NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 13 June 2018

THEME: Micrometastases and lymph node positive disease

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

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suggests that this population behaves similarly to those with node negative disease (the attention of the current draft guidance) and that some diagnostic profiling tools might be similarly useful in selecting patients for chemotherapy benefits (or not).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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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			remained below £30,000 per QALY gained across all scenarios	

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

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			• TransATAC node positive cohort (n=248):
			  ○ In the clinical validation study with 928 total patients from the TransATAC cohort, the results regarding the node negative and node positive subgroups from ABCSG-6 and ABCSG-8 were confirmed. EPclin was highly prognostic in both node negative and node positive patient subgroups (Hazard ratios: 3.90 (p<0.0001) for node negative and 9.49 (p=0.0001) for node positive) (Appendix A - Fig. 2).
			  ○ In both subgroups, EPclin consistently identified patients with a low enough risk of distant recurrence, that chemotherapy could safely be avoided (distant recurrence-free survival after 10 years: 94.1% in node negative and 95.0% in node positive disease). In the node positive group, 19% of patients were identified as low risk.	

26	Myriad Genetics	1.1	Additional literature to support the value of using tumour profiling testing in patients with LN-positive disease • *Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor – Positive Breast Cancer. A Secondary Analysis of a Randomized Clinical Trial - Sestak I. et al., JAMA Oncology. Published online February 15, 2018. doi:10.1001/jamaoncol.2017.5524)*	Thank you for your comment which the committee considered. The EAG noted that Sestak et al. 2018 is not new data as it relates to TransATAC and is a publication of an analysis that is almost identical to the analysis provided to the EAG. This analysis also excluded

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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THEME: Data collection

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

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

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

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

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THEME: Differences between EndoPredict, Oncotype DX and Prosigna

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

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

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

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Diagnostics Advisory Committee date: 13 June 2018

THEME: Differences between EndoPredict, Oncotype DX and Prosigna

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

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

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

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

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

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

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

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

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

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

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

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

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THEME: MammaPrint

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

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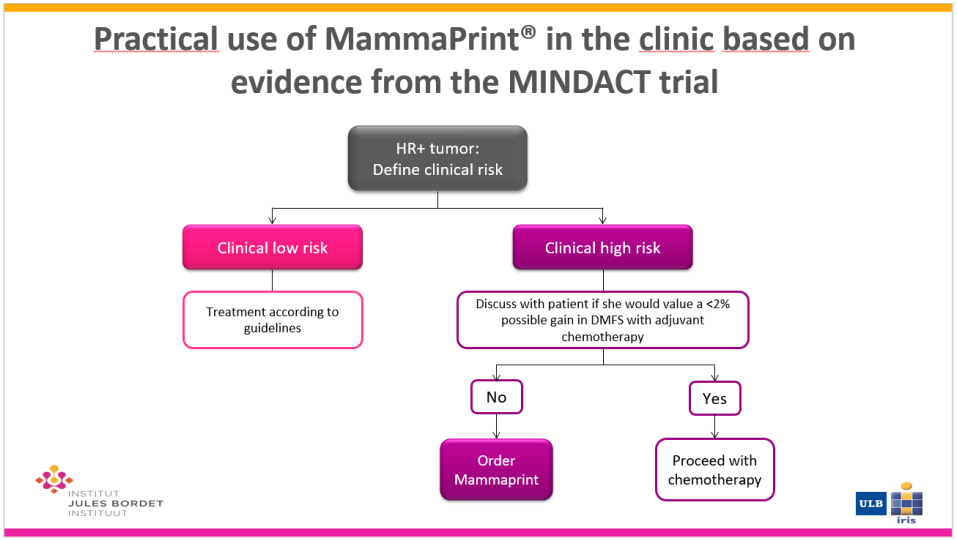
Comment number	Name and organisation	Section number	Comment	NICE response
			Figure 1 - Slide depicting MammaPrint use in clinical practice (reproduced with courtesy of M. Piccart)  As shown in MINDACT, ~46% of these clinical high-risk patients turn out to be genomic “low-risk” and could therefore be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

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

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<tr><td></td><td></td><td></td><td>
and avoid overtreatment as well as undertreatment as we know that in MINDACT, overall, MammaPrint Low Risk patients had a 5year DMFI of 97.2% without chemotherapy and a 93.4% DMFI at 5years for MammaPrint High Risk patients that were treated with chemotherapy.

Table 6A – Correlation between Adjuvant! Online and MammaPrint

<table>
<tr><th colspan="3"></th><th colspan="2">GENOMIC RISK (MAMMAPRINT)</th></tr>
<tr><th colspan="3"></th><th>MP low risk (%)</th><th>MP high risk (%)</th></tr>
<tr><td>ADJUVANT! ONLINE</td><td>Low risk</td><td>714 (64%)</td><td>505 (70.7%)</td><td>209 (29.3%)</td></tr>
<tr><td>CLINICAL RISK</td><td>High risk</td><td>411 (36%)</td><td>224 (54.5%)</td><td>187 (45.5%)</td></tr>
<tr><td>TOTAL</td><td colspan="2">1125</td><td>729 (65%)</td><td>396 (35%)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Table 6B – Correlation between PREDICT and MammaPrint

<table>
<tr><th colspan="3"></th><th colspan="2">GENOMIC RISK (MAMMAPRINT)</th></tr>
<tr><th colspan="3"></th><th>MP low risk (%)</th><th>MP high risk (%)</th></tr>
<tr><td>PREDICT</td><td>Low risk</td><td>939 (82.8%)</td><td>655 (69.8%)</td><td>284 (30.2%)</td></tr>
<tr><td>CLINICAL RISK</td><td>High risk</td><td>195 (17.2)</td><td>78 (40%)</td><td>117 (60%)</td></tr>
</table>
</td><td></td></tr>
</table>

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Comment number	Name and organisation	Section number	Comment				NICE response
			TOTAL	1134	733 **(64.6%)**	401 **(36.4%)**	

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

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

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

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

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

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

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THEME: MammaPrint

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

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THEME: MammaPrint

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

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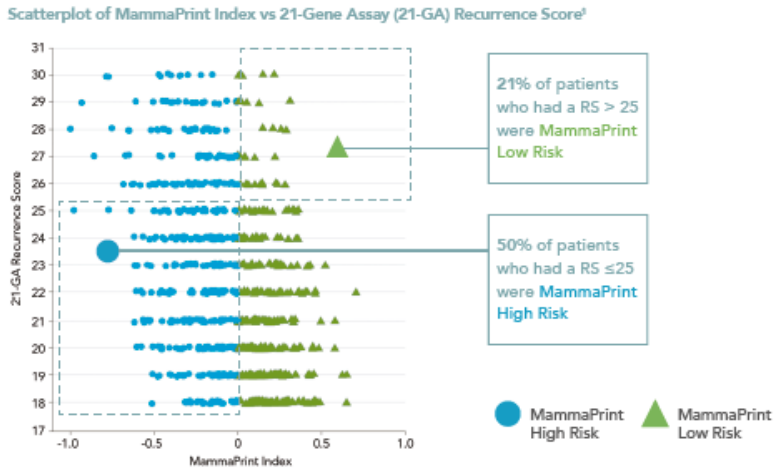
THEME: MammaPrint

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

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Comment number	Name and organisation	Section number	Comment	NICE response
			patients reclassified as High Risk by MammaPrint, 73% had an ODx Recurrence Score ≤25 and were not recommended for ACT by St. Gallen Guidelines (Goldhirsch, Winer et al. 2013), risking up to a 73% chance of undertreatment. *Figure 16 – Summary of chemotherapy recommendations for patients with OncotypeDx intermediate results pre and post-MammaPrint testing (representing overtreatment or undertreatment in this patient group)* **MammaPrint Low Risk (n= 374)** Pre-MammaPrint – No Chemo / Pre-MammaPrint – Chemo With MammaPrint – No chemo: 231 / 108 With MammaPrint – Chemo: 1 / 34 108 patients recommended to have chemotherapy based on the result of the 21-gene assay were classified as Low Risk by MammaPrint. This represents **29%** more Low Risk patients who were identified as having no significant benefit from chemotherapy and could thus potentially avoid over-treatment 108/374). **MammaPrint High Risk (n= 466)** Pre-MammaPrint – No Chemo / Pre-MammaPrint – Chemo With MammaPrint – No chemo: 55 / 2 With MammaPrint – Chemo: 171 / 238 171 patients previously indicated for no chemotherapy received a MammaPrint High Risk result and were identified as likely to benefit from it, representing **37%** more High Risk patients who potentially avoided under-treatment (171/466). The purpose of a prognostic test is to provide physicians and patients with definitive and actionable information in combination with other factors for accurate risk assessment. MammaPrint provides clinically actionable information regarding patients classified as intermediate risk by ODx and was associated with a change in treatment decision in 33.6% of these patients preventing both under and over treatment.	

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THEME: PREDICT tool

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

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THEME: PREDICT tool

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

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

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

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

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

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

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

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

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

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

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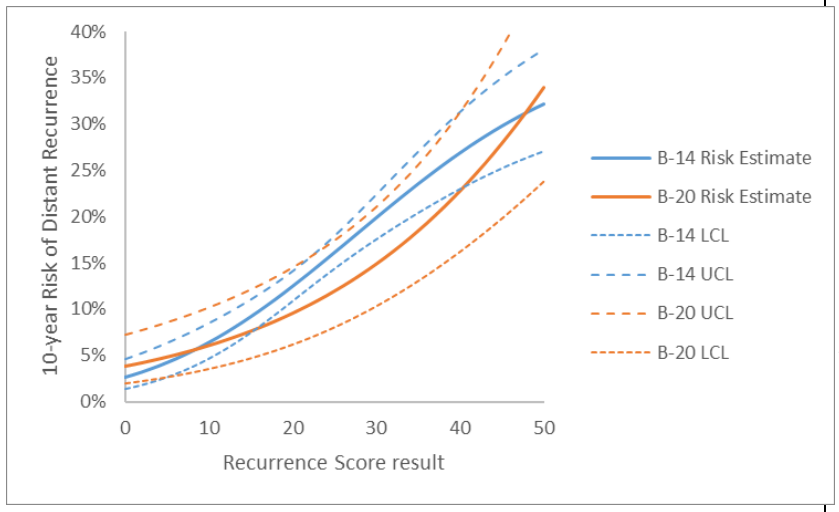
Comment number	Name and organisation	Section number	Comment	NICE response
		(version 19th April 2018) Response to comments by NSABP-B20 Lead biostatistician Comment number 148 regarding Section number 4.3.3, pages 97-112	the B-20 tamoxifen alone arm, and the blue lines depict the 10-year risks of distant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

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

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

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<table>
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<tr><td></td><td></td><td></td><td>
that the statistician provide the EAG and all stakeholders with a graph with the full RS scores from 0-100.

When depicting the 10 year risk of recurrence for low-risk patients for Intermediate, and for high-risk patients for both studies, then it becomes clear (see Table 7 below, and Table 6 in section 3 of “Addendum: EAG responses to key themes within the Comments on the Diagnostics Consultation Document, p12) that the recurrence risk for the low RS risk group in the B20 tamoxifen arm is 3.2%, much lower than the 6.8% recurrence risk in the B14 low Recurrence Score risk group. Whereas the risk of recurrence in the high RS risk group is much higher in the development series, 39.5% compared with 30.5% in the B14 validation series.

So this explains how the curves can have the same tendency (low->higher->top) but the increases happen at a different point. It also becomes clear that patients in the low Recurrence Score risk group may actually have some benefit of chemotherapy, since the risk for recurrence decreases from 6.8% to 4.4%.

Table 7. Comparison of Oncotype recurrence risk in B14 and B20
<table>
<tr><td rowspan="2">Oncotype Dx

RS score</td><td>NSABP-B14</td><td colspan="2">NSABP-B20</td></tr>
<tr><td>Tamoxifen treated</td><td>Tamoxifen treated</td><td>Tamo
+chemothera</td></tr>
</table>
</td><td></td></tr>
</table>

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<table>
<tr><th></th><th>Recurrence Risk</th><th>Percentage of TAM treated patients in total study population (n)</th><th>Recurrence Risk</th><th>Percentage of TAM treated patients in total study population (n)</th><th>Recurrence Risk</th><th>Percentage of TAM+CT treated patients in total study population</th></tr>
<tr><td>Low RS</td><td>6.8%</td><td>51% (388)</td><td>3.2%</td><td>60% (135)</td><td>4.4%</td><td>51% (218)</td></tr>
<tr><td>Intermediate RS</td><td>14.3 %</td><td>22% (149)</td><td>9.1%</td><td>20% (45)</td><td>10.9%</td><td>21% (89)</td></tr>
<tr><td>High RS</td><td>30.5</td><td>27% (181)</td><td>39.5%</td><td>21% (47)</td><td>11.9%</td><td>28% (117)</td></tr>
</table>
The results in Table 7 are not mirrored in Figure 14, where B20 low RS patients have a higher risk than the B14 patients (is reversed in Figure 14), and B20 High Risk patients have a lower risk of distant recurrence than B14 patients High Risk (also the opposite of the curves in Figure 14).

In the SWOG8814 study by Alban et al. the only statistical significant result for the RS is a 50-point difference in RS which we have just argued above is clinically meaningless, since hardly any (close to zero) patients exist with a RS over 50. **No clinically relevant data exists today that Oncotype Dx is predictive for**
</td><td></td></tr>
</table>

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

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

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

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

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

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

NICE National Institute for Health and Care Excellence

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

NICE National Institute for Health and Care Excellence

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				(section 5.13 of the diagnostics guidance).

NICE National Institute for Health and Care Excellence

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

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

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

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			Firstly, the titles for the three classification probabilities are mislabelled. Looking from the Parameters worksheet back through the linked cells to the Premodel worksheet we were able to trace back how they should be labelled. In Figure we have highlighted the mislabelled cells in blue. *Figure 2: Mislabelled cells in EAG model Parameters worksheet* Model parameters As shown in Figure , in the Parameters worksheet cell B15 is titled "NPI<3.4, Node-negative" but this analysis actually corresponds to the "MINDACT ITT population"	comparing like-with-like and in this instance the bias works in favour of the MammaPrint test. The EAG agrees that the labelling in the model could have been corrected. The results are however unaffected by this.

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

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

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Figure 3 - Corrected cell labels for Parameters worksheet

Model parameters

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

Classification probabilities: Patient number inputs and risk group proportions

In the Cardoso et al., 2016 publication “Clinical risk” is used to refer to mAOL (i.e. “Without test”) while “Genomic risk” is used to refer to MammaPrint (i.e. “With test”). In the EAG model the following labelling is used to direct to either the high risk (p(HR)) or low-risk (p(LR)) classification probabilities.

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

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Figure 4 - Incorrect patient number inputs (blue) and incorrect proportions (green)

Model parameters

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

As shown in Figure 4 , all the incorrect inputs correspond to the “Without-test” (mAOL/clinical risk only) risk classifications.

Correct inputs for MammaPrint based on Cardoso et al., 2016

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

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
To summarise this clearly, we have included this data in Table 2 below, indicating that the Without-test low-risk group contains 3337 patients, and the Without-test high-risk group contains 3356 patients.

Table 2 – Summary of mAOL risk group patient numbers

<table>
<tr><td>”Without-test” group</td><td>N in group</td><td>Percent of total patients (N=6693) in MINDACT</td></tr>
<tr><td>mAOL low-risk / Without-test low-risk</td><td>**C-low**/G-low + **C-low**/G-high
(2745+592) = 3337</td><td>49.9%</td></tr>
<tr><td>mAOL high-risk / Without-test high-risk</td><td>**C-high**/G-high + **C-high**/G-low
(1806+1550) = 3356</td><td>50.1%</td></tr>
</table>

It is important to note that the mAOL low-risk / **Without-test low-risk** group cannot contain ***any*** mAOL high-risk patients as all patients in this group are mAOL **low-risk**.(i.e. for mAOL low-risk Without test p(HR) = 0). Similarly, the mAOL high-risk/ Without-test high risk group contains zero mAOL low-risk patients as by definition it is the mAOL high-risk group.

Referring back to the Parameters sheet in the EAG model it is therefore clear that the patient numbers highlighted in blue and green in Figure 4 do not reflect the MINDACT data and should be corrected to correctly represent the risk classification in the “Without-test” situation.

Correct inputs for MammaPrint in the EAG model
</td><td></td></tr>
</table>

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<table>
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<tr><td></td><td></td><td></td><td>
To correct the error in the patient numbers for the comparator/mAOL/“Without-test” patient risk groups, we have updated these cells for the “MINDACT ITT population”, “mAOL high-risk” and “mAOL low-risk” analyses in the Parameters worksheet. The corrected patient input values for the Parameters worksheet are summarised in Table 3. The updated values are also shown (in red) in the Parameters worksheet in Figure 6 below.

Table 3 – Correct patient number inputs for MammaPrint in EAG model Parameters worksheet

<table>
<tr><th></th><th>Column B</th><th>Column D</th><th>Column E</th><th>Column F</th><th>Column H</th></tr>
<tr><th></th><th>Classification probabilities</th><th>Parameter 1</th><th>Parameter 2</th><th>Deterministic</th><th>Active value (for deterministic analysis)</th></tr>
<tr><td>Row 15</td><td colspan="5">MINDACT ITT population</td></tr>
<tr><td>Row 16</td><td>With test – p(LR)</td><td>4295</td><td>6693</td><td>0.64</td><td>0.64</td></tr>
<tr><td>Row 18</td><td>With test – p(HR)</td><td>2398</td><td>6693</td><td>0.36</td><td>0.36</td></tr>
<tr><td>Row 19</td><td>Without test – p(LR)</td><td>3337</td><td>6693</td><td>0.50</td><td>0.50</td></tr>
<tr><td>Row 21</td><td>Without test – p(HR)</td><td>3356</td><td>6693</td><td>0.50</td><td>0.50</td></tr>
<tr><td>Row 22</td><td colspan="5">mAOL high-risk</td></tr>
<tr><td>Row 23</td><td>With test – p(LR)</td><td>1150</td><td>3356</td><td>0.46</td><td>0.46</td></tr>
<tr><td>Row 25</td><td>With test – p(HR)</td><td>1806</td><td>3356</td><td>0.54</td><td>0.54</td></tr>
</table>
</td><td></td></tr>
</table>

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Comment number	Name and organisation	Section number	Comment						NICE response
			Row 26	Without test – p(LR)	**0**	3356	**0.00**	**0.00**	
			Row 28	Without test – p(HR)	**3356**	3356	**1.00**	**1.00**	
			Row 29	**mAOL low-risk**					
			Row 30	With test – p(LR)	2745	3337	0.82	0.82	
			Row 32	With test – p(HR)	592	3337	0.18	0.18	
			Row 33	Without test – p(LR)	**3337**	3337	**1.00**	**1.00**	
			Row 35	Without test – p(HR)	**0**	3337	**0.00**	**0.00**	

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Figure 6 - Corrected classification probability inputs

Model parameters

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

Deterministic Results – MammaPrint is now cost-effective

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

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Comment number	Name and organisation	Section number	Comment	NICE response
			MINDACT ITT population. In the mAOL low-risk analysis MammaPrint is dominated by current practice. *Figure 7 - Corrected deterministic results* **Determinstic results** Option / LYGs / QALYs / Costs / Inc/ LYGs / QALYs / Costs / ICER (per QALY gained) **MINDACT ITT population** MammaPrint: 16.218 / 13.489 / £8,897.45 / 0.09 / 0.08 / £1,452.81 / **£17,524** No test: 16.128 / 13.406 / £7,444.64 **mAOL high-risk** MammaPrint: 15.46 / 12.82 / £12,217.44 / 0.39 / 0.35 / -£342.74 / **Dominating** No test: 15.06 / 12.47 / £12,560.18 **mAOL low-risk** MammaPrint: 16.44 / 13.69 / £7,594.67 / -0.08 / -0.07 / £2,743.31 / **Dominated** No test: 16.52 / 13.76 / £4,851.36 **Deterministic sensitivity analyses** When we now perform the deterministic sensitivity analyses as shown in Figure 8 below, correction of the patient number parameter inputs in the EAG model results in MammaPrint dominating current practice in 18 out of 22 sensitivity analysis scenarios and being cost effective with ICERs <£1000 in the remaining 4 out of 22 analyses.	

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

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

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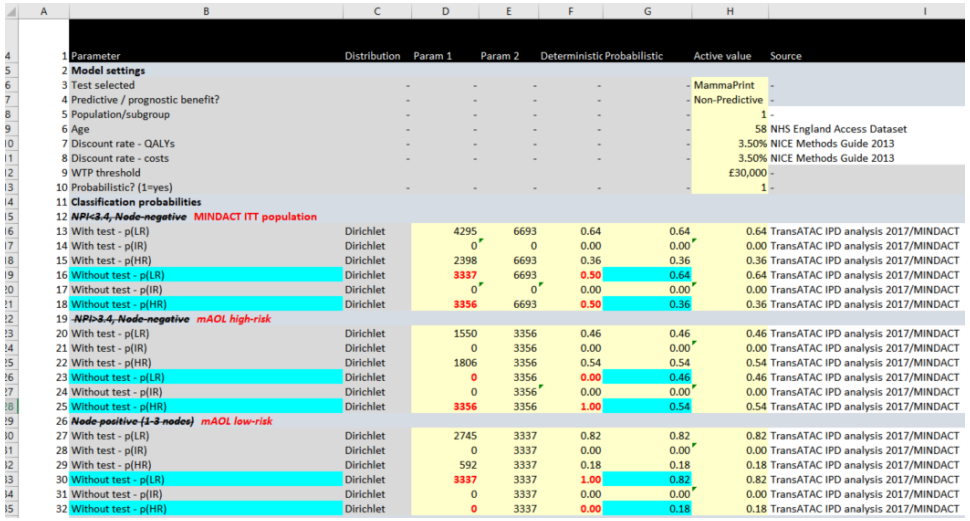
Comment number	Name and organisation	Section number	Comment	NICE response
		(theme: Probabilistic analysis)	in blue). The text and values in red correspond to the corrections made previously for the deterministic model (please see comment [155] for more details). *Figure 9- Incorrect patient proportions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

	A	B	C	D	E	F	G	H	I
4	1	Parameter	Distribution	Param 1	Param 2	Deterministic	Probabilistic	Active value	Source
5	2	**Model settings**							
6	3	Test selected	-	-	-	-	-	MammaPrint	-
7	4	Predictive / prognostic benefit?	-	-	-	-	-	Non-Predictive	-
8	5	Population/subgroup	-	-	-	-	-	1	-
9	6	Age	-	-	-	-	-	58	NHS England Access Dataset
10	7	Discount rate - QALYs	-	-	-	-	-	3.50%	NICE Methods Guide 2013
11	8	Discount rate - costs	-	-	-	-	-	3.50%	NICE Methods Guide 2013
12	9	WTP threshold						£30,000	-
13	10	Probabilistic? (1=yes)	-	-	-	-	-	1	-
14	11	**Classification probabilities**							
15	12	~~***NPI<3.4, Node-negative***~~ **MINDACT ITT population**							
16	13	With test - p(LR)	Dirichlet	4295	6693	0.64	0.64	0.64	TransATAC IPD analysis 2017/MINDACT
17	14	With test - p(IR)	Dirichlet	0	0	0.00	0.00	0.00	TransATAC IPD analysis 2017/MINDACT
18	15	With test - p(HR)	Dirichlet	2398	6693	0.36	0.36	0.36	TransATAC IPD analysis 2017/MINDACT
19	16	Without test - p(LR)	Dirichlet	**3337**	6693	**0.50**	0.64	0.64	TransATAC IPD analysis 2017/MINDACT
20	17	Without test - p(IR)	Dirichlet	0	0	0.00	0.00	0.00	TransATAC IPD analysis 2017/MINDACT
21	18	Without test - p(HR)	Dirichlet	**3356**	6693	**0.50**	0.36	0.36	TransATAC IPD analysis 2017/MINDACT
22	19	~~***NPI>3.4, Node-negative***~~ ***mAOL high-risk***							
23	20	With test - p(LR)	Dirichlet	1550	3356	0.46	0.46	0.46	TransATAC IPD analysis 2017/MINDACT
24	21	With test - p(IR)	Dirichlet	0	3356	0.00	0.00	0.00	TransATAC IPD analysis 2017/MINDACT
25	22	With test - p(HR)	Dirichlet	1806	3356	0.54	0.54	0.54	TransATAC IPD analysis 2017/MINDACT
26	23	Without test - p(LR)	Dirichlet	**0**	3356	**0.00**	0.46	0.46	TransATAC IPD analysis 2017/MINDACT
27	24	Without test - p(IR)	Dirichlet	0	3356	0.00	0.00	0.00	TransATAC IPD analysis 2017/MINDACT
28	25	Without test - p(HR)	Dirichlet	**3356**	3356	**1.00**	0.54	0.54	TransATAC IPD analysis 2017/MINDACT
29	26	~~***Node positive (1-3 nodes)***~~ ***mAOL low-risk***							
30	27	With test - p(LR)	Dirichlet	2745	3337	0.82	0.82	0.82	TransATAC IPD analysis 2017/MINDACT
31	28	With test - p(IR)	Dirichlet	0	3337	0.00	0.00	0.00	TransATAC IPD analysis 2017/MINDACT
32	29	With test - p(HR)	Dirichlet	592	3337	0.18	0.18	0.18	TransATAC IPD analysis 2017/MINDACT
33	30	Without test - p(LR)	Dirichlet	**3337**	3337	**1.00**	0.82	0.82	TransATAC IPD analysis 2017/MINDACT
34	31	Without test - p(IR)	Dirichlet	0	3337	0.00	0.00	0.00	TransATAC IPD analysis 2017/MINDACT
35	32	Without test - p(HR)	Dirichlet	**0**	3337	**0.00**	0.18	0.18	TransATAC IPD analysis 2017/MINDACT

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

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Figure 10 - Dirichlet sampling in EAG model (received January 2018 by Agendia)

Dirichlet sampling

Classification with or without test

Node negative NPI<3.4	Low	Intermediate	High	Total
Prior distribution parameters	0.01	0.01	0.01	0.03
Observed data	4295	0	2398	6693
Posterior distribution parameters	4295.01	0.01	2398.01	6693.03
Posterior distribution probabilities	0.64	0.00	0.36	1.00
Random numbers	0.60	0.78	0.67	-
Cumulative gamma/normal functions	4312.37	0.00	2419.99	6732.36
Random Dirichlet samples	0.64	0.00	0.36	1.00

Node negative NPI>3.4	Low	Intermediate	High	Total
Prior distribution parameters	0.01	0.01	0.01	0.03
Observed data	1550	0	1806	3356
Posterior distribution parameters	1550.01	0.01	1806.01	3356.03
Posterior distribution probabilities	0.00	0.00	0.00	0.00
Random numbers	0.69	0.03	0.22	-
Cumulative gamma/normal functions	0.00	0.00	0.00	0.00
Random Dirichlet samples	0.00	0.00	0.00	0.00

Node positive	Low	Intermediate	High	Total
Prior distribution parameters	0.01	0.01	0.01	0.03
Observed data	2745	0	592	3337
Posterior distribution parameters	2745.01	0.01	592.01	3337.03
Posterior distribution probabilities	0.00	0.00	0.00	0.00
Random numbers	0.17	0.93	0.37	-
Cumulative gamma/normal functions	0.00	0.00	0.00	0.00
Random Dirichlet samples	0.00	0.00	0.00	0.00

However, as detailed in comment [121] the “Observed data” (patient numbers) for the with-test and without-test situation are not identical. To correct this the Dirichlet worksheet was duplicated and 1 worksheet used for the with-test situation and the other for the without-test values. The “Dirichlet_Without_test” worksheet is used to calculate the correct parameters for “Without-test”, and “Dirichlet” worksheet calculates the values

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

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

Dirichlet sampling

Classification WITHOUT test

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

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

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

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

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Comment number	Name and organisation	Section number	Comment	NICE response
			Dirichlet sampling **Classification WITH test** ~~NPI<3.4, Node-negative~~ MINDACT ITT population Low / Intermediate / High / Total Prior distribution parameters: 0.01 / 0.01 / 0.01 / 0.03 Observed data: 4295 / 0 / 2398 / 6693 Posterior distribution parameters: 4295.01 / 0.01 / 2398.01 / 6693.03 Posterior distribution probabilities: 0.64 / 0.00 / 0.36 / 1.00 Random numbers: 0.26 / 0.07 / 0.70 / - Cumulative gamma/normal functions: 4253.85 / 0.00 / 2423.59 / 6677.43 Random Dirichlet samples: 0.64 / 0.00 / 0.36 / 1.00 ~~NPI>3.4, Node-negative~~ *mAOL high-risk* Low / Intermediate / High / Total Prior distribution parameters: 0.01 / 0.01 / 0.01 / 0.03 Observed data: 1550 / 0 / 1806 / 3356 Posterior distribution parameters: 1550.01 / 0.01 / 1806.01 / 3356.03 Posterior distribution probabilities: 0.46 / 0.00 / 0.54 / 0.00 Random numbers: 0.38 / 0.31 / 0.53 / - Cumulative gamma/normal functions: 1538.30 / 0.00 / 1809.07 / 3347.37 Random Dirichlet samples: 0.46 / 0.00 / 0.54 / 1.00 ~~Node positive (1-3 nodes)~~ *mAOL low-risk* Low / Intermediate / High / Total Prior distribution parameters: 0.01 / 0.01 / 0.01 / 0.03 Observed data: 2745 / 0 / 592 / 3337 Posterior distribution parameters: 2745.01 / 0.01 / 592.01 / 3337.03 Posterior distribution probabilities: 0.82 / 0.00 / 0.18 / 0.00 Random numbers: 0.92 / 0.52 / 0.80 / - Cumulative gamma/normal functions: 2817.99 / 0.00 / 612.54 / 3430.53 Random Dirichlet samples: 0.82 / 0.00 / 0.18 / 1.00	

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Parameters sheet

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

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

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

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Comment number	Name and organisation	Section number	Comment						NICE response
			Row 26	Without test – p(LR)	**0**	3356	**0.00**	**0.00**	
			Row 28	Without test – p(HR)	**3356**	3356	**1.00**	**1.00**	
			Row 29	**mAOL low-risk**					
			Row 30	With test – p(LR)	2745	3337	0.82	0.82	
			Row 32	With test – p(HR)	592	3337	0.18	0.18	
			Row 33	Without test – p(LR)	**3337**	3337	**1.00**	**1.00**	
			Row 35	Without test – p(HR)	**0**	3337	**0.00**	**0.00**	

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Figure 12 - Corrected Parameters worksheet for EAG Probabilistic model

Model parameters

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

Probabilistic Results – MammaPrint is now cost-effective

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

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

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

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

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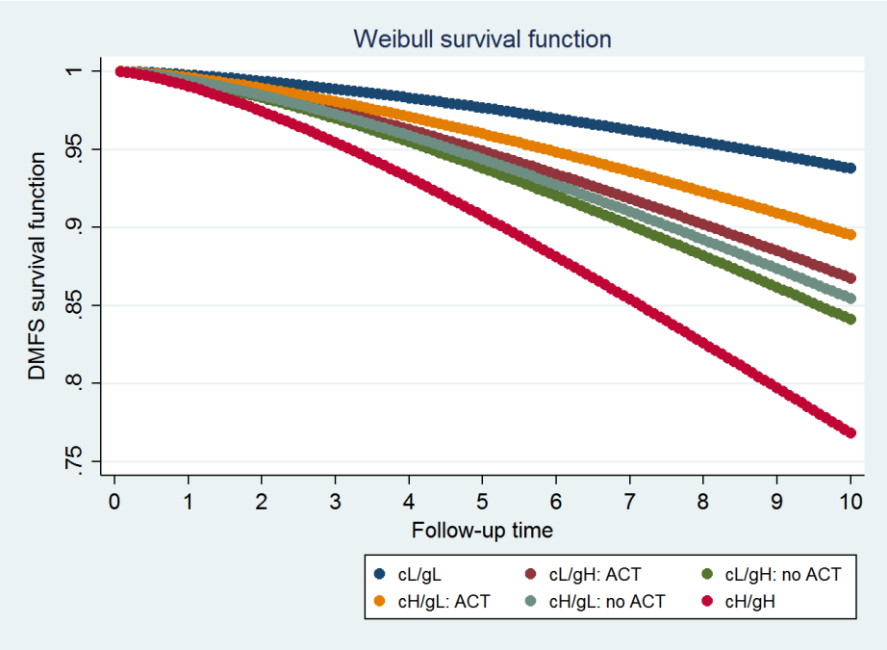
			Figure 22 - Weibull extrapolation for all risk and treatment subgroups: DMFS 0-10 yrs  	

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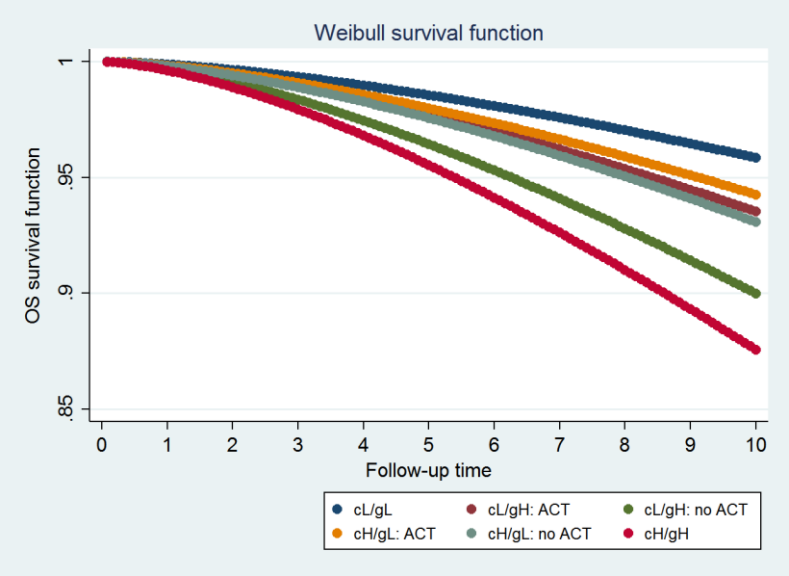
Comment number	Name and organisation	Section number	Comment	NICE response
			Figure 23 - Weibull extrapolation for all risk and treatment subgroups: OS 0-10 yrs  	
125	Agendia N.V.	Addendum: EAG responses to key themes within the	**Patient survival data for 10 year Weibull extrapolation** The EAG found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

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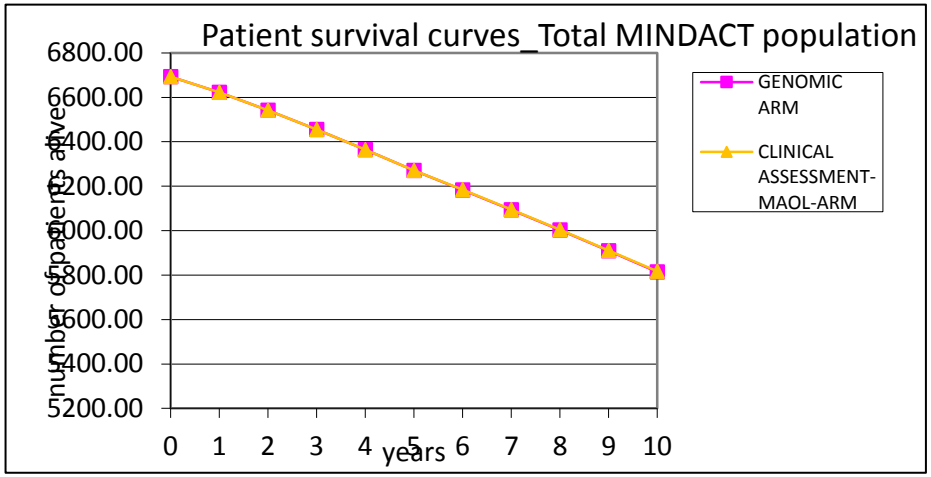
Comment number	Name and organisation	Section number	Comment	NICE response
		Comments on the Diagnostics Consultation Document (section 9. New model submitted by Agendia, p28-29 of 31) (theme: updated Agendia cost effectiveness model)	high-risk population. For ease of reference these graphs are also displayed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

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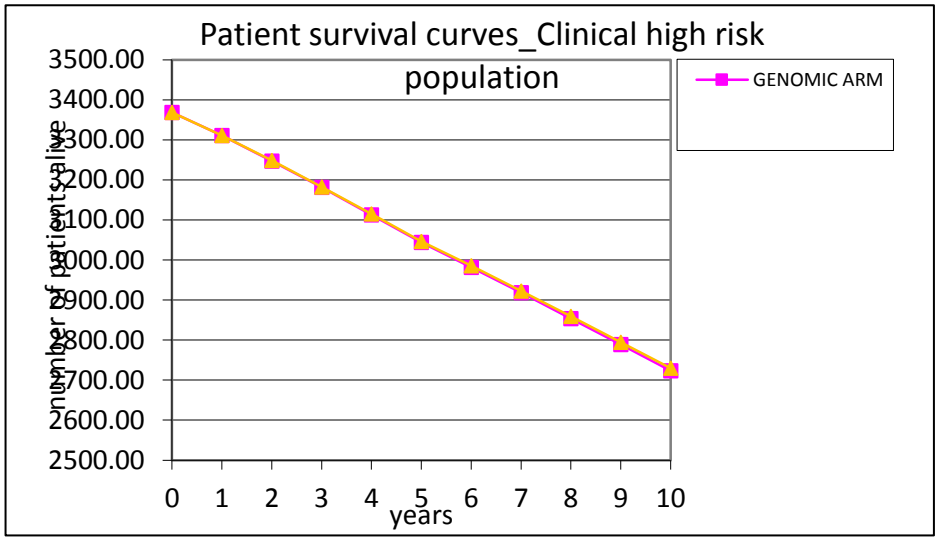
			Figure 18 - Number of patients alive, genomic and clinical assessment arm (mAOL) corrected Agendia model for total MINDACT population  In addition, we compared the Weibull extrapolation data to the original survival data from the EORTC MINDACT database. In figure 19 we show an example of the overlap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

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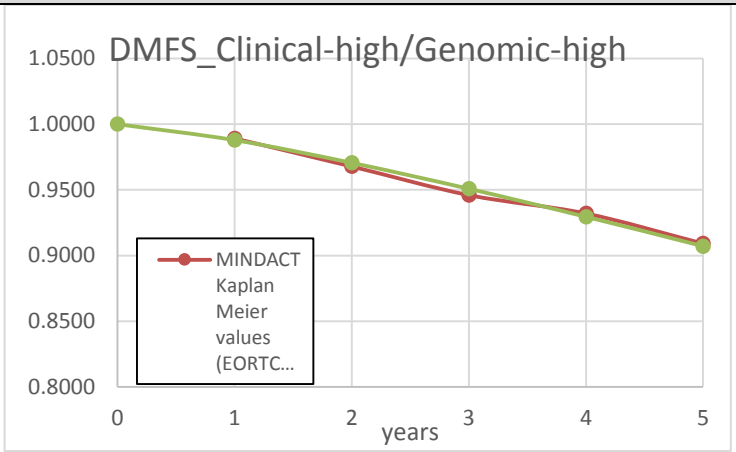
Comment number	Name and organisation	Section number	Comment	NICE response
				
126	Agendia N.V.	Updated Agendia model- fundamental change in structure	Before we go into detail on the adaptations that were made in the Agendia model based on the EAG suggestions, we would like to explain a fundamental change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

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

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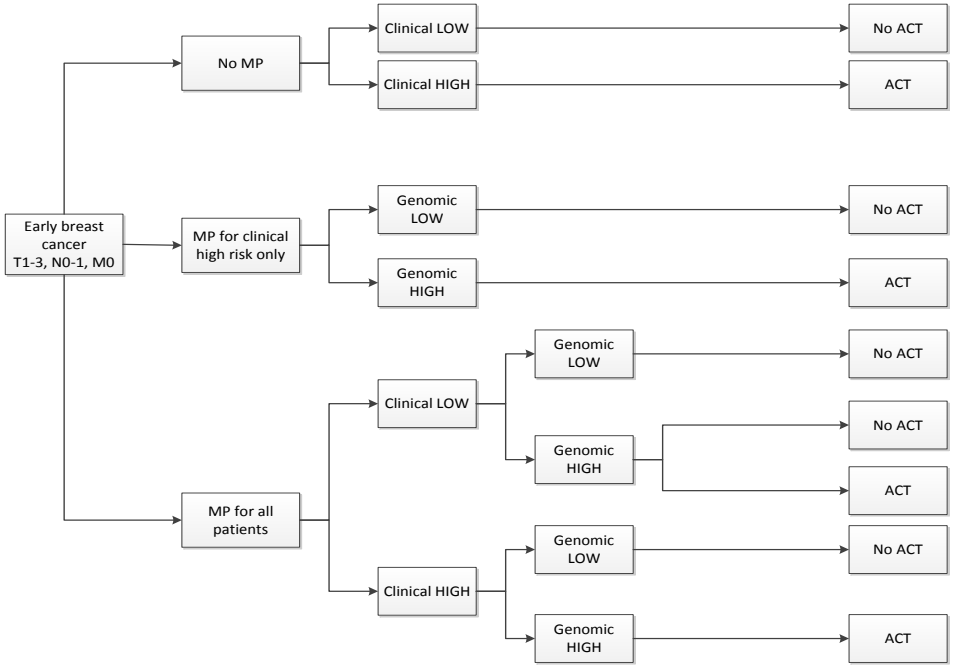
			Figure 20 – Updated Agendia model decision tree  The results below are the results of the base case analysis, (keeping (non-)compliance to MammaPrint recommendation into account based on Bloomfield et al., 2017.), which shows that MammaPrint is dominating mAOL in the clinical high-risk group and in the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

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

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

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Comment number	Name and organisation	Section number	Comment	NICE response
			Results (deterministic) discounted Diagnostic instrument / QALY's / Costs / incremental QALY / incremental COSTS / ICER costs/QALY / budget impact Scenario 1: Total MINDACT population 1 Genomic (MP) 6.6168 £15,003 0.0054 £687 £126,104 2 Clinical (MAOL) 6.6113 £14,316 Scenario 2: Clinical high risk — MP dominating — Annual cost savings UK assuming 25,000 patients per year 1 Genomic (MP) 6.4923 £20,940 0.0198 -£928 -£46,921 £23,210,618 2 Clinical (MAOL) 6.4725 £21,868 Scenario 3: Clinical high risk Er+/Her2- — MP dominating — Annual cost savings UK assuming 18,000 patients per year 1 Genomic (MP) 6.4577 £16,359 0.0399 -£1,447 -£36,250 -£26,053,789.22 2 Clinical (MAOL) 6.4177 £17,806 Sensitivity Analysis (using Cusumano and Stein adherence): Results (deterministic) discounted Diagnostic instrument / QALY's / Costs / incremental QALY / incremental COSTS / ICER costs/QALY / budget impact Scenario 1: Total MINDACT population 1 Genomic (MP) [redacted] £376.423 2 Clinical (MAOL) [redacted] Scenario 2: Clinical high risk — MP dominating — annual cost savings UK assuming 20,000 patients per year 1 Genomic (MP) [redacted] -£46.921 -£18.568.494 2 Clinical (MAOL) [redacted] Scenario 3: Clinical high risk Er+/Her2- — MP dominating — annual cost savings UK assuming 20,000 patients per year 1 Genomic (MP) [redacted] -£36.250 -£28.948.655 2 Clinical (MAOL) [redacted]	
129	Agendia N.V.	Page 323 DAP 37 evaluation report, Nov 2017	*The EAG noted the use of potentially outdated cost estimates in the Agendia model.* The corrected model now includes the cost estimates from as the EAG model (2015/2016adjusted costs) (see Sheet “parameters”, Cells range D490-D505, and sheet “cost countries”, range D1-D19.	Thank you for your comment which the committee considered. The EAG identified a number of errors in

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

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

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

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

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Comment number	Name and organisation	Section number	Comment	NICE response
			Results (deterministic) discounted Diagnostic instrument / QALY's / Costs / incremental QALY / incremental COSTS / ICER costs/QALY / budget impact Scenario 1: Total MINDACT population 1 Genomic (MP) 6,6139 £15.094 0,0059 £411 £70.045 2 Clinical (MAOL) 6,6080 £14.683 Scenario 2: Clinical high risk — MP dominating — annual cost savings UK assuming 20,000 patients per year 1 Genomic (MP) 6,4943 £20.718 0,0283 -£1.880 -£66.517 -£37.604.583 2 Clinical (MAOL) 6,4660 £22.598 Scenario 3: Clinical high risk Er+/Her2- — MP dominating — annual cost savings UK assuming 20,000 patients per year 1 Genomic (MP) 6,4616 £16.214 0,0570 -£2.068 -£36.250 -£41.355.221 2 Clinical (MAOL) 6,4046 £18.282 Sensitivity Analysis 2: using Cusumano probabilities of receiving chemotherapy Results (deterministic) discounted Diagnostic instrument / QALY's / Costs / incremental QALY / incremental COSTS / ICER costs/QALY / budget impact Scenario 1: Total MINDACT population 1 Genomic (MP) 6,6136 £15.171 0,0023 £855 £376.423 2 Clinical (MAOL) 6,6113 £14.316 Scenario 2: Clinical high risk — MP dominating — annual cost savings UK assuming 20,000 patients per year 1 Genomic (MP) 6,4923 £20.940 0,0198 -£928 -£46.921 -£18.568.494 2 Clinical (MAOL) 6,4725 £21.868 Scenario 3: Clinical high risk Er+/Her2- — MP dominating — annual cost savings UK assuming 20,000 patients per year 1 Genomic (MP) 6,4577 £16.359 0,0399 -£1.447 -£36.250 -£28.948.655 2 Clinical (MAOL) 6,4177 £17.806 Sensitivity Analysis 3: Only 50% adherence to treatment recommendation based on MammaPrint result	

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
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<tr><th colspan="7">Results (deterministic) discounted</th></tr>
<tr><th>Diagnostic instrument</th><th>QALY's</th><th>Costs</th><th>incremental QALY</th><th>incremental COSTS</th><th>ICER costs/QALY</th><th>budget impact</th></tr>
<tr><td>Scenario 1: Total MINDACT population</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 Genomic (MP)</td><td>6,6151</td><td>£15.444</td><td>0,0001</td><td>£1.543</td><td>£13.139.043</td><td></td></tr>
<tr><td>2 Clinical (MAOL)</td><td>6,6150</td><td>£13.901</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Scenario 2: Clinical high risk</td><td></td><td></td><td></td><td></td><td>MP dominating</td><td></td></tr>
<tr><td>1 Genomic (MP)</td><td>6,4804</td><td>£22.272</td><td>0,0006</td><td>£1.229</td><td>£2.173.906</td><td></td></tr>
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<tr><td>Scenario 3: Clinical high risk Er+/Her2-</td><td></td><td></td><td></td><td></td><td>MP dominating</td><td>annual cost savings UK assuming 20,000 patients per year</td></tr>
<tr><td>1 Genomic (MP)</td><td>6,4337</td><td>£17.227</td><td>0,0011</td><td>-£41</td><td>-£36.250</td><td>-£827.104</td></tr>
<tr><td>2 Clinical (MAOL)</td><td>6,4326</td><td>£17.269</td><td></td><td></td><td></td><td></td></tr>
</table>
</td><td></td></tr>
<tr><td>136</td><td>Agendia N.V.</td><td>Summary of updated Agendia CE model</td><td>To summarise current updated Agendia model: Using Weibull extrapolation, Bloomfield and Stein chemotherapy use probabilities, half cycle correction, conditional survival, updated UK costs as a base case, our conclusion is: When using the MammaPrint test for the clinical high-risk population, MammaPrint is dominating compared to mAOL, and in the ER+/Her2- population, MammaPrint is also dominating compared to mAOL.</td><td>Thank you for your comment which the committee considered.

The EAG identified a number of errors in the new Agendia model. Please refer to the addendum to responses to comments on DCD2 (5 June 2018).</td></tr>
</table>

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THEME: Alternative technologies

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

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THEME: Conflicts of interest

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

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THEME: TransATAC

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

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THEME: General comments

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

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THEME: General comments

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

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

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

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

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

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

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

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td>154</td><td>NHS Professional</td><td>2.1 (page 6)

3.28 (page 12)</td><td>"stage of disease" should be “stage & grade of disease" Same applies to 3.27"

Intermediate risk = >3.4 to =<5.4, NOT just >3.4 (the latter definition would include poor prognostic disease,).</td><td>Thank you for your comment. These changes have been made in the diagnostics guidance.</td></tr>
<tr><td>155</td><td>Agendia N.V.</td><td>Erratum (version 19th April 2018), Table 1, p13 of 16

(corresponds to Table 123, p355 in DAR)

(theme: incorrect risk classification probabilities)</td><td>Incorrect risk classification probabilities

The values displayed in Table 1 of the Erratum (p13 of 16) are incorrect and do not correspond to the values published in Cardoso et al., 2016, nor are they the values used in the EAG cost effectiveness model.

For easy reference the corrected values are displayed below in Table 1 in red text.

Table 1 – Corrected Risk classification probabilities using MammaPrint (MINDACT)
<table>
<tr><th>Population</th><th>Proportion of patients with risk classification</th><th></th></tr>
<tr><th></th><th>MammaPrint low-risk</th><th>MammaPrint high-risk</th></tr>
<tr><td>MINDACT ITT population (n=6,693)</td><td>0.64</td><td>0.36</td></tr>
<tr><td>MINDACT mAOL clinical high-risk subgroup (n=3,356)</td><td>0.46</td><td>0.54</td></tr>
<tr><td>MINDACT mAOL clinical low-risk subgroup (n=3,337)</td><td>0.82</td><td>0.18</td></tr>
</table></td><td>Thank you for your comment which the committee considered.

The EAG agreed that the values shown in the table of the erratum do not reflect the correct values for the model. The values in the table were calculated from the patient flow diagram presented in Figure 1 of the MINDACT paper reported by Cardoso et al. However, the model does not use these data. Instead, the model uses the corrected genomic risk data (see “Premodel” worksheet, table in cells B163:L171).</td></tr>
</table>

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

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

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

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

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

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