the base case and in order to get estimates for sufficient numbers of patients, the data should not be divided by IHC4 risk but only by NPI and RS. | |
| | | | • The classification of patients into low, intermediate and high Recurrence Score groups based on Onco*type* DX testing in the model is simply assumed (based on data from a different population) and applied to the modeled population (the registry population) that lacks description. This is a key driver of outcomes in the model and yet has not been investigated in the univariate sensitivity analysis. When the risk classification is adjusted in the model to match that observed from the Holt *et al.* study, then the cost-effectiveness of Onco*type* DX improves notably versus current practice. This is a fundamental aspect of the model, and its revision should be considered for the base case analysis. | The External Assessment Group had some concerns with the generalisability of the Holt study. The External Assessment Group used data from the ATAC trial as this provided data on the risk reclassification and risk of recurrence from the same source (as these 2 parameters are correlated). |
| | | | • As indicated earlier, we agree that the cost-effectiveness of Oncotype DX could be enhanced if the test was to be used in the group of patients for whom the benefit of chemotherapy remains unclear with traditional clinical and pathological criteria. These patients, in the absence of a test like | A subgroup analysis, based on NPI>3.4 was explored to test this assumption |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | Oncotype DX, may frequently receive chemotherapy. UK physicians currently use the Oncotype DX test to inform chemotherapy decisions for those patients. Over 1,100 tests have been ordered for patients in the UK among whom 55% had low Recurrence Scores and were therefore potentially spared un-necessary chemotherapy. A sub-group analysis modeling this patient population (i.e. intermediate and high risk according to traditional criteria) that reflects current clinical practice with the Oncotype DX test in the UK should be considered. | |
| 61 | Consultee 1: (Sponsor - Genomic Health) | 6.4 | As highlighted in section 5.29, the cost-effectiveness analysis of IHC4 should not be considered as it is based on unsubstantiated assumptions. NICE therefore cannot reasonably conclude any potential for IHC4 to dominate clinical practice until further evidence is gathered on this test.<br>It should be noted that there are many unsupported assumptions made concerning IHC4 and several of them have great uncertainty:<br>• IHC4 is currently not available commercially. The price is assumed to be low but, in order to achieve acceptable reproducibility in local laboratories, significant investments may be needed. There are thus significant uncertainties regarding whether IHC4 will ever become commercially available and if it does, what the actual price will be for the eventual process that includes the activities | Thank you for your comment.<br><br>The Committee agrees that there are limitations in the evidence supporting IHC4 and has recommended further research into the analytical validity, clinical validity and clinical utility of the test.<br><br>The sponsor of IHC4 confirms that the test is available to the NHS and, therefore, qualifies for NICE guidance. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | necessary to deliver sufficient accuracy, precision and reproducibility. Any model used for health economical assessment should take this into account.<br>• IHC4 as a prognosticator is not thoroughly validated. The external validation cohort (Nottingham) presented in the initial manuscript is not in a relevant patient population (less than 50% of patients had received endocrine treatment) (Cuzick et al. J Clin Oncol. 2010) and recently another external population has been reported but the risk of recurrence at 8 years in this cohort is significantly higher than that reported in transATAC (Christiansen et al. J Clin Oncol 30, 2012 (suppl; abstr 517)) which is of significant concern.<br>• The reproducibility of IHC4 in local labs has not been demonstrated and there are still major reproducibility issues with in particular Ki67 (Luporsi E et al, BCRT 2012; Varga Z etal, PLOS one 2012) but also the other proteins included in IHC4 (Wolf AC et al, 2007; Perez EA et al, JCO 2006; Hammond et al, Arch Pathol Lab Med 2010; Rhodes A, J Clin Pathol, 2000). | |
| 62 | Consultee 1: (Sponsor - Genomic Health) | 6.7 | It is stated that the committee expressed "a general concern over the lack of information on the impact of the use of gene expression profiling tests on clinical decisions in the UK". The Holt et al. study describes the use of the Onco*type* DX test on clinical decision-making in Wales. Another decision impact study with | Thank you for your comment.<br><br>This point is noted. The Committee believed that relative to the body of evidence available for all tests, information on the impact of these tests on clinical decision-making in England is |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | a similar design is on-going in Bristol (principal investigator is Dr Jeremy Braybrooke from Bristol Haematology and Oncology Centre) where 137 patients have been recruited to date. | low. |
| 63 | Consultee 2: (NHS Professional) | 7 | nil to add | Thank you for your comment. |
| 64 | Consultee 11: (NHS Professional) | 7 | In the light of the recent further controversy about over treatment, particularly of screen detected breast cancer, the expense and morbidity of chemotherapy and the likelihood that implementation of regular testing with Oncotype DX could safely spare up to 70% of women currently prescribed chemotherapy, I welcome any research which will accelerate the introduction of gene expression analysis. Although the TAILORx trial is full recruited, it is expected to take a further 3 to 5 years to report. I am unsure we should be submitting the women of the UK to such high levels of exposure to unnecessary chemotherapy in the meantime. | Thank you for your comment.<br><br>The Committee found that Oncotype DX was a clinically effective (based on its ability to predict prognosis but not chemotherapy benefit) and cost-effective (at the revised confidential price used in the access proposal) use of NHS resources in patients deemed to be at intermediate risk of distant recurrence. Therefore, the technology has been recommended for adoption in this patient group – please refer to section 1 of the guidance. |
| 65 | Consultee 3: (Health Professional Europe) | 7 | The Mindact study, using the prognostic capacities of the MammaPrint test to select for adjuvant systemic therapy strategies, has closed accrual in summer 2011!. The trial accrued very successfully the over 6600 required patients in about 3 years time. Accrual rate was above expectations (unfortunately very limited in the UK), and more importantly, compliance to treatment allocations were excellent (as judges by the IDMC), reflecting the patients and doctors trust in the design of the trial and the prognostic significance of the test. | Thank you for your comment.<br><br>The sentence 'The Committee encourages participation in these studies.', in paragraph 7.3, has been interpreted as encouraging patient recruitment as oppose to its intended purpose of encouraging continued participation of already enrolled patients. This sentence has been removed to avoid confusion. |
| 66 | Consultee 4: | 7 | Both MINDACT and TAILORx have been closed for | Thank you for your comment. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | (Sponsor – Agendia) | | enrolment. | The sentence 'The Committee encourages participation in these studies.', in paragraph 7.3, has been interpreted as encouraging patient recruitment as oppose to its intended purpose of encouraging continued participation of already enrolled patients. This sentence has been removed to avoid confusion. |
| 67 | Consultee 5: (University Faculty) | 7 | Of course those two large clinical trials will provide more informative data. However, their validity and robustness will be subject to scrutiny. Sitting on current data, the patients and physicians will do whatever they believe if we cannot provide some concrete guidance. I cannot see how these recommendations are really meaningful for the patients. I can see that IHC is cheap and probably a strong prognostic factor and may be predictive of chemotherapy as well. Is it worth to wait for another 10 years to show that this is true???? | Thank you for your comment.<br><br>The Committee found that Oncotype DX was a clinically effective (based on its ability to predict prognosis but not chemotherapy benefit) and cost-effective (at the revised confidential price used in the access proposal) use of NHS resources in patients deemed to be at intermediate risk of distant recurrence. Therefore, the technology has been recommended for adoption in this patient group – please refer to section 1 of the guidance.<br><br>The Committee has highlighted further research that will be helpful in answering important questions arising from this assessment. |
| 68 | Consultee 6: (Patient Representative) | 7 | We agree that robust evidence of analytical validity, clinical validity and clinical utility is essential, to ensure those women who will benefit from chemotherapy receive the treatment and those who do not need it do not have to suffer unnecessary side effects. This evidence will ensure that the tests | Thank you for your comment.<br><br>The Committee found that Oncotype DX was a clinically effective (based on its ability to predict prognosis but not chemotherapy benefit) and cost-effective (at the revised |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | can accurately predict this, so that patients are not denied treatment they may benefit from or given treatments they do not require. We therefore welcome the committee's recommendation for these tests to be used in research and hope this can happened as quickly as possible. | confidential price used in the access proposal) use of NHS resources in patients deemed to be at intermediate risk of distant recurrence. Therefore, the technology has been recommended for adoption in this patient group – please refer to section 1 of the guidance.<br><br>The Committee has highlighted further research that will be helpful in answering important questions arising from this assessment. |
| 69 | Consultee 1: (Sponsor - Genomic Health) | 7.3 | Participation in MINDACT and TAILORx is encouraged by the committee. However, it should be noted that patient enrolment for both of these studies has been closed. It's thus not possible for NHS patients to participate in these studies. | Thank you for your comment.<br><br>The sentence 'The Committee encourages participation in these studies.', in paragraph 7.3, has been interpreted as encouraging patient recruitment as oppose to its intended purpose of encouraging continued participation of already enrolled patients. This sentence has been removed to avoid confusion. |
| 70 | Consultee 3: (Health Professional Europe) | 8 | My advice would be to allow for conditional implementation programs/studies of these tests, providing reimbursement of these test under specific conditions and prospective registration of patients/clinical decisions/treatments/cost benefit analysis. | Thank you for your comment.<br><br>The Committee found that Oncotype DX was a clinically effective (based on its ability to predict prognosis but not chemotherapy benefit) and cost-effective (at the revised confidential price used in the access proposal) use of NHS resources in patients deemed to be at intermediate risk of distant recurrence. Therefore, the technology has been recommended for adoption in this patient |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | | group – please refer to section 1 of the guidance.<br><br>The Committee has highlighted further research that will be helpful in answering important questions arising from this assessment. |
| 71 | Consultee 6: (Patient Representative) | 8 | To ensure that the necessary evidence can be obtained as quickly as possible it would be useful to expand this section to include more specific information on how these activities can make a positive difference to driving forward research in this area. | Thank you for your comment.<br><br>The Committee has recommended further research on all of the technologies and provided further details in section 7 of the guidance. |
| 72 | Consultee 6: (Patient Representative) | 9 | No comment | Thank you for your comment. |
| 73 | Consultee 6: (Patient Representative) | 10 | No comment | Thank you for your comment. |
| 74 | Consultee 11: (NHS Professional) | 10 | A full copy of the paper currently under consideration for publication on the use of Oncotype DX in the UK, "A DECISION IMPACT, DECISION CONFLICT AND ECONOMIC ASSESSMENT OF ROUTINE ONCOTYPE DX® TESTING OF 146 UK WOMEN WITH NODE ?VE, ER +VE BREAST CANCER<br><br>Authors: S Holt, G Bertelli, I Humphreys, W Valentine, S Durrani, D Pudney, M Rolles, M Moe, S Khawaja, Y Sharaiha, E Brinkworth, S Whelan, S Jones, H Bennett, C J Phillips," is available to the committee, academic in confidence, by request to Mr | Thank you for your comment.<br><br>At the time of the systematic review conducted by the External Assessment Group, only the original poster/abstract of the interim results of the Holt study was available which included 106 patients. The subsequent abstract referred to 142 patients. For the economic model, the full dataset (142 patients) was available and used. The guidance has been updated to reflect this. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | S Holt at simon.holt@wales.nhs.uk. | |
| 75 | Consultee 3: (Health Professional Europe) | 10 | Nguyen B, Cusumano PG, Deck K, Kerlin D, Garcia AA, Barone JL, Rivera E, Yao K, de Snoo FA, van den Akker J, Stork-Sloots L, Generali D. Comparison of molecular subtyping with BluePrint, MammaPrint, and TargetPrint to local clinical subtyping in breast cancer patients. Ann Surg Oncol. 2012 Oct;19(10):3257-63.<br><br>doi: 10.1245/s10434-012-2561-6. Epub 2012 Aug 15. PubMed PMID: 22965266.<br><br>2: Yang M, Rajan S, Issa AM. Cost effectiveness of gene expression profiling for early stage breast cancer: A decision-analytic model. Cancer. 2012 Oct 15;118(20):5163-70. doi: 10.1002/cncr.27443. Epub 2012 Feb 22. PubMed PMID: 22359236.<br><br>3: Kondo M, Hoshi SL, Ishiguro H, Toi M. Economic evaluation of the 70-gene prognosis-signature (MammaPrint®) in hormone receptor-positive, lymph node-negative, human epidermal growth factor receptor type 2-negative early stage breast cancer in Japan. Breast Cancer Res Treat. 2012 Jun;133(2):759-68. PubMed PMID: 22315134.<br><br>4: Rutgers E, Piccart-Gebhart MJ, Bogaerts J, Delaloge S, Veer LV, Rubio IT, Viale G, Thompson AM, Passalacqua R, Nitz U, Vindevoghel A, Pierga JY, Ravdin PM, Werutsky G, Cardoso F. The EORTC 10041/BIG 03-04 MINDACT trial is feasible: results of the pilot phase. Eur J Cancer. 2011 | Thank you for your comment. |

| Comment number | Name and organisation | Section number | Comment | Response |
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| | | | Dec;47(18):2742-9. Epub 2011 Nov 1. PubMed PMID: 22051734. | |

*Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.*