DIAGNOSTICS ASSESSMENT PROGRAMME

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

Draft guidance – Themed comments

Diagnostics Advisory Committee date: 29 November 2023

THEME: General comments on the recommendations

Comment number	Name and organisation	Section number	Comment	NICE response
1	Web comment	General	I fully support the proposed NICE recommendation to use tumour profiling tests in patients with early breast cancer with 1-3 nodes. In my centre, we have been using Oncotype (via locally agreed funding) for node positive patients which has reduced the number of patients needing chemotherapy which has both benefits for the patients (as they can avoid the chemotherapy related toxicities) and for the trust (reducing cost). The evidence supporting Oncotype Dx is robust, based on the RxPonder trial. I would question the use of Endopredict as no similar randomised trial to support use in node positive patients.	Thank you for your comment, which the committee has considered. Evidence was available in LN+ populations that supported the prognostic ability of EndoPredict.
2	Web comment	General	1. This evidence review demonstrates that the use of tumour profiling tests as approved in this recommendation has the ability to reduce the number of breast cancer patients with hormone receptor positive, HER2 negative, lymph node positive (1-3 nodes) who are recommended receipt of adjuvant chemotherapy. This will have valuable effects on both resources/NHS services and, more importantly, for patients and is thus very much supported. I am not aware of any evidence not included in the analysis. Rather than having a detrimental effect regarding equality of opportunity, I believe, this decision will facilitate equity of access to tumour profiling tests in node positive breast cancer patients, which is presently variable around the UK. 3. Additional research on the value of such tests in different sub-groups by ethnicity and gender is to be strongly supported.	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			4. I very much support the statement (p21) encouraging clinicians to promote recruitment to the OPTIMA trial, which will provide valuable information on additional tests. 5. I strongly support the recommendation for research on the patient information provided (p21), as an unmet need.	
3	Web comment	General	This would be a very welcome addition to the management strategy for ER+ patients with low burden nodal involvement. This will direct chemo to those who will benefit most, and undoubtedly spare many women from undergoing chemo unnecessarily.	Thank you for your comment, which the committee has considered.
4	Web comment	1.1	1 Recommendations I fully support this recommendation as with the results of the RxPonder trial and lack of NICE guidance to date we are currently seeing a postcode lottery for patients who could safely avoid chemotherapy and potentially under-treating some who may have mild co-morbidities yet would benefit.	Thank you for your comment, which the committee has considered.
5	Web comment	General	As a breast cancer surgeon, this is an important decision making tool for chemotherapy use in post menopausal N1 patients. This saves some women/men having chemotherapy.	Thank you for your comment, which the committee has considered.
6	Web comment	General	I wholeheartedly agree with the NICE recommendation here for post-menopausal women to be able to access genomic testing for N1 breast cancer. This will save hundreds of patients from having to undergo chemotherapy as well as saving the NHS considerable money and vital chair space in chemotherapy units. It is a decision that is clearly best for patients and the NHS as a whole.	Thank you for your comment, which the committee has considered.
7	Web comment	General	I fully support the use of profiling in node positive post menopausal women. We have used Oncotype Dx in this group for several years and audited our data. We have spared many women from chemotherapy and although it is early, have not seen 'unexpected' recurrences.	Thank you for your comment, which the committee has considered.
8	Web comment	General	On behalf of breast cancer MDT at Oxford, we are fully supportive of this guidance. Oxford MDT has been using the test for node positive women even before the Rxponder data was published (since 2014). The MDT has gradually gained confidence in the genomic assay (Oxford uses oncotype DX, which was strengthened by the trial data, for assessing the need for chemotherapy promoting personalised care and avoiding unnecessary toxicity for those who are unlikely to benefit from the chemotherapy.	Thank you for your comment, which the committee has considered.
9	Web comment	General	I am a Consultant Breast Surgeon and Clinical Lead for Breast Cancer at the Norfolk and Norwich University Hospital, we have a large Unit seeing approximately 700 new cases of breast cancer per year.	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			We have been using the Oncotype DX test for many years for node negative patients and more recently for 1-3 node +ve post-menopausal patients. We discussed the draft NICE guidance regarding node positive patients at our Unit Operational Policy Meeting on 20/11/2023. As an MDT, we are fully in favour of the use of this test - we find it an invaluable tool that brings extra confidence to decision making and spares large numbers of women a toxic treatment that will not affect their outcome (not to mention the benefits to our extremely stretched Oncology Department and the financial benefits). We are fully supportive of this draft guidance.	
10	Myriad	1.1, page 3	We agree with the recommendation for EndoPredict as an option to guide adjuvant chemotherapy decisions for women and men with ER+ HER2- early breast cancer with 1 to 3 positive lymph nodes.	Thank you for your comment, which the committee has considered.
11	Breast Cancer Now	1, page 3	Recommendations We are pleased to see that a number of tests have been recommended for use as options to guide adjuvant chemotherapy decisions for certain patients with oestrogen receptor or progesterone receptor positive, HER2 negative early breast cancer with 1 to 3 positive lymph nodes. A diagnosis of breast cancer can cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be extremely shocking and impact on people's emotional wellbeing, whilst in the longer-term, the fear of breast cancer returning or spreading to other parts of the body (such as the bone, liver, lung, and brain) which is known as secondary (or metastatic) breast cancer and is incurable can be extremely frightening and distressing for patients. The availability of tumour profiling tests in lymph node negative patients has helped tailor treatment pathways for a number of patients and has spared some patients from the potential short- and long-term effects of chemotherapy. They have also meant less time attending hospital appointments and avoiding the impact that chemotherapy may have had on work and/or caring responsibilities. It is a welcome step to expand the use of some tumour profiling tests to some patients with lymph node positive early breast cancer as this will enable more patients to safely avoid the gruelling side effects of chemotherapy. This will provide an opportunity to improve the quality of life for this group of patients, provide them with confidence regarding how their condition is managed and potentially give them additional reassurance. As the guidance highlights, it could also identify people who would be considered to have a low risk of disease recurrence based on	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			clinical factors, but who may actually benefit from chemotherapy. Therefore, providing patients and clinicians with more information to help inform shared decision-making.	
12 13 14 15 16 17	Web comment	1, 1.1, 3.4, 3.7, 3.9, 3.19	Recommendations I am a breast cancer patient, diagnosed in 2005 with ER+/ Her2- locally advanced (lymph nodes) breast cancer. I had chemotherapy which was horrible and threw me into an early menopause which was ghastly and was compounded by 10 years of oestrogen blocking drugs. But I am still here and disease free in 2023. I welcome this report on the use of tumour profiling tests to guide treatment decisions. But, I feel that your recommendation to use EndoPredict and Oncotype DX tests to guide chemotherapy decisions in early breast cancer is premature. The evidence is insufficient! The evidence is just not there yet for the ability of either test to PREDICT response to chemotherapy. It is clear from sections 3.7 and 3.10 (and in other places in the document 3.17 & 3.19) that the evidence for prediction is uncertain. You use complex reanalyses of SWOG-8814 and RxPONDER to tentatively suggest that Oncotype DX may have some predictive value for chemo decisions. And, I could see no evidence presented for EndoPredict being predictive of chemo response. In 2.13 the company making the test claim it can be used to predict chemo response - but no evidence is presented! The evidence is just not there yet for the ability of either test to PREDICT response to chemotherapy.	Thank you for your comments, which the committee has considered. For EndoPredict and Prosigna, the evidence identified in a mostly lymph node-positive populations was on prognostic ability (to predict the risk of disease recurrence). Prognostic tests can be useful to guide chemotherapy decisions as the absolute benefit of chemotherapy is dependent on the absolute level of risk (see section 3.6). With only prognostic ability considered, the committee concluded that EndoPredict and Prosigna were likely to be cost-effective uses of NHS resources when used to guide chemotherapy decision making with postmenopausal women. For Oncotype DX, the committee acknowledged the uncertainty in the evidence but concluded that it is likely that the test has some predictive ability (see sections 3.9 and 3.10). Although the committee suggested that the size of the difference in chemotherapy benefit may be overestimated between those with low and high risk according to Oncotype DX, the test

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				was still cost effective if this was reduced (see section 3.18).
18	Web comment	3.4	I think it is very dangerous to conflate risk of recurrence and prognostic ability with the prediction of chemotherapy benefit. They are not the same and there is just not enough evidence YET for these tests being predictive of chemotherapy benefit.	Thank you for your comment, which the committee has considered. The committee acknowledged that some tests only have evidence for prognostic ability in populations that are mostly lymph node positive. However, prognostic tests can be useful to guide chemotherapy decisions as the absolute benefit of chemotherapy is dependent on the absolute level of risk (see section 3.6). So, the test does not necessarily have to be predictive of chemotherapy benefit to be useful and cost-effective. With only prognostic ability considered, the committee concluded that EndoPredict and Prosigna were likely to be cost-effective uses of NHS resources when used to guide chemotherapy decision making with postmenopausal women (see sections 3.16 and 3.19).
19 20	Web comment	1, 3.5, 3.7, 3.10, 31.7	I am writing to you about the above draft guidance. Below I have added the sentences from the report in italics and then added my specific comments, for each one. The work of the committee has been considerable, but I argue that the evidence to support the use of multigene signatures to predict chemotherapy response in ER+ve,PR+ve,HER2-ve breast cancer, is insufficient at present. Draft recommendations	Thank you for your comment, which the committee has considered. The committee acknowledged that some tests only have evidence for prognostic ability in populations that are mostly lymph node positive. However, prognostic tests can be useful to guide chemotherapy decisions as the absolute benefit of

Comment number	Name and organisation	Section number	Comment	NICE response
			Use EndoPredict or Oncotype DX as options to guide adjuvant chemotherapy decisions for oestrogen receptor (ER)- or progesterone receptor (PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer with 1 to 3 positive lymph nodes. They can be used for women who have been through the menopause and men, only if: • information provided by the test would help them choose, with their healthcare professional, whether or not to have adjuvant chemotherapy • the companies provide the tests to the NHS with the discounts agreed in the access proposals. This is the main recommendation in the draft guidance NICE DG10075, which in my view is not supported by the evidence cited in the report. Predictive Ability 3.5 The EAG did not identify any evidence on the predictive ability of EndoPredict or Prosigna in a population that was mostly people with LN-positive breast cancer. So, these tests could only be considered to have prognostic ability. Section 3.5 clearly states that there is no evidence of predictive ability for chemotherapy with EndoPredict, so the recommendation is not supported by any evidence. Section 3.7 The committee felt that the evidence was uncertain, but the results of SWOG-8814 and RxPONDER together suggest it is likely that Oncotype DX is predictive of chemotherapy benefit in postmenopausal women with ER- or PR-positive, HER2-negative early breast cancer with 1 to 3 positive lymph nodes. If the evidence is uncertain from 2 trials, then how does putting them together make that evidence certain. When as clinicians we examine the benefits of two different treatments, or the risks of predispositions from SNPs and breast cancer, we are advised to multiply the numbers we get. Surely 2 databases which are in themselves uncertain, will simply be more uncertain if you put them together – all sorts of unknown biases may be introduced. 3.10	chemotherapy is dependent on the absolute level of risk (see section 3.6). So, the test does not necessarily have to be predictive of chemotherapy benefit to be useful and cost-effective. With only prognostic ability considered, the committee concluded that EndoPredict and Prosigna were likely to be cost-effective uses of NHS resources when used to guide chemotherapy decision making with postmenopausal women (see sections 3.16 and 3.19). For Oncotype DX, the committee acknowledged the uncertainty in the evidence but concluded that it is likely that the test has some predictive ability (see sections 3.9 and 3.10). Although the committee suggested that the size of the difference in chemotherapy benefit may be overestimated between those with low and high risk according to Oncotype DX, the test was still cost effective if this was reduced (see section 3.18). With regard to impact on chemotherapy decisions, the committee concluded that it was reasonable to generalise decision impact data between tests, as other methods of assessing tests other than Oncotype DX would be more

Comment number	Name and organisation	Section number	Comment	NICE response
			The committee concluded that it was unclear whether evidence on how test results affected chemotherapy decisions was generalisable between tumour profiling tests. As stated elsewhere this means that implementation research is required. 3.17 The committee recalled its discussions on the uncertainty around the predictive ability of Oncotype DX for postmenopausal women (see section 3.7), and that the was likely overestimated in SWOG-8814 and underestimated in RxPONDER. It also noted that the economic model used a constant hazard ratio for the effect of chemotherapy over time. This may overestimate the effect because the greatest benefit of chemotherapy is seen in the first few years (see section 3.15). It concluded that it was likely that Oncotype DX has some predictive ability for chemotherapy benefit in this population, but that the predictive effect was possibly overestimated in the economic model. It is evident that there is plenty of uncertainty.	uncertain (see section 3.13). However, the committee included decision impact research for EndoPredict and Prosigna in their considerations (see section 3.22).

THEME: Similarities and differences between tests

Comment number	Name and organisation	Section number	Comment	NICE response
21	Web comment	3.9	Committee discussion – Effect of menopausal status An important point is that all these tests represent surrogate markers of prognosis and/or prediction of response. They do not interrogate the tumour tissue on the presence or absence of molecules directly involved in tumour survival, progression or response to therapy. Predictive and prognostic functions may be strengthened by additional parameters not intrinsic to the test, for instance menopausal status, that similarly lack direct involvement in the assessing the molecular elements of the tissue that interact with the proposed therapy. Therefore, while each of these tests assesses present of different transcripts, none of the transcripts is biased and they collectively represent a surrogate marker. On these grounds, it can	Thank you for your comment, which the committee has considered. The committee heard that there is a plausible biological explanation for the difference in chemotherapy benefit between pre- and postmenopausal women, and that the risk of incorrectly foregoing chemotherapy is higher in premenopausal women than in

Comment number	Name and organisation	Section number	Comment	NICE response
			be extrapolated that if one surrogate marker can be used to assess response in premenopausal women, there is no theoretically barrier that precludes the use of the other tests in a similar cohort, even is there is currently no supporting information.	postmenopausal women. Given that an effect of menopausal status was seen for Oncotype DX, the committee concluded that it is reasonable to assume that similar differences would be seen for other tests (see section 3.12).
22	Web comment	3.10	Committee discussion - Effect of test results on chemotherapy decisions This is an important point. Specifically, the concordance between risk groups obtained by different tests. In other word a patient deemed to be low risk with Endopredict, may be high risk with Oncotype. This highlight the fact that these tests define probabilities and that within those probabilities there remain responders and non responders, and patient that will experience recurrence and those who will not. This raises the question as to whether a single surrogate marker can be relied upon for the individual patient. We continue to treat population with little regard for the individual. You may want to decide whether it would be beneficial to invest in assessing the concordance between all or some of these tests.	Thank you for your comment, which the committee has considered. The committee recognised that the tests categorise different numbers of people as low, intermediate or high risk, but there was not enough comparative evidence to compare the tests directly (see section 3.21). When assessed individually against the comparator (decision making without the use of tumour profiling tests), EndoPredict, Oncotype DX and Prosigna were all found to be clinically effective.
23	UCL Cancer Institute	3.9, page 15	“The committee recalled that different tests measure the expression of different genes.” Whilst this statement is correct, there is some overlap in individual genes and in particular in the functions that these represent. Specifically, all 4 tests considered include measures of hormone receptor signalling and proliferation. How these are calculated and weighted in the final output differ. Notwithstanding, there is a substantial albeit incomplete agreement in how the tests classify individual tumours so the tests should not be considered to be completely independent of each other. Reference: Bartlett et al, J Natl Cancer Inst. 2016, PMID 27130929	Thank you for your comment. The committee considered your comment in their deliberations on whether the evidence on decision impact could be generalised between tests. Please see further detail in section 3.13.
24	UCL Cancer Institute	3.9, page 15	The [NICE] committee “also noted that the way different tests defined risk groups resulted in large differences in the number of people who would be assigned as having low, intermediate or high risk”.	Thank you for your comment, which the committee has considered.

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			All 4 tests provide prognostic estimates. However, the extent of lymph node involvement is an important component of clinical risk estimates, as exemplified by the Nottingham Prognostic Index. Both EndoPredict (EPClin) and Prosigna provide prognostic estimates that are adjusted for tumour stage whilst Oncotype DX and MammaPrint do not. Oncotype DX in particular underestimates the risk of patients with 1-3N+ disease because of this so is a much less accurate prognostic tool than EndoPredict and Prosigna. It can only work if it is predictive in which case stage considerations are less important. Reference: Sestak et al, JAMA Oncol. 2018, PMID 29450494	For Oncotype DX, the committee acknowledged the uncertainty in the evidence but concluded that it is likely that the test has some predictive ability (see sections 3.9 and 3.10).

THEME: Generalisability of decision impact data

Comment number	Name and organisation	Section number	Comment	NICE response
25	Web comment	3.19	3.19 The only available evidence on how test results influenced chemotherapy recommendations or decisions was for Oncotype DX. Recommendations and implementation are likely to be more affected by behavioural factors in clinic from both patients and doctors, than any difference in test results.	Thank you for your comment. The committee considered your comment in their deliberations on whether the evidence on decision impact could be generalised between tests. Please see further detail in section 3.13.
26	Veracyte	3.10 and 3.19, pages 16 and 20	In section 3.10 and 3.19 it is noted that the only available evidence on how test results influenced chemotherapy recommendations or decisions was for Oncotype DX. This evidence, as we understand was taken for 12 decision impact studies that were conducted in the UK. These studies showed a wide variation in the potential for reduction of chemotherapy (28% to 75%) and do not account for patient outcome beyond the initial decision in guiding treatment. One of the main studies cited was the decision impact study by Holt et al. As far as we are aware this study has not yet undergone peer review or been published so we would request that the committee considers whether the study should be included in the absence of peer review.	Thank you for your comment, which the committee has considered. NICE considers all types of evidence in its evaluations, including unpublished data (see section 3.3.1 in NICE's manual on health technology evaluations).
27	Exact Sciences	3.10, page 16	It was our understand from the open session of the Committee meeting on 26th October that the Committee concluded that the evidence for Oncotype DX could not be generalised to the other	Thank you for your comment, which the committee has considered.

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			tests. Unless the committee changed their mind during the closed session, we request that the below wording be amended to reflect this decision. "The committee concluded that it was unclear whether evidence on how test results affected chemotherapy decisions was generalisable between tumour profiling tests."	The committee discussed this point further and concluded that evidence on how test results affected chemotherapy decisions could reasonably be generalised between tumour profiling tests. Please see section 3.13 for more detail.
28	Exact Sciences	3.10, page 16	In the absence of any evidence of their impact on chemotherapy treatment decisions, it is not clear how a recommendation for use in clinical practice can be made for any of the other tests. This does not seem to have been explained by the committee. "The only available evidence on how test results influenced chemotherapy recommendations or decisions was for Oncotype DX. The committee recalled that different tests measure the expression of different genes. It also noted that the way different tests defined risk groups resulted in large differences in the number of people who would be assigned as having low, intermediate or high risk, even between tests with the same number of risk categories. So, clinicians may not interpret the risk classifications from EndoPredict, MammaPrint or Prosigna in the same way that they would for Oncotype DX."	Thank you for your comment, which the committee has considered. The committee discussed this point further and concluded that evidence on how test results affected chemotherapy decisions could reasonably be generalised between tumour profiling tests. Please see section 3.13 for more detail.
29	Exact Sciences	3.15, 3.19, pages 18 & 20	It may be questionable whether the full uncertainty associated with applying Holt et al. data to the EndoPredict test and other tests has been adequately tested. The NICE committee's conclusion is based on scenario analyses using other studies for the Oncotype DX test, which are also not applicable to the other tests. It is possible that the uncertainty associated with this approach was underestimated. This has important consequences for patient outcomes and cost-effectiveness results.	Thank you for your comment, which the committee has considered. The committee concluded that evidence on how test results affected chemotherapy decisions could reasonably be generalised between tumour profiling tests. However, further research on decision impact in other tests would be helpful to reduce uncertainty. Please see sections 3.13 and 3.22 for more detail.
30	UCL Cancer Institute	DAR 4.3, pages 123-4	Pre-test probability of receiving adjuvant chemotherapy The use of (confidential and unpublished) information from the Holt decision impact study (DAR refs 17 & 35) to estimate the frequency of chemotherapy use in standard clinical practice is both	Thank you for your comment, which the committee has considered. The EAG note that the pre-test chemotherapy probability for all

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			a strength and a weakness. On the one hand it provides information on real world clinical decision making across a range of centres. On the other hand, we have absolutely no idea how decisions were actually made. A key question is the extent to which clinicians used prognostic tools, particularly PREDICT in this study in order to optimise pre-test decision making. Other unknowns are whether the premenopausal patients recruited by this study are included in the estimates and whether the proportions of patients with each level of lymph node involvement as reported in DAR reference 17 has been maintained. A criticism of all decision impact studies is that baseline/ pre-test decisions on chemotherapy use are potentially influenced by the very knowledge of participating clinicians that they are recruiting into a decision impact study.	base case analyses was estimated to be 0.80, based on Holt et al. (2023). Estimates for pre-menopausal and post-menopausal subgroups within this study were nearly identical (0.81 and 0.79, respectively).

THEME: Predictive ability and cost-effectiveness of MammaPrint

Comment number	Name and organisation	Section number	Comment	NICE response
31	Agendia	Page 1	The advisory committee is interested in comments answering the following question: *"Has all of the relevant evidence been taken into account?"* As for MammaPrint, the relevant evidence from MINDACT for post-menopausal women (aged >50) with HR+/HER2-/LN+ Clinical-High / Genomic-low (C-high/G-low) breast cancer has not been taken into account. Patients with C-high/G-low tumors are the most relevant group for the assessment to guide chemotherapy use, and this was truly randomized in MINDACT between chemo versus no chemo. This should be the group primarily evaluated in the EAG modeling. To underpin the findings of the MINDACT trial and the de-escalation of chemotherapy informed by MammaPrint, we requested the PIs of the MINDACT trial, namely [redacted]	Thank you for your comment. The committee considered the comments from Agendia and the MINDACT investigators in the second committee meeting, which included the evidence referred to in the comment. The EAG's modelling for MammaPrint was focused on the clinical high-risk population as described in MINDACT. The committee concluded that there was not enough evidence to definitively say whether or not MammaPrint is predictive of chemotherapy benefit.

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<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>[redacted], to provide their insights.
We anticipate that the presented letter from these esteemed experts will provide confidence in the demonstrated value of MammaPrint for post-menopausal women (aged >50) in HR+/HER2-/LN+ disease.

A copy of the letter can be found in [comment 33] and in PDF on the NICE Docs portal.</td><td></td></tr>
<tr><td>32</td><td>Agendia</td><td>Page 1</td><td>The advisory committee is interested in comments answering the following question:

“Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?“

As for MammaPrint, the summaries of clinical and cost-effectiveness evidence are incomplete, as the evidence for the post-menopausal (aged >50) subgroup from MINDACT has not been included in the evidence interpretation.
For the group of patients who are post-menopausal with HR+/HER2-/LN+ C-high/G-low disease, and randomized between chemo and no chemo, shown below, there is only a very small non-significant chemotherapy benefit at 8-years for the endpoint DMFI of 0.2%, and no benefit of chemotherapy at 8-years for Overall Survival, -1.1%.

We highlight here this post-menopausal patient group, as the Committee paid specific attention to this group in the draft guidance, however, these specific data were not considered for the MammaPrint evaluation.

<table>
<tr><th colspan="8">C-High/G-low HR+/HER2-/LN+ >50 population</th></tr>
<tr><th colspan="4">5-year DMFI</th><th colspan="3">8-year DMFI</th><th>DMFI</th></tr>
<tr><th></th><th>Survival estimates</th><th>Absolute diff.</th><th>Relative Risk</th><th>Survival estimates</th><th>Absolute diff.</th><th>Relative Risk</th><th>Adjusted Hazard Ratio</th></tr>
<tr><td>ACT</td><td>96.0%</td><td rowspan="2">-0.7%</td><td rowspan="2">1.21</td><td>91.4%</td><td rowspan="2">0.2%</td><td rowspan="2">0.98</td><td>0.88 (0.46-1.68)</td></tr>
<tr><td>no ACT</td><td>96.7%</td><td>91.2%</td><td>Reference</td></tr>
<tr><th colspan="4">5-year Overall Survival</th><th colspan="3">8-year Overall Survival</th><th>Overall Survival</th></tr>
<tr><th></th><th>Survival estimates</th><th>Absolute diff.</th><th>Relative Risk</th><th>Survival estimates</th><th>Absolute diff.</th><th>Relative Risk</th><th>Adjusted Hazard Ratio</th></tr>
<tr><td>ACT</td><td>97.5%</td><td rowspan="2">-0.6%</td><td rowspan="2">1.32</td><td>94.8%</td><td rowspan="2">-1.1%</td><td rowspan="2">1.27</td><td>0.99 (0.45-2.18)</td></tr>
<tr><td>no ACT</td><td>98.1%</td><td>95.9%</td><td>Reference</td></tr>
</table>
</td><td>Thank you for your comment, which the committee has considered.
The committee appreciated that the subgroup analysis for people aged over 50 with 1-3 lymph nodes was provided. The EAG conducted a threshold analysis using the HR of 0.88 in the genomic low risk group, and HRs of 0.10 to 1.0 for the genomic high risk group. This analysis is presented in addendum 4. The committee considered the analyses in this comment, as well as the EAG’s additional analyses. The committee concluded that there was not enough evidence to definitively say whether or not MammaPrint is predictive of chemotherapy benefit. This was because there was no evidence for the size of chemotherapy benefit in the clinical high, genomic high risk group. Additionally, the committee understood that the effect of chemotherapy in the overall MINDACT clinical high-risk, MammaPrint low-risk cohort (including LN-negative and LN</td></tr>
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			The clinically not meaningful benefit of 0.2%, represents a relevant and very high Negative Predictive Value (NPV). As stated in the physician letter: "The NPV of MammaPrint is defined as MammaPrint correctly predicting that a patient will not benefit from chemotherapy. With the absolute difference of 0.2 percent, the NPV of MammaPrint would be 99.8%. This metric implies that a physician must treat 500 women with chemotherapy, to prevent one event. While for all other women, chemotherapy will only unnecessarily deteriorate the patients' health due to chemotherapy related side effects." And as also stated: *"This is different from the Positive Predictive Value (PPV) of genomic signatures, defined as a genomic signature correctly predicting that a patient will benefit from chemotherapy. Investigating the PPV of a genomic signature for all breast cancer patients would be highly unethical, as we would have to refrain treating patients with chemotherapy who are clearly in high need of chemotherapy. Hence, MINDACT did not, and could not, investigate the PPV of MammaPrint in clinical high and genomic high risk patients. However, the absence of a PPV randomization in the clinical high risk genomic high risk group, does not detract from the strong NPV MammaPrint has as clearly demonstrated in MINDACT."* In alignment with the DAP71 assessment's goal of evaluating the absence of chemotherapy benefits and identifying patients who do not require it, it is crucial to disentangle the positive predictive value and negative predictive value. Specifically, the focus should be on negative predictive value to accurately assess the absence of treatment benefits. Notably, this is what was specifically explored in MINDACT. MINDACT tested the chemotherapy de-escalation and showed a Relative Risk (RR) for chemotherapy benefit in the HR+/HER2-/LN+ C-High/G-low (all ages) population of 0.85. If we limit this group to post-menopausal women (aged >50), as favoured for Oncotype DX and EndoPredict in the draft guidance, the RR for MammaPrint is 0.98. In the EAG modelling, chemotherapy benefit has been applied as a RR of 0.71 for all patients. The EAG states "that a non-significant benefit is not necessarily the same as no benefit and in addition, that there was no evidence to estimate the size of chemotherapy benefit in the	positive breast cancer) was significant (HR 0.66, 95% CI 0.46 to 0.95). So, the fact that the effect of chemotherapy in the LN-positive subgroup was non-significant may be because the confidence interval is wider for the smaller number of participants, rather than evidence of no benefit from chemotherapy in that subgroup (see section 3.8). The committee also considered a scenario in which MammaPrint was considered to be prognostic only, but used the hazard ratio from the >50 population across both risk groups. Using the MINDACT subgroup analysis HR across both risk groups would imply a lower benefit of chemotherapy overall than was seen in the EBCTCG meta-analysis, which included a much larger population than MINDACT. So, the committee concluded that the EAG's base case was more appropriate (see section 3.17). The EAG note that the value of 0.71 used in the model is a hazard ratio, not relative risk. This was derived from the event rates observed in EBCTCG, and differs slightly from the approach used in DG34, which used a 10-year relative risk of 0.76.

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			MammaPrint high risk group. Therefore, the predictive ability of MammaPrint remained uncertain." -Page 14/23 of Draft guidance The RR of 0.71 used in the current EAG assessment is a number that is derived from the EBCTCG data which is based on all patients without genomic risk stratification, which is not justified for the MammaPrint G-low group. Based on our argumentation, we are of the opinion that the more appropriate approach would be to use the data observed in MINDACT to inform the Clinical High Genomic Low Risk Hazard Ratio, and only to use the EBCTCG 0.71 HR for Genomic High risk, because as explained this was unethical and was not randomized in MINDACT. To make the difference in the approach tangible, we hereby want to quantify the modelled chemotherapy benefit at 8-years with the two modelling approaches. **When using the RR of 0.98** in the G-low group, as observed in MINDACT, a chemotherapy benefit at 8-years would be accumulated of ~0.2%. <u>This is in line with observations from MINDACT</u> **When using the RR of 0.71** in the G-low group, derived from the EBCTCG analysis, a chemotherapy benefit at 8-years would be accumulated of ~2.6%. <u>This is 13 times higher than observed in the Phase 3 Prospective Randomized MINDACT Trial. A clear overestimation of chemotherapy benefit.</u> To conclude, the randomized aspect of the trial clearly shows that there is no chemotherapy benefits in women >50 with HR+/HER2-/LN+ with a Clinical High risk and MammaPrint Low Risk. This, when properly incorporated into the EAG model, leads to MammaPrint being a highly cost-effective and dominant treatment strategy.	
33	Agendia	1, page 4	On Page 4 of the draft guidance the following is stated: *"MammaPrint is less clinically effective and costs more than standard care."* This is not what is observed when focusing on the post-menopausal/ >50y group from MINDACT. Applying these inputs from MINDACT in the EAG model will result in MammaPrint being a highly cost effective strategy.	Thank you for your comment. The scenarios outlined in this comment were considered by the committee, but all scenarios assume MammaPrint has predictive ability. The committee concluded that there was not enough evidence

<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 prepare Scenario 7 (MammaPrint) to run analyses for post-menopausal patients, the following settings should be changed:
• “Settings” cell C5 should be changed to 62
• “Settings” cell C6 should be changed to 0
• “Settings” cell C7 should be changed to 38
• “Settings” cell C15 should be changed to “Holt et al., 2023, LN+ post-menopausal, 2-level”

When the EAG model is based on MINDACT results, as clarified in the previous comments, and as attested in the letter of the PIs, MammaPrint is a clinically effective and cost-saving treatment strategy. The only parameter (outside of the settings) in the EAG model that should be changed is the Relative Risk reduction (or Hazard Ratio) for the genomic low risk group for MammaPrint.

When the Hazard Ratio of 0.88 of DMFI is used for G-low (as reported in the HR+/HER2-/LN+ >50 subgroup), keeping the G-high HR at 0.71, results of the EAG model are as shown in the table below. MammaPrint is a dominating treatment strategy in the deterministic and probabilistic analysis with 0.02 to 0.04 QALYs gained, and £1038 to £1497 in cost-savings per patient.

<table>
<tr><th colspan="9">EAG Model: HR+/HER2-/LN+ >50 with G-low Hazard Ratio set at 0.88</th></tr>
<tr><td rowspan="3">Deterministic</td><td>Option</td><td>LYGs</td><td>QALYs</td><td>Costs</td><td>Inc. LYGs</td><td>Inc. QALYs</td><td>Inc. Costs</td><td>ICER</td></tr>
<tr><td>MammaPrint</td><td>20.68</td><td>10.75</td><td>£37396</td><td>0.001</td><td>0.02</td><td>-£1038</td><td>MammaPrint dominating</td></tr>
<tr><td>Usual care</td><td>20.68</td><td>10.73</td><td>£38434</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td rowspan="3">Probabilistic</td><td>Option</td><td>LYGs</td><td>QALYs</td><td>Costs</td><td>Inc. LYGs</td><td>Inc. QALYs</td><td>Inc. Costs</td><td>ICER</td></tr>
<tr><td>MammaPrint</td><td>20.57</td><td>10.39</td><td>£38184</td><td>0.06</td><td>0.04</td><td>-£1497</td><td>MammaPrint dominating</td></tr>
<tr><td>Usual care</td><td>20.51</td><td>10.34</td><td>£39681</td><td>-</td><td>-</td><td>-</td></tr>
</table>

In MINDACT the follow-up is most robust at 8-years, with 70.4% of patient’s follow-up until 8-years. A Hazard Ratio is calculated over the full follow-up period of MINDACT, which is up to 12 years. However, at 10-years the follow-up percentage drops below 20%. Therefore, the survival estimate at 8-years is most certain within MINDACT and subsequently displays the best estimate of the chemotherapy benefit. For this reason, Agendia believes it is more appropriate to inform</td><td>to definitively say whether or not MammaPrint is predictive of chemotherapy benefit (see section 3.8). So, it preferred scenarios in which MammaPrint had only prognostic benefit. In these scenarios, MammaPrint was less clinically effective and cost more than standard care (see section 3.17).
The EAG note that the value of 0.71 used in the model is a hazard ratio, not relative risk. This was derived from the event rates observed in EBCTCG, and differs slightly from the approach used in DG34, which used a 10-year relative risk of 0.76.

The committee preferred to use hazard ratios over the relative risk because they account for the event rates over the whole study period rather than at a specific timepoint.</td></tr>
</table>

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<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>the input parameter for chemotherapy benefit in G-low in the EAG model with the observed benefit in MINDACT at 8-years. This observed benefit can be displayed as the Relative Risk (RR) for DMFI at 8-years, which is 0.98 for patients with G-low risk. Furthermore, the EBCTCG input parameter for the G-high group is set at 0.71 and is based on the EBCTCG estimate, which is to our understanding also calculated like a RR, rather than an actual Cox Model Hazard Ratio.

With the HR for the G-low group (MammaPrint Low Risk) put at 0.98 and the HR for G-high put at 0.71, results are as presented in the table below. MammaPrint is a dominating treatment strategy in the deterministic and probabilistic analysis with 0.06 to 0.09 QALYs gained, and £1845 to £2408 in cost-savings per patient.
<table>
<tr><th colspan="9">EAG Model: HR+/HER2-/LN+ >50 with G-low Hazard Ratio set at 0.98</th></tr>
<tr><td rowspan="3">Deterministic</td><td>Option</td><td>LYGs</td><td>QALYs</td><td>Costs</td><td>Inc. LYGs</td><td>Inc. QALYs</td><td>Inc. Costs</td><td>ICER</td></tr>
<tr><td>MammaPrint</td><td>20.67</td><td>10.74</td><td>£37521</td><td>0.10</td><td>0.06</td><td>-£1845</td><td>MammaPrint</td></tr>
<tr><td>Usual care</td><td>20.57</td><td>10.69</td><td>£39366</td><td>-</td><td>-</td><td>-</td><td>dominating</td></tr>
<tr><td rowspan="3">Probabilistic</td><td>Option</td><td>LYGs</td><td>QALYs</td><td>Costs</td><td>Inc. LYGs</td><td>Inc. QALYs</td><td>Inc. Costs</td><td>ICER</td></tr>
<tr><td>MammaPrint</td><td>20.56</td><td>10.38</td><td>£38280</td><td>0.17</td><td>0.09</td><td>-£2408</td><td>MammaPrint</td></tr>
<tr><td>Usual care</td><td>20.39</td><td>10.29</td><td>£40688</td><td>-</td><td>-</td><td>-</td><td>dominating</td></tr>
</table>
In conclusion when applying the observed MINDACT results to the EAG model, MammaPrint is a highly cost effective treatment strategy, which would justify the recommendation for MammaPrint use in HR+/HER2-/LN+ disease in post-menopausal women, alongside other recommended GEP-tests.</td><td></td></tr>
<tr><td>34</td><td>Agendia</td><td>Page 1</td><td>The advisory committee is interested in comments answering the following question:

“Are the recommendations sound, and a suitable basis for guidance to the NHS?“

As explained in comments [31 through 33], we believe that the recommendation for MammaPrint in its current form is not a suitable basis for guidance to the NHS. The draft guidance should take in consideration the data for the post-menopausal (aged >50) subgroup from MINDACT, that clearly shows the absence of benefit for post-menopausal patients with HR+/HER2- C-high/G-low breast cancer with up to three lymph nodes involved, as also attested in the physician letter, presented in the next comment.</td><td>Thank you for your comment, which the committee has considered. Please refer to the responses to comments 31 to 33.</td></tr>
<tr><td>35</td><td>Agendia</td><td></td><td>This comment presents the physician letter from [redacted]</td><td>Thank you for your comment, which the committee has considered.</td></tr>
</table>

Comment number	Name and organisation	Section number	Comment	NICE response
			[redacted], that attests for the proven Negative Predictive Value of MammaPrint in postmenopausal women (aged >50) with HR+/HER2-/LN+ C-high/G-low breast cancer. To whom it may concern, I trust this letter finds you well. My name is [redacted], and I am writing to you in my capacity as a medical oncologist, principal investigator of the MINDACT trial, co-founder of the Breast International Group, and former president of the European Organisation for Research and Treatment of Cancer and the European Society of Medical Oncology. I represent the MINDACT collaborative group, consisting of 112 institutions across 9 European countries, and aim to address concerns shared by Agendia NV about how the MammaPrint genomic signature is sometimes evaluated in health technology assessments. We are very keen to prevent misinterpretation of the objectives and outcomes of the MINDACT trial that may negatively influence the patient access landscape for MammaPrint in Europe. Throughout this letter, I intend to clarify the goal of the trial and summarize the trial's findings, specifically focusing on patients aged 50 and above with HR+HER2- invasive early-stage breast cancer, involving up to three affected lymph nodes. It is my sincere hope that this clarification will contribute to a better understanding of the MammaPrint evaluation, providing valuable insights for consideration. The primary aim of MINDACT was to test our hypothesis that the group of patients with early (potentially curable) breast cancer who would be seen as at high risk of developing a non-curable recurrence of their breast cancer, based on traditional risk factors (**high clinical risk**), but whose cancer was in fact NOT at such a high risk of recurrence as defined by the MammaPrint® test (**low genomic risk**), would have NO clinically meaningful benefit from being given chemotherapy. This objective of MINDACT was clearly met. The primary endpoint of MINDACT was a predetermined "non-inferiority" threshold set as having at least 92% Distant Metastasis Free Survival (DMFS) at 5 years. This was the minimum acceptable outcome for 5-year DMFS for the cohort at clinical high risk, but genomic low risk that did not receive chemotherapy. In the NEJM 2016 publication of MINDACT 5-years DMFS was 94.7% (95% CI = 92.5 to 96.2) and in the Lancet 2021 publication, 95.1% (95% CI = 93.1 to 96.6), in which nearly all (92%) patients had at least 5 years of follow-up.	The committee concluded that there was not enough evidence to definitively say whether or not MammaPrint is predictive of chemotherapy benefit. This was because there was no evidence for the size of chemotherapy benefit in the clinical high, genomic high risk group. The committee recognised that the design of MINDACT meant that this data would not be available to populate the economic model. Additionally, the committee understood that the effect of chemotherapy in the overall MINDACT clinical high-risk, MammaPrint low-risk cohort (including LN-negative and LN positive breast cancer) was significant (HR 0.66, 95% CI 0.46 to 0.95). So, the fact that the effect of chemotherapy in the LN-positive subgroup was non-significant may be because the confidence interval is wider for the smaller number of participants, rather than evidence of no benefit from chemotherapy in that subgroup (see section 3.8).

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We were informed that throughout a number of European Health Technology Assessments, the randomization conducted in MINDACT for the clinical high risk and MammaPrint genomic low risk group is seen as the most important in assessing the clinical utility of MammaPrint. Therefore, I would like to specifically comment on the results of the randomization in MINDACT for the endpoints that take into account the “events” that are life-threatening (DMFS and Distant Metastasis Free Interval [DMFI]) and long-term Overall Survival (OS). The results from MINDACT provided in the table below, demonstrate that it is safe to spare chemotherapy in postmenopausal women at high clinical risk (up to three positive nodes) but with a low genomic risk as attested by a MammaPrint low risk.

<table>
<tr><th colspan="6">ITT C-High/G-Low HR+/HER2- LN0&LN+ >50 years population</th></tr>
<tr><th rowspan="2">Endpoint</th><th rowspan="2">Allocated Treatment</th><th rowspan="2">N</th><th colspan="2">5-year</th><th colspan="2">8-year</th></tr>
<tr><th>Survival estimate</th><th>Abs. Diff.</th><th>Survival estimate</th><th>Abs. Diff.</th></tr>
<tr><td rowspan="2">DMFS</td><td>ACT</td><td>441</td><td>95.0 (92.4-96.7)</td><td rowspan="2">-0.9%</td><td>90.2 (86.8-92.7)</td><td rowspan="2">0.2%</td></tr>
<tr><td>No ACT</td><td>453</td><td>95.8 (93.5-97.4)</td><td>90.0 (86.6-92.6)</td></tr>
<tr><td rowspan="2">DMFI</td><td>ACT</td><td>441</td><td>96.1 (93.8-97.6)</td><td rowspan="2">-0.9%</td><td>91.8 (88.6-94.2)</td><td rowspan="2">0.2%</td></tr>
<tr><td>No ACT</td><td>453</td><td>97.0 (94.9-98.2)</td><td>91.6 (88.4-94.0)</td></tr>
<tr><td rowspan="2">OS</td><td>ACT</td><td>441</td><td>97.6 (95.6-98.7)</td><td rowspan="2">0.1%</td><td>93.9 (91.1-95.9)</td><td rowspan="2">-1.6%</td></tr>
<tr><td>No ACT</td><td>453</td><td>97.5 (95.5-98.6)</td><td>95.6 (93.0-97.2)</td></tr>
</table>
Source: Piccart et al. Lancet Oncol 2021 – DMFS in Table S13 & Full Analysis Report v2.0 page 158 – prepared by Coralie Poncet, Senior Statistician EORTC – DMFI and OS – Data made available for health technology assessment purposes

From all the knowledge we currently have, and are accumulating, on the natural history of breast cancer, it is clear that chemotherapy effect is detectable during the first 5 years of follow-up, and beyond that point there is no further improvements in outcomes for those patients given chemotherapy.[1] However, it is well known that in the population of patients with early ER+ HER2- breast cancer, the risk of late relapse persists for many years, BUT they are attributed to cells that are in a state of dormancy (and so unresponsive to chemotherapy) that get reactivated. Results presented in the table above show clearly that there is no chemotherapy benefit for DMFS and DMFI at both 5- and 8-years of follow-up, and that chemotherapy does not translate into a benefit of OS at long-term (8-years). The observed possible 0.2 percent benefit aper 8-years from chemotherapy can be disregarded, both because there is no
</td><td></td></tr>
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Comment number	Name and organisation	Section number	Comment	NICE response
			evidence that this numeric difference is statistically real, and in view of the well documented short and long-term side effects of chemotherapy. The Appendix of this letter demonstrates that results are highly similar in subgroup analyses by lymph node status. 1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365(9472): 1687-71 With that, MINDACT has appropriately addressed the Negative Predictive Value (NPV) of MammaPrint. Here, the NPV of MammaPrint is defined as MammaPrint correctly predicting that a patient will not benefit from chemotherapy. **With the absolute difference of 0.2 percent, the NPV of MammaPrint would be 99.8%. This metric implies that a physician must treat with chemotherapy 500 such women with clinical high risk but genomic low risk early breast cancer to prevent one extra woman developing metastatic breast cancer.** While for all other women, chemotherapy will only unnecessarily deteriorate the patients' health due to chemotherapy related side effects. This is different from the Positive Predictive Value (PPV) of genomic signatures, defined as a genomic signature correctly predicting that a patient will benefit from chemotherapy. Investigating the PPV of a genomic signature for all breast cancer patients would be highly unethical, as we would have to refrain treating patients with chemotherapy who are clearly in high need of chemotherapy. Hence, MINDACT did not, and could not, investigate the PPV of MammaPrint in clinical high and genomic high risk patients. However, the absence of a PPV randomization in the clinical high risk genomic high risk group, does not detract from the strong NPV MammaPrint has as clearly demonstrated in MINDACT. In conclusion, we wish to express our sincere appreciation for the scrutiny of any health technology assessment agency has dedicated to evaluating the clinical effectiveness and/or cost-effectiveness of medical devices and innovative treatments. MammaPrint, a European-developed and validated treatment planning tool, has garnered positive evaluations in many European countries due to its proven ability to judiciously de-escalate chemotherapy in women with breast cancer, whose tumor characteristics alone would have not facilitated such critical therapeutic decisions. This success underscores the effectiveness and reliability of MammaPrint in tailoring treatments.	

Comment number	Name and organisation	Section number	Comment	NICE response
			Here, we presented findings from the MINDACT trial, particularly highlighting the absence of benefits of adjuvant chemotherapy for women aged 50 and above with HR+HER2- invasive early-stage breast cancer and up to 3 positive lymph nodes, if found to be MammaPrint low risk. We hold firm confidence that the 20 years of European innovation related to MammaPrint, coupled with the comprehensive insights provided in this letter and the robustness of the MINDACT data, will significantly contribute to the consideration of recommending MammaPrint. I thank you in advance for taking my comments into consideration for your health technology assessment. Respectfully, [redacted]	

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Appendix: MINDACT results in the C-high/G-low HR+/HER2- >50 years population split by nodal status
<table>
<tr><td colspan="6">ITT C-High/G-Low HR+/HER2- LN0 >50 years population</td></tr>
<tr><td rowspan="2">Endpoint</td><td rowspan="2">Allocated Treatment</td><td rowspan="2">N</td><td colspan="2">5-year</td><td colspan="2">8-year</td></tr>
<tr><td>Survival estimate</td><td>Abs. Diff.</td><td>Survival estimate</td><td>Abs. Diff.</td></tr>
<tr><td>DMFS</td><td>ACT</td><td>228</td><td>94.9 (91.0-97.1)</td><td>-0.6%</td><td>90.4 (85.5-93.7)</td><td>0.5%</td></tr>
<tr><td></td><td>No ACT</td><td>235</td><td>95.6 (91.9-97.6)</td><td></td><td>89.9 (84.8-93.3)</td><td></td></tr>
<tr><td>DMFI</td><td>ACT</td><td>228</td><td>96.7 (93.3-98.4)</td><td>-0.6%</td><td>92.6 (88.0-95.5)</td><td>0.5%</td></tr>
<tr><td></td><td>No ACT</td><td>235</td><td>97.3 (94.1-98.8)</td><td></td><td>92.1 (87.3-95.1)</td><td></td></tr>
<tr><td>OS</td><td>ACT</td><td>228</td><td>97.7 (94.6-99.0)</td><td>0.8%</td><td>93.2 (88.8-95.9)</td><td>-2.0%</td></tr>
<tr><td></td><td>No ACT</td><td>235</td><td>96.9 (93.6-98.5)</td><td></td><td>95.3 (91.4-97.4)</td><td></td></tr>
<tr><td colspan="6">ITT C-High/G-Low HR+/HER2- LN+ >50 years population</td></tr>
<tr><td rowspan="2">Endpoint</td><td rowspan="2">Allocated Treatment</td><td rowspan="2">N</td><td colspan="2">5-year</td><td colspan="2">8-year</td></tr>
<tr><td>Survival estimate</td><td>Abs. Diff.</td><td>Survival estimate</td><td>Abs. Diff.</td></tr>
<tr><td>DMFS</td><td>ACT</td><td>212</td><td>95.5 (91.5-97.6)</td><td>-0.7%</td><td>90.4 (85.1-93.8)</td><td>0.2%</td></tr>
<tr><td></td><td>No ACT</td><td>218</td><td>96.2 (92.5-98.1)</td><td></td><td>90.1 (84.9-93.6)</td><td></td></tr>
<tr><td>DMFI</td><td>ACT</td><td>212</td><td>96.0 (92.1-98.0)</td><td>-0.7%</td><td>91.4 (86.3-94.7)</td><td>0.2%</td></tr>
<tr><td></td><td>No ACT</td><td>218</td><td>96.7 (93.1-98.4)</td><td></td><td>91.2 (86.2-94.4)</td><td></td></tr>
<tr><td>OS</td><td>ACT</td><td>212</td><td>97.5 (94.1-99.0)</td><td>-0.6%</td><td>94.8 (90.5-97.2)</td><td>-1.1%</td></tr>
<tr><td></td><td>No ACT</td><td>218</td><td>98.1 (95.0-99.3)</td><td></td><td>95.9 (91.9-97.9)</td><td></td></tr>
</table>
Source: Post hoc analysis – prepared by Coralie Poncet, Senior Statistician EORTC - Data made available for health technology assessment purposes
</td><td></td></tr>
<tr><td>36</td><td>Agendia</td><td>3.15, page 18</td><td>The EAG argues that the EndoPredict data with few people remaining in the study at 15 years influences the survival estimates and advocates for the use of the 10 year data as there is follow-up for more patients at this time point, and this is reflected in the report with the sentence below:

“The EAG noted that the data from Filipits et al. was taken at 15 years, when there were few people remaining in the study.“</td><td>Thank you for your comment.

The committee considered this analysis but preferred analyses that used hazard ratios over relative risk, because they account for the</td></tr>
</table>

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<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>Along the same line of this argument, is the use of the Relative Risk from the 8-year DMFI of MINDACT, which is 0.98. At 8-years, 70.4% of patients have follow-up data available. While at the time point at which the hazard ratio is calculated (the end of the cox proportional model, i.e., 12 years) there is follow-up available for less than 5% of MINDACT patients. This advocates for the use for the observed relative risk reduction of chemotherapy at a time point when there is a sufficient proportion of patients followed-up: being the 8-year point for MINDACT.

Of note here is the difference in the level of evidence for the two tests, where EndoPredict only has data of retrospective nature, and MammaPrint has been researched in a Phase III prospective randomized trial, MINDACT.

Find below the same summary of the results when applying this method as in Comment [#33], for your convenience:
When applying the RR of 0.98, MammaPrint is a dominating treatment strategy in the deterministic and probabilistic analysis with 0.06 to 0.09 QALYs gained, and £1845 to £2408 in cost-savings per patient.

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<tr><td rowspan="3">Probabilistic</td><td>Option</td><td>LYGs</td><td>QALYs</td><td>Costs</td><td>Inc. LYGs</td><td>Inc. QALYs</td><td>Inc. Costs</td><td>ICER</td></tr>
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<tr><td>Usual care</td><td>20.39</td><td>10.29</td><td>£40688</td><td>-</td><td>-</td><td>-</td><td>dominating</td></tr>
</table>
</td><td>event rates over the whole study period rather than at a specific timepoint.</td></tr>
<tr><td>37</td><td>Agendia</td><td>3.16, page 19</td><td>The draft guidance states the following:
“This effect could be explored further if data stratified by menopausal status was available for the LN-positive population in MINDACT.“

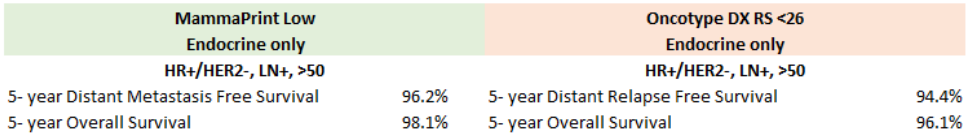
Please refer to comments [31 through 35] of this document concerning the results of this specific analysis in the post-menopausal population from MINDACT.</td><td>Thank you for your comment, which the committee has considered. Section 3.17 of the guidance has been updated to reflect the committee discussion of these analyses. Please also refer to the responses to comments 31 to 35.</td></tr>
</table>

<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>38</td><td>Agendia</td><td>N/A</td><td>During the committee meeting on October 26, one of the committee members asked if the baseline clinical risk of the different trial was comparable, and what the impact on the health economic modelling would be.

Agendia believes this is an important question because the baseline clinical risk of a trial certainly impacts the assessment and the generalizability of results into clinical practice. In the evidence review, there are two matters that should be taken into consideration:

1. Only MammaPrint and Oncotype DX have randomized prospective evidence available for the group of interest, with 8-years and 5-years of follow-up, respectively.
2. Only MINDACT randomized a strictly clinical high risk cohort (NPI > 3.4) those who are considered for chemotherapy to answer the question if there is a lack of chemotherapy benefit.
a. MINDACT: 100% NPI > 3.4
b. RxPONDER: ~80% NPI > 3.4
c. EndoPredict & Prosigna were researched retrospectively in TransATAC, which was a cohort of patients that <u>were not treated with chemotherapy by physician's choice</u>

That being said, MINDACT is the trial only that is 100% in line with the true population of interest. Even with a higher base-line clinical risk, the prognosis at 5-years in the no chemotherapy groups of comparable endpoints are better as observed in MINDACT than in RxPONDER.

 
<table><tr><th>MammaPrint Low
Endocrine only
HR+/HER2-, LN+, >50</th><th></th><th>Oncotype DX RS <26
Endocrine only
HR+/HER2-, LN+, >50</th><th></th><th></th></tr><tr><td>5- year Distant Metastasis Free Survival</td><td>96.2%</td><td>5- year Distant Relapse Free Survival</td><td>94.4%</td><td>-1.8%</td></tr><tr><td>5- year Overall Survival</td><td>98.1%</td><td>5- year Overall Survival</td><td>96.1%</td><td>-2.0%</td></tr></table>
Adding to the points raised in comments [31 through 35], Agendia believes the recommendation for MammaPrint should be separately addressed for postmenopausal patients based on the available evidence proving MammaPrint's ability to predict the absence of benefit in C-high/G-low patients with HR+/HER2-/LN+ breast cancer.</td><td>Thank you for your comment, which the committee has considered. The population for this assessment was not limited by NPI score. The committee considered the analyses presented for the postmenopausal population, and its deliberations are described in section 3.17 of the guidance. Please also refer to the responses to comments 31 to 35.</td></tr>
<tr><td>39</td><td>Agendia</td><td>N/A</td><td>Providing context from DG34, we want to quote that during the committee discussion MINDACT was seen as a well-designed study and the finding of MammaPrint low risk patients being able to let patients forgo chemotherapy without a statistically significant increase in 5-year risk of distant</td><td>Thank you for your comment, which the committee has considered.</td></tr>
</table>

Comment number	Name and organisation	Section number	Comment	NICE response
			recurrence was recognized. What was mentioned in the discussion, is that longer-term follow was desired. **In DAP71 the long-term follow-up is available only for MINDACT**, and these data have adequately shown that there is no survival benefit of chemotherapy in post-menopausal patients (aged >50) with HR+/HER2-/LN+ disease who are Clinical High risk and MammaPrint Low Risk. *Section 5.7 in DG34:* *"The committee noted that MINDACT (see section 4.32) was a well-designed study. The results suggested that patients with high clinical risk and MammaPrint low-risk scores can forgo chemotherapy without a statistically significant increase in the 5-year risk of distant recurrence. However, a clinical expert explained that the risk of recurrence often continues beyond 5 years and noted that the MINDACT authors (Cardoso et al. 2016) stated that long-term follow-up and outcome data will be essential."* *Section 4.32 in DG34:* *"For the group who were high risk with modified Adjuvant! Online and low risk with MammaPrint, 5-year distant metastasis-free survival was 95.9% with chemotherapy and 94.4% without chemotherapy, a non-statistically significant absolute difference of 1.5% (adjusted hazard ratio for distant metastasis or death with chemotherapy compared with no chemotherapy, 0.78; 95% CI 0.50 to 1.21; p=0.27)."* To add to that, in the EAG model used to inform DG34 incorporated the results of MINDACT as observed in the trial and was authored by several members that are in the current EAG as well. Here, the DG34 EAG modelled a Chemotherapy arm and a No Chemotherapy arm based on the results observed in MINDACT. The 95.9% 5-year DMFS for the Chemotherapy arm and the 94.4% 5-year DFMS for the no chemotherapy arm were extrapolated. In case the RR of 0.98 for the post-menopausal (aged >50) HR+/HER2-/LN+ C-high/G-low from MINDACT is implemented in the DAP71 EAG model, the results would resemble the methodology used in DG34 and would recreate a Markov Trace for the chemotherapy arm and no chemotherapy arm as observed in the MINDACT trial. As was already displayed in Comment [33], Agendia believes this would be the correct methodology to model MINDACT results. The results already displayed in Comment [33] are repeated here for convenience:	The scenario outlined in this comment was considered by the committee, but it assumes MammaPrint has predictive ability. The committee concluded that there was not enough evidence to definitively say whether or not MammaPrint is predictive of chemotherapy benefit (see section 3.8). So, it preferred scenarios in which MammaPrint had only prognostic benefit. In these scenarios, MammaPrint was less clinically effective and cost more than standard care (see section 3.17). The committee preferred analyses that used hazard ratios over relative risk, because they account for the event rates over the whole study period rather than at a specific timepoint.

<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>When applying the RR of 0.98, the EAG DAP71 would have a similar methodology as used in DG34, then MammaPrint is a dominating treatment strategy in the deterministic and probabilistic analysis with 0.06 to 0.09 QALYs gained, and £1845 to £2408 in cost-savings per patient.
<table>
<tr><th colspan="9">EAG Model: HR+/HER2-/LN+ >50 with G-low Hazard Ratio set at 0.98</th></tr>
<tr><td rowspan="3">Deterministic</td><td>Option</td><td>LYGs</td><td>QALYs</td><td>Costs</td><td>Inc. LYGs</td><td>Inc. QALYs</td><td>Inc. Costs</td><td>ICER</td></tr>
<tr><td>MammaPrint</td><td>20.67</td><td>10.74</td><td>£37521</td><td>0.10</td><td>0.06</td><td>-£1845</td><td>MammaPrint dominating</td></tr>
<tr><td>Usual care</td><td>20.57</td><td>10.69</td><td>£39366</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td rowspan="3">Probabilistic</td><td>Option</td><td>LYGs</td><td>QALYs</td><td>Costs</td><td>Inc. LYGs</td><td>Inc. QALYs</td><td>Inc. Costs</td><td>ICER</td></tr>
<tr><td>MammaPrint</td><td>20.56</td><td>10.38</td><td>£38280</td><td>0.17</td><td>0.09</td><td>-£2408</td><td>MammaPrint dominating</td></tr>
<tr><td>Usual care</td><td>20.39</td><td>10.29</td><td>£40688</td><td>-</td><td>-</td><td>-</td></tr>
</table></td><td></td></tr>
<tr><td>40</td><td>Agendia</td><td>N/A</td><td>Lastly, for your consideration, in 2023 MammaPrint has been positively assessed for reimbursement in two neighbouring European countries with MINDACT as the primary evidence source. In these cases, the chemotherapy versus no chemotherapy randomization, in specific the absolute benefit, or rather the lack of benefit, has been the deciding factor for the positive reimbursement conclusions.

After a successful pilot program permanently reimbursed in Belgium since January 1st, 2023: Women aged 45 or older with HR+/HER2- early stage breast cancer with 0 to 3 lymph nodes involved. (Link)
Announced on October 30th, 2023, with retrospective effect since June 28th, 2022, in the Netherlands: Women over 50 with HR+/HER2- early stage breast cancer with 0 to 3 lymph nodes involved. (Link)</td><td>Thank you for your comment, which the committee has considered.</td></tr>
</table>

THEME: Prognostic and predictive ability of Oncotype DX

Comment number	Name and organisation	Section number	Comment	NICE response
41	Veracyte	2.21, page 10	Subsequent analyses of the TAILORx study for LN- breast cancer have shown a significant impact of additional clinical factors on the prognostic estimates for Oncotype DX Recurrence Scores. These factors include age, tumour grade, tumour size, and type of endocrine therapy (Sparano, JCO 2021 DOI: 10.1200/jco.20.03007). The developed model, RSClin, is provided to clinicians through the Exact Sciences portal (account access required). Given this observation, similar findings are highly likely for LN+ disease as well. Have NICE inquired of Exact Sciences	Thank you for your comment, which the committee has considered. Oncotype DX was evaluated as a standalone test and the committee concluded that it was likely to be a cost-effective use of NHS resources

Comment number	Name and organisation	Section number	Comment	NICE response
			whether such a model will be developed for LN+ disease? If not, what is the rationale for thinking these factors are not significant for LN+ disease? If so, then is the endorsement of using the current Oncotype DX only approach currently supportable?	when used in this way (see section 3.18). The committee emphasised that tumour profiling test results should be considered alongside all available information which includes the clinical factors mentioned in the comment (see section 3.1).
42	Web comment	General	I believe the data is currently insufficient to support the decision that the genomic assay Oncotype Dx should be used to aid the decision of whether adjuvant chemotherapy should be used in patients with early breast cancer ER+ HER2- and nodes 1-3. The RxPonder trial on which the decision was made was not a non-inferiority trial and furthermore neither patients nor clinicians were blinded to the Oncotype result. As a result, 21% of patients did not have their assigned treatment, 16.2% in the chemotherapy group and 5.8% in the endocrine therapy alone. In the intention to treat analysis, any potential benefit of chemotherapy is weakened. My main concern is the interpretation of the results across all the potential patients irrespective of clinical risk. Patients who were high grade accounted for only 10.1% of patients in RxPonder trial, 58% had T1 tumours, 36.7% T2 and 5.0% T3. For patients with 1 node +ve 65.7%, 2 nodes +ve 24.8% and 3 nodes +ve 9.1%. This means that the patients of RxPonder were in the lower end of clinical risk category for node positive patients. As the test is essentially a prognostic test, the RxPonder trial is informing us about prognosis and potential benefit of chemotherapy at the lower end of clinical risk in the nodes 1-3 category. If NICE approve the test for the whole of the nodes 1-3 category, there will be many patients at the higher end of risk who will not receive chemotherapy but who may well have benefitted from this. Clinicians will interpret NICE approval that every patient who falls in this category of nodes 1-3 as not benefitting. This could result in patients at high clinical risk, for example grade 3 and three nodes positive, not receiving chemotherapy when they could have benefitted from this.	Thank you for your comment, which the committee has considered. The committee acknowledged that the overall clinical risk in RxPONDER was relatively low for a LN1-3 population, and therefore the effect of chemotherapy may be underestimated in this population (see section 3.10). However, a scenario analysis in which the effect of chemotherapy was 1.0 (rather than 1.12) in the RS0-25 group did not change the results of the economic model (see section 3.18). The committee also emphasised that tumour profiling tests should not be considered to definitively determine treatment plans, and that results should be considered alongside all available risk factors, which will include tumour grade and number of nodes. The language on this has been strengthened in recommendations 1.1 and 1.8, and further expanded in section 3.1.
43	Veracyte	2.21, page 10	We would ask that the committee provides clarification on the cut points used to consider this data. In section 4.24 of DG34 the following is stated. “The 2 reanalyses of RCTs suggest that	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			Oncotype DX may predict differences in relative treatment effects for chemotherapy. Hazard ratios for disease-free survival for patients having chemotherapy compared with those having no chemotherapy suggested that the greatest relative treatment effect was for patients in the Oncotype DX high-risk category. Unadjusted interaction tests between Oncotype DX risk group and relative treatment effects were mainly statistically significant. Adjusted interaction tests were statistically significant in an analysis of patients with HER2-negative, LN-negative disease, but in patients with LN-positive disease the interaction test was not significant when hormone receptor status was adjusted for. However, the data for the population with LN-negative disease came from the derivation cohort for Oncotype DX and may overestimate predictive performance". This remains true in the current analysis. However, the cut points in subsequent studies have been changed, further confounding the analyses. RxPONDER does not prove chemotherapy prediction as discussed and agreed during the committee meeting and is based on a differing cut off to SWOG-8814. We ask if NICE can please provide clarification on which cut point was used to perform this analysis, and if the committee considers the differential design of the studies to be of significance and applicability? If not, how can prediction be considered proved? Moreover, even if the predictive performance is assumed based on SWOG-8814, the hazard ratio was only significant for RS>30, whereas the economic modelling appears to apply the hazard ratio to RS 26-30 as well, resulting in a more favourable assessment of Oncotype DX. Since this is the primary basis for finding Oncotype DX to be of predictive value, hence cost effective and endorsed, would this be the case if the 0.59 hazard ratio was only applied for RS>30?	The EAG acknowledged that it is a limitation that data for the RS31+ group from SWOG-8814 was used to inform the benefit of chemotherapy in the EAG's economic model for the RS26+ group. However, when combined with the results of RxPONDER, the committee concluded that it was likely that Oncotype DX has some predictive ability in the population of interest (see 3.9 and 3.10). The EAG's scenario analysis in which the difference in chemotherapy benefit between risk groups was reduced did not have a large effect on the cost-effectiveness estimate (addendum 4).
44	Exact Sciences	3.7, page 14	We suggest adding a little more context to the sentence: "A clinical expert noted that RxPONDER was not powered as a non-inferiority trial, so this finding could be considered uncertain." For example, if the EAG agrees, it could be further mentioned that despite not being powered as a non-inferiority trial, if we were to apply a post-hoc 3% non-inferiority margin to the RxPONDER results, it's very likely that the power would exist to detect that margin and it would be possible to demonstrate that endocrine therapy alone was non-inferior to chemoendocrine therapy.	Thank you for your comment, which the committee has considered. It was not possible to consider this analysis further as it has not been presented in full. No change has been made to the text.
45	Exact Sciences	3.7, page 14	Again, we suggest adding further context to the sentence: "In RxPONDER, 65% of the people randomised had 1 positive lymph node which may result in an underestimate of the effect of chemotherapy." It could be added that in the RxPONDER publication, results were consistent when examined by number of positive nodes (Figure 3A and 3B).	Thank you for your comment, which the committee has considered. The following text was added to section 3.10: "In RxPONDER, the overall clinical

Comment number	Name and organisation	Section number	Comment	NICE response
			Furthermore, conducting scenario analyses involving modifying the treatment effect for postmenopausal women with RS 0-25 suggests that Oncotype DX remains cost-effective for all reasonable scenarios.	risk was relatively low for a population with 1 to 3 positive lymph nodes. The EAG noted that of the people randomised, 65% had 1 positive lymph node, 25% 2 nodes and 9% 3 nodes. Some people had micrometastases and 24% had low-grade cancer. Additionally, the EAG identified possible selection bias because people had their test result before agreeing to randomisation, and there was some crossover between trial arms. Therefore, the results may underestimate the effect of chemotherapy in a wider population with LN-positive breast cancer with higher overall clinical risk. The company highlighted a subgroup analysis of RxPONDER which indicated that the effect of chemotherapy on invasive disease-free survival was non-significant in people with 1 positive node and in people with 2 or 3 positive nodes."
46	UCL Cancer Institute	3.7, pages 14 &15	Predictive ability The committee's opinion that Oncotype DX is likely to have "some predictive ability for chemotherapy benefit in postmenopausal women" meeting the eligibility criteria is based on the SWOG-8814 re-analysis and the RxPONDER trial results. Both studies have a high level of uncertainty and even when their results are considered together this uncertainty persists. In contrast, multiple EBCTCG meta-analyses have failed to demonstrate any tumour characteristic (including tumour grade) is associated with a differential chemotherapy benefit. This includes	Thank you for your comment, which the committee has considered. The committee agreed that the evidence is uncertain, but commented it is unlikely that more evidence will be generated to reduce this uncertainty. However, the committee concluded that it was

Comment number	Name and organisation	Section number	Comment	NICE response
			analyses restricted to patients with ER-positive disease. This does not preclude the possibility that complex biomarkers such as the tumour profiling tests considered here may have predictive ability, but it does demand a robust level of evidence that is currently lacking. References: EBCTCG, The Lancet 2012, PMID 22152853 (DAR reference 15) EBCTCG, The Lancet 2019, PMID 30739743 EBCTCG, The Lancet 2023, PMID 37061269	likely that Oncotype DX has some predictive ability for chemotherapy benefit in this population (and is therefore cost effective), but that the difference in chemotherapy benefit between risk groups was possibly overestimated in the economic model. The EAG's scenario analysis in which the difference in chemotherapy benefit between risk groups was reduced did not have a large effect on the cost-effectiveness estimate (addendum 4).
47	UCL Cancer Institute	3.7, pages 14 & 15 And DAR: 3.5.2, 3.5.8, pages 61-63, 69	The SWOG 8814 study (Albain et al, 2010) was discussed in detail in the DAR and by the committee. As pointed out, some of the analyses were performed in the 1-3 N+ subgroup (n=267) only and some in the entire trial cohort (n=367) that also included patients with 4-9 involved nodes. The study was published in 2010 and was considered by NICE alongside NSABP B20 (conducted in patients no nodal involvement) in both DG10 and DG34; neither appraisal found the claims that Oncotype DX has predictive ability made by these two studies to be convincing. There has been no update to the SWOG analysis since its original publication in contrast to NSABP B20 (Geyer et al, 2018). The biggest concern about SWOG 8814 is the inclusion of patients retrospectively identified as having HER2-positive disease, who comprised 11.7% of the study population; it is a reasonable assumption that they were proportionally distributed between 1-3N+ and 4-9N+ subgroups although this is not stated. The NSABP B20 re-analysis (Geyer et al, 2018) adjusted for the 12.7% of the original patients/ tumours that had been retrospectively identified as HER2-positive; 81.7% of this group had Recurrence Scores ≥31 and 7.3% had Recurrence Scores ≤18. There is absolutely no reason to think that the distribution of HER2-positive tumours by Recurrence Score in SWOG 8814 would not be very similar. Additionally, there was an imbalance between the proportion of patients with HER2-positive tumours who received endocrine therapy only (8.8%) and chemo-endocrine therapy (13.7%) in the entire SWOG 8814 cohort.	Thank you for your comment, which the committee has considered. The committee agreed that the population of SWOG-8814 may lead to an overestimation of the effect of chemotherapy in the Oncotype DX high-risk group (see section 3.10). However, the committee concluded that it was likely that Oncotype DX has some predictive ability for chemotherapy benefit in this population (and is therefore cost effective), but that the difference in chemotherapy benefit between risk groups was possibly overestimated in the economic model. The EAG's scenario analysis in which the difference in chemotherapy benefit between risk groups was reduced

Comment number	Name and organisation	Section number	Comment	NICE response
			If the chemotherapy predictive hypothesis is correct then it is entirely plausible that the benefit experienced by patients with high Recurrence Score tumours will differ according to HER2 status. (Publications from the EBCTCG (e.g. DAR reference 15) show that the relative benefit of chemotherapy is independent of HER2 status.) Irrespective of whether or not these patients experienced the same chemotherapy benefit as HER2-negative patients, they undoubtedly have a poorer prognosis as this trial predates the trastuzumab era and they may have less endocrine therapy (tamoxifen)-sensitive tumours. Inclusion of these patients in the analysis therefore makes its conclusions highly uncertain. References: Albain et al, Lancet Oncol 2010, PMID 20005174 (DAR reference 31) Geyer et al, npj Breast Cancer 2018, PMID 30456299.	did not have a large effect on the cost-effectiveness estimate (addendum 4).
48	UCL Cancer Institute	3.7, page 14-15 And DAR: 3.5.3 3.5.8, pages 63-65, 69	The RxPONDER postmenopausal result is highly uncertain. 1. In evaluating the trial, the DAR considered the DRFI endpoint analysis. This is highly appropriate to adjuvant chemotherapy trials as it measures distant metastases and breast cancer mortality which are the events that chemotherapy aims to prevent. The data, which are currently only available from a conference presentation of outcomes at a median follow-up of 6.1 years, shows no difference between patients randomised to chemotherapy or to endocrine therapy alone (5-year DRFI 95.8% [chemotherapy + endocrine therapy] vs 96.6% {endocrine therapy]; 163 events, 3329 patients). The reported adjusted HR was 1.12 with very broad confidence 95% intervals [0.82-1.59]. The DRFI analysis was performed in the ITT population. 2. The RxPONDER postmenopausal population had favourable tumour characteristics notwithstanding lymph node involvement. In addition to the inclusion of an unreported number patients with lymph node micrometastases (see comment [50]), only 9.2% had 3 involved nodes. Additionally, there was a far higher proportion of patients with grade 1 tumours (24.3%) than is normally encountered. Overall, 17% of participants were classified as MINDACT low risk (equivalent to a Nottingham Prognostic Index <3.4). The primary analysis of RxPONDER was performed using IDFS, which is a far broader outcome measure than DRFI. The consequence of the low clinical risk of the postmenopausal patients is that 53% of events captured by IDFS in the 5.3 year analysis were unrelated to breast cancer (second cancers, 28.6%; deaths not due to breast or other cancers, 24.7%); this data is not available for the 6.3 year analysis. There was no difference in the rate of these unrelated events	Thank you for your comment, which the committee has considered. The following text was added to section 3.10: “In RxPONDER, the overall clinical risk was relatively low for a population with 1 to 3 positive lymph nodes. The EAG noted that of the people randomised, 65% had 1 positive lymph node, 25% 2 nodes and 9% 3 nodes. Some people had micrometastases and 24% had low-grade cancer. Additionally, the EAG identified possible selection bias because people had their test result before agreeing to randomisation, and there was some crossover between trial arms. Therefore, the results may underestimate the effect of chemotherapy in a wider population with LN-positive breast cancer with

Comment number	Name and organisation	Section number	Comment	NICE response
			between the trial arms, which is consistent with multiple EBCTCG meta-analyses that have failed to show any impact of chemotherapy on either death without prior breast cancer recurrence or the incidence of common second cancers. Within the context of the RxPONDER analysis, the inclusion of these events will narrow the confidence interval of the HR estimate thereby providing a misleading impression of the level of certainty. 3. The low risk characteristics of the RxPONDER population means that it can tell us very little about patients at the higher clinical risk end of the 1-3N+ group, specifically patients with large tumours and/or 3 involved nodes. 4. There was a significant cross-over between trial arms; 4.7% of postmenopausal patients randomised to endocrine therapy were treated with chemotherapy whilst 18.1% rejected chemotherapy. This dilutes any difference trial arms. A per-protocol analysis was performed as part of the 5.3 year analysis but only for the IDFS endpoint. This showed a very similar result to the ITT analysis although curiously the HR favoured chemotherapy which is what one might expect. 5. RxPONDER set out to prove the predictive hypothesis by establishing a difference in response rates to chemotherapy between subgroups with a higher and lower range of Recurrence Score. No such difference was observed. Any claim that the trial supports the predictive hypothesis must therefore rely on its failure to establish chemotherapy benefit in a population where a benefit is to be expected, accepting the EBCTCG demonstration that patients with ER-positive (HER2-negative) benefit from chemotherapy as a whole. This however requires a convincing demonstration of non-inferiority rather than an absence of superiority. As pointed out by the committee, the trial was never intended to demonstrate non-inferiority however and no such analysis has been presented. Given these multiple uncertainties, to claim that the trial establishes that there is no difference between arms and that chemotherapy has no value in postmenopausal patients with 1-3 involved lymph nodes and an RS in the 0-25 range seems to be a very optimistic interpretation of the data. References: RxPONDER 5.3 year analysis: Kalinsky et al, N Engl J Med 2021, PMID 34914339 (DAR	higher overall clinical risk. The company highlighted a subgroup analysis of RxPONDER which indicated that the effect of chemotherapy on invasive disease-free survival was non-significant in people with 1 positive node and in people with 2 or 3 positive nodes." However, taking the results of SWOG-8814 and RxPONDER together, the committee concluded that it was likely that Oncotype DX has some predictive ability for chemotherapy benefit in this population (and is therefore cost effective), but that the difference in chemotherapy benefit between risk groups was possibly overestimated in the economic model. The EAG's scenario analysis in which the difference in chemotherapy benefit between risk groups was reduced did not have a large effect on the cost-effectiveness estimate (addendum 4).

Comment number	Name and organisation	Section number	Comment	NICE response
			reference 28) RxPONDER 6.1 year analysis: Kalinsky et al, Cancer Res 2022, doi: 10.1158/1538-7445.SABCS21-GS2-07 (DAR reference 76)	
49	UCL Cancer Institute	DAR: 4.3.2, page 121	The economic model for Oncotype DX used baseline DRFI estimates taken from RxPONDER for patients with a tumour Recurrence Score in the range 0-25. These are too low as most patients recruited by RxPONDER had low clinical risk (see comment [48]). The baseline DRFI used for patients with higher tumour Recurrence Scores is taken from transATAC, which is an historic estimate (see comment [65])	Thank you for your comment, which the committee has considered. Please see the response to comment 48.
50	UCL Cancer Institute	DAR: 3.4.4, pages 53-54, table 6	Prognostic data from prospective RCT of Oncotype DX (RxPONDER) The RxPONDER trial is universally described as a study performed on patients with LN1-3 disease, including in this report. However, an unknown number of participants had lymph node micrometastases. The inclusion of these patients was not revealed in the primary study publication (Kalinsky et al 2021). The initial study protocol (published as an appendix to Kalinsky et al 2021) however states that patients with pN1mi were eligible to participate. This was removed in protocol revision 8 (notified to sites in March 2014), at about halfway through the recruitment period. A post-hoc analysis of outcomes in premenopausal women with lymph node micrometastases and macrometastases was reported in Kalinsky et al 2022. In the presentation slides, 12.8% of patients included had micrometastases only. The proportion of postmenopausal patients with micrometastases has not been disclosed. For consistency with the description of other studies in the current report (e.g. table 8), would it not be more accurate to describe the trial population as "LNmic, LN1-3"? References: Kalinsky et al, N Engl J Med 2021, PMID 34914339 (DAR reference 28) Kalinsky et al, Cancer Res 2022, doi: 10.1158/1538-7445.SABCS21-GS2-07 (DAR reference 76)	Thank you for your comment, which the committee has considered. Please see the response to comment 48.
51	UCL Cancer Institute	DAR: 4.3.2, page 122 table 33	The HR for chemotherapy benefit for low risk patients of 1.16 used in the BC2 analysis is taken from the 6.1 year ITT analysis of RxPONDER. There was significant cross-over between trial arms however (see comment [48]). Both ITT and per-protocol analyses of the trial for its primary IDFS outcome were reported in the 5.3 year analysis. The reported HRs are 1.02 (0.82–1.26) and 0.97 (0.77-1.22) respectively. No PP analysis has been reported for the DRFI outcome, but it is likely that that there would be a similar effect on HR to that observed for IDFS. Therefore it would seem sensible to explore the effect of using 1.0 in place of 1.16 in BC2.	Thank you for your comment, which the committee has considered. The EAG have provided this analysis in addendum 4. It did not have a large effect on the cost-effectiveness estimate (Oncotype

Comment number	Name and organisation	Section number	Comment	NICE response
			References: RxPONDER 5.3 year analysis: Kalinsky et al, N Engl J Med 2021, PMID 34914339 (DAR reference 28) RxPONDER 6.1 year analysis: Kalinsky et al, Cancer Res 2022, doi: 10.1158/1538-7445.SABCS21-GS2-07 (DAR reference 76)	DX remained dominating clinical practice).
52	Agendia	3.17, page 19	The draft guidance states the following about the results of Oncotype DX when the relative risk reduction of chemotherapy is informed with the EBCTCG estimate: *"In scenario analyses in which Oncotype DX had prognostic ability only, testing resulted in reduced costs but also fewer QALYs than standard care (savings of more than £30,000 per QALY lost with confidential price discounts applied)."* This sentence from the Draft Guidance is illustrative to how it is impossible to show cost-effective results when modelling the data of a Randomized Controlled Trial that is confounded with a Hazard Ratio from an **unstratified EBCTCG cohort**. The core driver of the EAG model results is the Hazard Ratio applied to the Genomic Low Risk group, which is logical because GEP-tests are primarily used to de-escalate therapy. The evidence synthesis in MINDACT, TAILORx and RxPONDER all focused on showing the lack of chemotherapy benefit. In the EAG model both for MammaPrint and for Oncotype DX, the product will become dominated if data of MINDACT or RxPONDER are not considered. Even if the PPV of Oncotype DX from SWOG 8814 would be modelled in G-high, together with the EBCTCG data or G-low, Oncotype DX would still be dominated. This exemplifies that in the assessment the focus should be on the ability to predict the lack of chemotherapy benefit. As concluded in an editorial, by the PIs of MINDACT (Dr. Piccart), RxPONDER (Dr. Kalinsky) and TAILORx (Dr. Sparano): "Safe chemotherapy sparing is demonstrated - across three large prospective precision medicine clinical trials - for endocrine therapy-treated postmenopausal women at high clinical risk (up to three positive nodes) but with a low genomic risk, as attested by an Oncotype-Dx RS <26 or a 'low risk' MammaPrint® signature."	Thank you for your comment, which the committee has considered. The committee concluded that Oncotype DX was likely to have predictive ability and so did not use this scenario for decision-making. For MammaPrint, the key driver of the economic model is whether the test is predictive or not. This can be seen by comparing the suggested scenarios in comment 32 (predictive - dominating) and the EAG's BC7 (non-predictive – dominated). The committee concluded that there was not enough evidence to definitively say whether or not MammaPrint is predictive of chemotherapy benefit (see section 3.8). So, it preferred scenarios in which MammaPrint had only prognostic benefit. In these scenarios, MammaPrint was less clinically effective and cost more than standard care (see section 3.17).

Comment number	Name and organisation	Section number	Comment	NICE response
			Piccart MJ, Kalinsky K, Gray R, Barlow E, Poncet C, Cardoso F, Winer E, Sparano J. Gene expression signatures for tailoring adjuvant chemotherapy of luminal breast cancer: stronger evidence, greater trust. Editorial Annals of Oncology https://doi.org/10.1016/j.annonc.2021.05.804	

THEME: Predictive ability of EndoPredict

Comment number	Name and organisation	Section number	Comment	NICE response
53	Myriad	1.5, page 4	We would like to point out again that use EndoPredict provides an individual estimate of absolute chemotherapy benefit in addition to prognostic information (Sestak I. et al.,2019). These results are supported by preliminary real life data results from 2 registries which will be published beginning of 2024 (SABCS 2022 posters TUM, Klein at al. and Charité, Schmitt et al.)	Thank you for your comment, which the committee has considered. These data were considered by the EAG but were excluded from the review as more than 20% of the population was not LN1-3.
54	Myriad	2.6, page 6	We explicitly support the statements of the importance of clinical or pathological prognostic factors and would like to point out that EndoPredict score combines gene expression and clinical risk factors (tumour size and nodal status) which makes it a more powerful predictive tool. (Buus R. et al.,2016 and Sestak I. et al.,2018).	Thank you for your comment, which the committee has considered.
55	Myriad	2.13, page 8	We want to highlight that a prospective confirmation of chemotherapy benefit prediction is backed by real-world data from Technical University of Munich (TUM) and Charité University of Berlin– data will be published in Q1Q2 /2024 but posters were submitted to NICE.	Thank you for your comment, which the committee has considered. These data were considered by the EAG but were excluded from the review as more than 20% of the population was not LN1-3.
56	Myriad	3.5, page 13	We would like to comment on the following statement “The EAG did not identify any evidence on the predictive ability of EndoPredict … in a population that was mostly people with LNpositive breast cancer”. This statement is correct but again there is a clear rational behind it. The clinical validation studies were conducted on mixed nodal status populations, with a consistent representative proportion of patients with node-positive disease (around one third), which led to a regulatory approval in both nodal populations. EP’s predictive benefit was demonstrated and validated using a cross comparison between 5 RCTs: TransATAC, ABCSG-6 and 8 (including	Thank you for your comment, which the committee has considered. These data were considered by the EAG but were excluded from the review as more than 20% of the population was not LN1-3.

Comment number	Name and organisation	Section number	Comment	NICE response
			both N0 and N+ population), GEICAM 9906 and 2003/02 (including N0 and N+ in high clinical risk population), Sestak et al. (2019)). The 5-year results of the German real-life registries (Klein et al. (2022), Schmitt et al. (2022)) prospectively confirm the predictive benefit of Endopredict® in mixed nodal status populations (Klein et al. (2022): 23,9% LN+ (1-3); Schmitt et al. (2022) :29,9%).	
57	Myriad	3.15, page 18	We agree with the conclusion that EndoPredict is likely to be a cost-effective use of NHS resources when used to help guide adjuvant chemotherapy decision making for postmenopausal women with LN-positive breast cancer but we disagree with the fact that the modelling did not consider the assumption of EndoPredict's predictive ability for chemotherapy benefit. Independently of the predictive assumption, EndoPredict is expected to be cost-effective without confidential price (ICER: £4,113 per QALY gained) and to dominate standard care with confidential price discount.	Thank you for your comment, which the committee has considered. The EAG did not identify any data for the predictive ability of EndoPredict in a mostly LN+ population, so assessed the test as having prognostic ability only.

THEME: Cost effectiveness of Prosigna

Comment number	Name and organisation	Section number	Comment	NICE response
58	NHSE Genomics Unit	3.18, Page 20	At what price point would Prosigna be considered cost effective for use in the NHS? Would it become cost effective as an assay if delivered locally?	Thank you for your comment, which the committee has considered. The modelled cost of Prosigna includes staff time and equipment rental for local delivery. The confidential price reduction for Prosigna used in the EAG's initial report was incorrect. With updated analyses the committee concluded that Prosigna was likely to be a cost-effective use of NHS resources (see section 3.19).
59	Veracyte	3.18, page 20	In dialogue with NICE the list price and confidential price to use in the base case and the ICER calculation has been clarified which should lead to a different base case ICER and ICER based on confidential discount to be used for decision making and recommendation. Veracyte hope	Thank you for your comment, which the committee has considered. The

Comment number	Name and organisation	Section number	Comment	NICE response
			that the base case can still be updated in the final report and of course that the agreed upon confidential discount will lead to recommendation which is of course most important.	updated list-price analyses were presented in addendum 2. With the updated confidential price reduction analyses, the committee concluded that Prosigna was likely to be a cost-effective use of NHS resources (see section 3.19).

THEME: Impact on chemotherapy use

Comment number	Name and organisation	Section number	Comment	NICE response
60	Web comment	3.13	Impact on chemotherapy services Currently there is a shortage of oncologists and the wider supporting team and several centres are experiencing long waits for adjuvant therapies. Some units that are delivering standard care are unable to offer new NICE approved therapies or open trials due to capacity issues to focussing breast chemotherapy on those that need it will improve care for more breast patients. This should be taken into consideration. In addition we know little about the economic impact on the wider health economy about long term chemotherapy issues as this is not well studied and these patients present to a variety of services eg cardiology so any cost saving on this front will be an underestimate.	Thank you for your comment, which the committee has considered. The committee recognised that infusion services are often under a lot of pressure. For more detail see section 3.20 in the guidance.
61	Exact Sciences	1.1 & 3.10, pages 3 and 16	The draft guidance rightly emphasises the importance of shared decision making, helping patients to understand the factors that can support decisions on chemotherapy, and reducing anxiety about treatment decisions. Whilst test providers and healthcare providers clearly play a key role in this (see below comment about how Exact Sciences continues to support advancements in these areas), we suggest that the NICE guidance itself could also do considerably more to supporting these important objectives. Specifically, the guidance could provide much clearer and more transparent information about the types of outcome measures provided by the tests to LN+ patients to help guide their	Thank you for your comment, which the committee has considered. More information on the differences in test risk classification probabilities has been added in section 3.21 of the guidance. The committee noted that there was not enough comparative evidence to compare the tests directly, and that

Comment number	Name and organisation	Section number	Comment	NICE response
			chemotherapy decisions and, crucially, what this means in terms of the very different expected impact of each test on chemotherapy recommendations (see additional comment about this below). We propose that certain key information should be included upfront in the recommendations section to make the evidence about the intended use of each test more accessible to the lay reader, and also include much more explicit and clear information in the body of the report. The NICE Committee concluded that the Oncotype DX test likely has some predictive ability. The RxPONDER study results demonstrated that the test identifies a large proportion of postmenopausal LN+ patients who will not benefit from chemotherapy and can safely avoid unnecessary chemotherapy side-effects. In contrast prognostic-only tests do not directly inform chemotherapy effect and are expected to lead to high rates of chemotherapy use. Based on the current draft guidance, we feel that it is very unlikely that most patients would understand the significant implications of having one test vs. another, so the guidance could do more to support informing patients and promoting shared decision making. Please see below example recommendations for the tests, which we propose would better serve to help patients and healthcare providers to understand important differences between the tests, including their intended use and the important limitations of the supporting data for the EndoPredict test: “Use Oncotype DX as an option to guide adjuvant chemotherapy decisions for oestrogen receptor (ER)- or progesterone receptor (PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer with 1 to 3 positive lymph nodes. This test can be used to estimate risk of recurrence with endocrine therapy and identify those whose risk is not likely to be reduced (not likely to benefit) by adding chemotherapy treatment.” “Use EndoPredict as an option to guide adjuvant chemotherapy decisions for oestrogen receptor (ER)- or progesterone receptor (PR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer with 1 to 3 positive lymph nodes. This test can be used to estimate risk of recurrence with endocrine therapy. The impact of this test on chemotherapy treatment decisions for LN+ breast cancer has not yet been demonstrated.”	all 3 recommended tests had ICERs below £20,000 per QALY gained when compared to not using tumour profiling tests.

Comment number	Name and organisation	Section number	Comment	NICE response
62	Exact Sciences	3.10, page 16	The very different expected impact of the tests on chemotherapy recommendations should be made much more explicit in the guidance report. • Without testing it has been shown that ~80% of postmenopausal LN+ patients receive adjuvant chemotherapy. • According to the EAG's analysis, use of the EndoPredict test is expected to lead to 76% of postmenopausal LN+ patients still receiving chemotherapy (only a 4% absolute reduction). • In contrast, use of the Oncotype DX test has been proven to lead to 20% of postmenopausal LN+ patients receiving chemotherapy (a 60% absolute reduction). • During the Committee meeting, the EAG presented their estimates that for every 1,000 patients tested the EndoPredict test is only expected to lead to 39 patients avoiding chemotherapy, whilst the Oncotype DX test is expected to help 594 patients avoid chemotherapy. We ask the Committee to reconsider whether patients can reasonably be expected to find and understand the above crucial information from the draft NICE guidance, when deciding on which test to use to inform their decisions on chemotherapy. We also ask the Committee to consider what the consequences could be for patients of later finding out this information only after having undergone chemotherapy treatment based on a prognostic-only test and finding out that another test was available that could have directly determined whether they could safely avoid chemotherapy treatment. The patient testimonial from the Committee meeting highlighted the importance of patients having adequate information to support them in making the right individualised chemotherapy	Thank you for your comment, which the committee has considered. More information on the differences in test risk classification probabilities has been added in section 3.21 of the guidance. Additionally, recommendation 1.8 has been added which states "An oncologist should explain to the person what their tumour profiling test results mean, and the risks and benefits of treatment options based on all available risk factors." In section 3.1, it is noted that suitable educational materials will be needed for healthcare professionals to help them understand the evidence behind tumour profiling test results.

Comment number	Name and organisation	Section number	Comment	NICE response
			treatment decision and to minimise doubt and anxiety. The patient expert did not seem to have been given all of the relevant available information that may have further supported her decision making with confidence. Multiple stakeholders must play a role in helping to provide information to patients, including NICE via its guidance, and we question whether the current draft guidance goes far enough in doing so. We propose that a simple table be included in section 3.10, showing the expected % chemotherapy treatment rates for postmenopausal patients, based on clinical risk assessment (no genomic test), following the Oncotype DX test, and following the EndoPredict test. The UK decision impact study by Holt et al. provides this specific data for the Oncotype DX test. It should be clearly stated that the assumption for the EndoPredict test in the above-described table is based on data for the Oncotype DX test because no data exists to demonstrate the impact of the EndoPredict test on treatment decisions.	
63	Exact Sciences	3.4, page 13	“Clinical experts noted that the absolute benefit of chemotherapy is dependent on the absolute level of risk, so people with low risk of recurrence will have a lower absolute benefit from chemotherapy than people with a high risk of recurrence. So, tests with prognostic ability are useful to help guide chemotherapy decisions even if they are unable to predict chemotherapy benefit.” The above statement holds true as a simplified assumption in the absence of the ability to predict chemotherapy effect. We would suggest that prognostic-only tests become less useful for guiding chemotherapy treatment decisions when a test is available that is also predictive of treatment effect. The gold standard is to be able to directly predict treatment effect and move away from the historical approach of extrapolating treatment effect from treatment-naïve prognosis, as it is known that the two are not well correlated. This concept is well exemplified by the LN+ breast cancer patient group in question for this NICE review, whereby 60-80% are considered high risk, but chemotherapy has an effect/benefit in less than 10% of patients.	Thank you for your comment, which the committee has considered. The difference between the prognostic and predictive ability of tumour profiling tests has been outlined in sections 3.6 and 3.7 of the guidance. More information on the differences in test risk classification probabilities has been added in section 3.21 of the guidance. The committee noted that there was not enough comparative evidence to compare the tests directly, and that all 3 recommended tests had ICERs below £20,000 per QALY gained when compared to not using tumour profiling tests.

Comment number	Name and organisation	Section number	Comment	NICE response
			Some LN+ patients who benefit from chemotherapy can have a lower baseline risk of recurrence and many LN+ patients who do not benefit from chemotherapy have a higher baseline risk of recurrence. An ideal test to help guide chemotherapy decisions would identify with certainty all patients who will benefit from chemotherapy vs. all patients who will not benefit from chemotherapy. Therefore, with an ideal test, among the 'no chemo benefit' patient group, higher risk would not mean higher absolute benefit of chemotherapy and vice versa. A key point for patients and healthcare providers to be made aware of in this NICE guidance, is that prognostic information informs the risk of recurrence with endocrine therapy (without chemotherapy) but does not directly inform whether chemotherapy would be of benefit. It is clear from the EAGs analysis that prognostic-only tests which rely on extrapolating chemotherapy effect from prognosis being used as a proxy, is likely to lead to continuation of overtreatment of LN+ patients because higher risk doesn't in reality mean chemotherapy benefit for most patients. With the EndoPredict test which classifies up to 77% of LN+ patients as high risk, the level of overtreatment would remain high (only a 4% reduction in expected CT rates vs. the 80% in current practice). Since 2021, the Oncotype DX test has been proven to directly identify ~85% of postmenopausal LN+ patients who will not benefit from chemotherapy. Many of these patients would otherwise be classified as high risk by a prognostic only test and would likely receive chemotherapy. Using a predictive approach with the Oncotype DX test chemotherapy overtreatment can be reduced by 60%, with confidence that these patients would not have benefited. Clinicians across the UK are already leading the way in addressing the overtreatment issue for postmenopausal LN+ patients by adopting the new paradigm of treatment decision-making, whereby clinicians directly identify which postmenopausal LN+ patients will not benefit from chemotherapy treatment, using the Oncotype DX test. However, we suggest that it is very unlikely that patients would understand the important differences between the tests based on the current draft guidance. We believe that breast cancer	

Comment number	Name and organisation	Section number	Comment	NICE response
			patients should be aware of which treatment decision making paradigm they are choosing when opting for one genomic test compared to another. We urge NICE to include clear and accessible information about these important differences between the tests to help patients to understand the potential consequences for their treatment decision.	

THEME: Comments on modelling

Comment number	Name and organisation	Section number	Comment	NICE response
64	Web comment	General	The committee may find it useful to know that it is likely that a new version of the PREDICT tool will be made available in the coming months. Given the 2-3-fold reduction in breast cancer mortality seen over the last 2-3 decades the absolute benefits from systemic therapy notably chemotherapy have also fallen to he same degree. The 'existing' version of PREDICT based on pts treated 20+ years ago does not currently reflect these reduced benefits of chemotherapy. The new, as yet unreleased, version does and demonstrates absolute chemotherapy benefits which are substantially smaller. This will make a major difference to adjuvant chemotherapy decision-making and potentially the use of tumour profiling tests. Guidance issued without an appreciation of the potential effects of the use of more recent (and accurate) estimation of absolute chemotherapy benefits is likely to become outdated very quickly.	Thank you for your comment, which the committee has considered. The EAG noted that the risk of death from distant metastases in the economic model is based on a rebuilt model of abemaciclib, which it believes is the most appropriate source for the risk of death from distant metastases. However, it provided a scenario in which the overall risk of mortality was reduced by 25% to examine the effect of reduced mortality from breast cancer (see addendum 4). This did not have a large effect on the cost-effectiveness estimates.
65	UCL Cancer Institute	3.15 & 3.18, pages 18	The majority of the cost-effectiveness analyses have been performed using old data to estimate baseline DRFI risk for patients treated with endocrine therapy alone. Specifically, the transATAC trial, used in the cost-effectiveness analyses of Oncotype DX, EndoPredict and Prosigna, completed recruitment in 2000. Outcomes for patients with breast cancer have substantially	Thank you for your comment, which the committee has considered. The EAG noted the Taylor paper was published after its searches

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<tr><td></td><td></td><td>&20

And

DAR: 4.3, page 109</td><td>improved over time however. The EAG seem to be unaware of the publication by Taylor et al from June 2023. This is a detailed analysis of data from over 500,000 women with breast cancer collected by the National Cancer Registration and Analysis Service diagnosed with breast cancer during the time period 1993-2015. The main findings of relevance to NICE are:

1. Breast cancer mortality for women with ER-positive disease has fallen steadily by period of diagnosis. The adjusted annualised mortality rate for patients with 1-3 involved nodes by period of diagnosis with a 5-year perspective is:
<table>
<tr><td>Period of diagnosis</td><td>Annual mortality rate (95%CI)</td><td>Rate ratio</td></tr>
<tr><td>1993-99</td><td>2.49 (2.32-2.60)</td><td>1.0</td></tr>
<tr><td>2000-04</td><td>1.82 (1.73-1.92)</td><td>0.73</td></tr>
<tr><td>2005-09</td><td>1.27 (1.22-1.33)</td><td>0.51</td></tr>
<tr><td>2010-15</td><td>0.76 (0.72-0.81)</td><td>0.31</td></tr>
</table>
In effect all enrolment into the ATAC study took place during 1993-1999.

2. There has been no significant change in the rate of non-breast cancer mortality in this population during the same time period. Therefore, whilst breast cancer death was the dominant cause of death in this population at the beginning of the analysis period, rates of breast cancer and non-breast death are now similar.

3. A highly detailed mortality analysis is provided for the most recent (2010-15) period. This shows the cumulative breast cancer mortality for patients aged 50-70 with ER-positive HER2-negative 1-3N+ disease according to a number of scenarios (grade, tumour size, method breast cancer diagnosis). In all cases, the 5-year mortality is less than 10%.

There are inevitable limitations to the data, but these do not negate the findings.
1. HER2 status is only available for the 2010-15 period. Based on this data, approximately 11% of the ER-positive population is also expected to be HER2-positive. HER2-targeted therapy was not available in the NHS prior to 2006 and it is likely that its use was limited initially limited. Nevertheless, the mortality reductions shown in the table span the entire duration of the study indicating that the use of HER2-targeted treatment does not explain the mortality improvement.</td><td>were completed (April 2023), and does not report data on mortality from distant recurrence, which is the relevant parameter in the EAG's model. It also noted that the risk of death from distant metastases in the economic model is based on a rebuilt model of abemaciclib, which it believes is the most appropriate source for the risk of death from distant metastases. However, it provided a scenario in which the overall risk of mortality was reduced by 25% to examine the effect of reduced mortality from breast cancer (see addendum 4). This did not have a large effect on the cost-effectiveness estimates.</td></tr>
</table>

Comment number	Name and organisation	Section number	Comment	NICE response
			2. Details of treatment are not available. Whilst this creates difficulty in using the data to assess baseline risk, it is a reasonable assumption that all patients aged 50-70 with ER-positive HER2-negative 1-3N+ in the higher clinical risk groups were treated with chemotherapy. Applying the EAG estimate of a 0.71 HR for chemotherapy benefit to these groups, all but the highest risk are likely to have less than a 3% gain from chemotherapy where the risks of serious harm caused by chemotherapy become comparable to its potential benefit. 3. Mortality data has not been reported over a more-relevant 10-year period. Some analyses have been reported for a 5-15 year period and the authors are likely to be amenable to requests for additional subgroup data if NICE considers that would be of value. Reference: Taylor et al, BMJ 2023, PMID 37311588	
66	UCL Cancer Institute	DAR: 4.3	The EBCTCG has reported that chemotherapy benefits taper with time (e.g. ref 15). The most detailed analysis is contained in EGCTCG 2019, which includes separate analyses of patients with ER-positive and ER-negative disease. For patients with ER-positive disease, most of the effect of chemotherapy on recurrence is realised within the first 5-years; data contained in KM plots indicate this is about 80%. The effect appears to be independent of the number of involved nodes and whilst the analysis includes both distant and local recurrence, in a separate analysis, the time course of the chemotherapy effect on local and distant recurrence are very similar. Most of the trials in this meta-analysis are comparatively recent but nevertheless the ER-positive group will contain some patients that are also HER2-positive; this is unlikely to have substantially affected the time course of the chemotherapy effect to any substantial degree. The most recent (2023) EBCTCG chemotherapy meta-analysis also indicates that the chemotherapy effect wanes with time; the magnitude of the effect differs between trial groupings included in the various analyses, and the number of patients included in the ER-positive subgroup analysis is small and has a limited duration of follow-up. All three of these publications demonstrate that patients with ER-positive breast cancer continue to experience recurrence for as long as follow-up data is available. This is the effect explored by Pan et al (ref 156); about half of the patients in that analysis were treated with chemotherapy. It is unclear whether the economic model allows for the tapering of chemotherapy benefit, which if it does not is arguably is a significant deficiency.	Thank you for your comment, which the committee has considered. The EAG's base case did not include tapering of chemotherapy benefit over time. The EAG did investigate the effect of risk of distant metastases decreasing over time in scenario analyses – this did not have a large effect on the cost-effectiveness results. Additionally, the EAG provided scenario analyses to assess the effect of a total loss of chemotherapy benefit after 5 years or after 10 years. It considers these extreme scenarios. These changes did not have sufficient impact on the cost-effectiveness results to alter the committee's conclusions (see addendum 4).

Comment number	Name and organisation	Section number	Comment	NICE response
			References: EBCTCG, The Lancet 2012, PMID 22152853 (DAR reference 15) EBCTCG, The Lancet 2019, PMID 30739743 EBCTCG, The Lancet 2023, PMID 37061269	

THEME: Patient experience, education and confidence in treatment

Comment number	Name and organisation	Section number	Comment	NICE response
67	Web comment		I was part of a team of researchers across the universities of Leeds and Edinburgh who conducted qualitative research on patient experiences of a tumour profiling technique (Oncotype DX) in 2017-2019. This was part of a larger project on patient and practitioner experiences of genomic cancer medicine. Or research on ODX was published in 3 peer-reviewed articles, though it used small sample sizes (as is usual for qualitative research) and took place when the intermediate category was still in use. References: Ross, E., Kerr, A., Swallow, J., Chekar, C. K., & Cunningham-Burley, S. (2023). Unsettling the treatment imperative? Chemotherapy decision-making in the wake of genomic techniques. Sociology of Health & Illness, 1–19. https://doi.org/10.1111/1467-9566.13637 Ross, E., Swallow, J., Kerr, A., Chekar, C. K., & Cunningham-Burley, S. (2021). Diagnostic layering: Patient accounts of breast cancer classification in the molecular era. Social Science & Medicine, 278,113965. https://doi.org/10.1016/j.socscimed.2021.113965 Ross, E., Swallow, J., Kerr, A., & Cunningham-Burley, S. (2019). Online accounts of gene expression profiling in early-stage breast cancer: Interpreting genomic testing for chemotherapy decision making. Health Expectations, 22(1), 74–82. https://doi.org/10.1111/hex.12832	Thank you for your comment, which the committee has considered.
68	Web comment	3.1	Committee discussion - Shared decision making	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			Our research on LN- patient experiences of Oncotype DX showed that shared decision-making can be difficult or even unwelcome in the fraught context of cancer, which could influence patient engagement with this test. Oncotype DX was generally welcomed, often seen as resolving difficult decisions about a highly feared treatment. It is important to acknowledge these wider social contexts in clinical discussion of these techniques. Ross, E., Kerr, A., Swallow, J., Chekar, C. K., & Cunningham-Burley, S. (2023). Unsettling the treatment imperative? Chemotherapy decision-making in the wake of genomic techniques. Sociology of Health & Illness, 1–19. https://doi.org/10.1111/1467-9566.13637	
69	Web comment	3.2	Committee discussion - Shared decision making Our research on LN- patient experiences of Oncotype DX supports the view that patients can be poorly informed about how the result figures in clinical recommendations about treatment. This may be because it's not been clearly explained, or because patients cannot take it in when overwhelmed following diagnosis. Our respondents generally did not discuss their ODX result as just 'one piece of the puzzle' to be interpreted alongside other clinical markers, but often framed it as guiding their treatment decision. This was also attributable to an awareness of the 'hype' around personalised medicine and understanding of the test as superior to established prognostic tools. This demonstrates the significance of wider social contexts in shaping patient engagement with these techniques. Ross, E., Swallow, J., Kerr, A., Chekar, C. K., & Cunningham-Burley, S. (2021). Diagnostic layering: Patient accounts of breast cancer classification in the molecular era. Social Science & Medicine, 278, 113965. https://doi.org/10.1016/j.socscimed.2021.113965	Thank you for your comment, which the committee has considered. The committee has emphasised that tumour profiling tests should form part of a comprehensive management plan, and recommendation 1.8 has been added which states “An oncologist should explain to the person what their tumour profiling test results mean, and the risks and benefits of treatment options based on all available risk factors.”
70	Web comment	3.2	Committee discussion – Anxiety from test results Our qualitative research on LN- patient experiences of Oncotype DX does not provide evidence of anxiety provoked by the technique, but the issue was raised in a more nuanced way e.g. some articulated a concern about having made the 'wrong decision' by forgoing chemotherapy, but didn't explicitly label this as anxiety. Indeed, throughout our research patients framed chemotherapy decisions in terms of there being a 'right' and 'wrong' decision, with Oncotype DX portrayed as enabling them to make the 'right' decision where other prognostic tools could not.	Thank you for your comment, which the committee has considered. The committee has emphasised that tumour profiling tests should form part of a comprehensive management plan, and recommendation 1.8 has been added which states “An oncologist should explain to the person what

Comment number	Name and organisation	Section number	Comment	NICE response
			This again points to a need for patients to be informed about how tumour profiling test results figure in clinical chemotherapy recommendations. Ross, E., Kerr, A., Swallow, J., Chekar, C. K., & Cunningham-Burley, S. (2023). Unsettling the treatment imperative? Chemotherapy decision-making in the wake of genomic techniques. Sociology of Health & Illness, 1–19. https://doi.org/10.1111/1467-9566.13637 Ross, E., Swallow, J., Kerr, A., & Cunningham-Burley, S. (2019). Online accounts of gene expression profiling in early-stage breast cancer: Interpreting genomic testing for chemotherapy decision making. Health Expectations, 22(1), 74–82. https://doi.org/10.1111/hex.12832	their tumour profiling test results mean, and the risks and benefits of treatment options based on all available risk factors.”
71	Web comment	3.3	Committee discussion – Anxiety from test results In our publication, "A UK Prospective Multicentre Decision Impact, Decision Conflict and Economic Analysis of the use of Oncotype DX assay to guide chemotherapy decisons in 680 women with N1-3, HR+, HER2- Breast Cancer", (SABCS P6-01-11, 2022), we showed that confidence was increased by using the test: Oncologist (N, %) Patient (N, %) More Confident 365 (55.0) 465 (70.9) Unchanged 221 (33.3) 147 (22.4) Less Confident 78 (11.8) 44 (6.7). Increased confidence could be considered as a surrogate for reduced anxiety about their decision and conversely decreased confidence could be associated with increased anxiety. Since there was a significant increase in confidence express by both Oncologists and patients following the use of the test, it seems reasonable to conclude that anxiety related to chemotherapy decisions is reduced by the use of Oncotype DX.	Thank you for your comment, which the committee has considered.
72	Breast Cancer Now	3.2, page 12	We recognise the complex issues associated with patient understanding of tests results and ensuring that they have the necessary information to enable them to be adequately involved in decision making with their healthcare professionals.	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			Providing accessible, patient-focused information is important to individuals diagnosed with breast cancer and is something that Breast Cancer Now provides to them. For example, our Healthcare Information pages provide information on Primary breast cancer prognosis, Oncotype DX, and EndoPredict. When the final guidance is published, we will ensure that any relevant information we provide to patients is updated in an accessible way.	
73	Exact Sciences	1.5, 4.1, pages 4 and 21	Exact Sciences agrees with the Committee's proposal that: "More research is needed: on the types and formats of information that would help people with lymph node-positive breast cancer to understand all the factors that can support decisions on chemotherapy" Exact Sciences has made advancements in this area to support education specifically regarding patient and doctor communication. We are currently also completing improvements to the patient information booklet for the Oncotype DX test. We are committed to continuing to support patients having access to all relevant information that would help them make the best individualised treatment decisions. Exact Sciences is actively engaged in pursuing initiatives related to this subject with topic experts.	Thank you for your comment, which the committee has considered.
74	Exact Sciences	3.3	Exact Sciences agrees that patient anxiety about cancer treatment decisions is of paramount importance, and it is the shared responsibility of multiple stakeholders, including test providers, to seek to minimise anxiety experienced by patients during a difficult time in their lives. Having access to all the relevant information is crucial for patients to have confidence in their treatment decisions. Exact Sciences has made advancements in this area to support education specifically regarding patient and doctor communication. We are currently also completing improvements to the patient information booklet for the Oncotype DX test. We are committed to continuing to support patients having access to all relevant information that would help them make the best individualised treatment decisions. Exact Sciences is actively engaged in pursuing initiatives related to this subject with topic experts. Whilst the importance of this topic is rightly emphasised in the draft guidance, as described in the comment above we believe there is a gap in the information proposed to be provided to patients in the draft guidance. Specifically, clarity around the implications of the different types of	Thank you for your comment, which the committee has considered. The difference between the prognostic and predictive ability of tumour profiling tests has been outlined in sections 3.6 and 3.7 of the guidance. More information on the differences in test risk classification probabilities has been added in section 3.21 of the guidance.

Comment number	Name and organisation	Section number	Comment	NICE response
			information provided by the tests on expected chemotherapy treatment decisions/treatment rates. Section 3.3 states: *"Patient experts stated that anxiety could be increased for people with test results that indicate high risk of recurrence"*. The draft guidance does not clearly present the fact that the prognostic-only test EndoPredict is expected to lead to 77% of postmenopausal patients being classified as 'high risk'. In contrast, the Oncotype DX test classifies only ~14% of postmenopausal LN+ patients with a high Recurrence Score result, reflecting the proportion of patients most likely to benefit from chemotherapy to reduce their risk of recurrence. Section 3.3 also states: "They also said that people who choose to forego chemotherapy based on tumour profiling test results may experience anxiety over whether they have made the right decision". The draft guidance does not clearly and simply describe for the lay reader the differences between the tests in terms of the information conveyed by a low-test score. • It is not known whether a person choosing to forego chemotherapy based on a low score from a prognostic-only test would have gained a clinically meaningful benefit from having chemotherapy. • In contrast, it has been proven in a large Phase III randomised trial that a postmenopausal LN+ patient choosing to safely forego chemotherapy based on a low RS result from the Oncotype DX test would not have benefitted from chemotherapy. If patients are made adequately aware of the evidence supporting the ability to safely forego chemotherapy based on a low RS result from the Oncotype DX test, based on information presented in the NICE guidance, from their treating physician and from patient information materials provided by Exact Sciences, it could reasonably be expected that anxiety levels would be minimised for people making such a treatment decision. Exact Sciences suggest that the final guidance should include more explicit information about the following key factors, presented in an easily understandable format such as simple tables	

Comment number	Name and organisation	Section number	Comment	NICE response

			where possible, which will help patients to feel as confident as possible in their decision whether or not to have a genomic test, which test to have and in their subsequent treatment decision:
			
			• The definitions of what a low vs. high test score means for each recommended test for postmenopausal LN+ patients e.g.,
			  ○ Oncotype DX:
			  ▪ A low score means adding chemotherapy is not expected to be of benefit.
			  ▪ A high score means adding chemotherapy is likely to be of benefit.
			  ○ EndoPredict:
			  ▪ A low score means a lower risk of recurrence with endocrine therapy (without chemotherapy) but does not directly inform whether chemotherapy would be of benefit.
			  ▪ A high score means a higher risk of recurrence with endocrine therapy (without chemotherapy) but does not directly inform whether chemotherapy would be of benefit.
			• The proportion of patients classified by each test into the low vs. high test risk groups.
			• The expected % chemotherapy treatment rates for patients, based on current clinical practice (no genomic test), following the Oncotype DX test, and following the EndoPredict test (clearly caveating that no evidence is yet available for the EndoPredict test regarding chemotherapy allocation and the estimation is based on evidence for the Oncotype DX test).	

THEME: Equalities considerations

Comment number	Name and organisation	Section number	Comment	NICE response
75 76 77 78 79 80	Web comment	1.1, 1.5, 3.9, 3.11, 3.13, 3.19, 4.1	It is also clear that the evidence is not yet sufficient for these tests being used to guide chemotherapy decisions for non-white ethnic groups nor for transgender, non-binary or intersex breast cancer patients.	Thank you for your comments, which the committee has considered. There was not enough evidence to say whether the ability of tumour profiling tests to predict risk may differ across ethnic groups. It is important to clarify that this does not necessarily mean that the tests are less appropriate for use in non-white ethnic groups. The committee concluded that more evidence is needed to examine whether there is a difference in prognostic or predictive ability across different ethnic groups (see 4.1). The committee acknowledged that there was no evidence in trans, non-binary or intersex people, but that decisions on adjuvant chemotherapy in these populations would be individualised to the person considering their hormonal profile, their circumstances and any gender-affirming treatment, in addition to other clinical and pathological factors (see section 3.15). So, the committee recommended further research in these populations (4.1), but considered that it may be

Comment number	Name and organisation	Section number	Comment	NICE response
				appropriate to use the tests for some individuals depending on their hormonal profile (see 1.1).
81	Myriad	1.5, page 4	We agree the notice made for more research whether tumour profiling tests have the same prognostic or predictive ability across different ethnic groups but would also like to refer to a single-centre retrospective study was conducted by Jung et al. (2022) in South Korea on a cohort of 207 patients with early-stage RO+/HER2- breast cancer who were indicated for adjuvant chemotherapy based on the EPclin score between 2015 and 2019 (prospective testing). The patients, aged on average 50 (29-76) years, were followed for a median of 54.1 months (8.2-76.6). 7.7% (16) of patients were pN+. EndoPredict® identified a low risk of recurrence in 74.4% (154) of patients. 81.1% (41) of patients with a high EPclin score received chemotherapy compared with 0.6% (1) of patients with a low EPclin score. The 5-year disease-free survival rates were 100% and 88.9% respectively for patients with low and high EPclin scores (p<0.001). This first clinical study in Asian patients shows that the prognostic performance of the EPclin score is similar to that observed in patients of Caucasian ethnicity	Thank you for your comment, which the committee has considered. These data were considered by the EAG but were excluded from the review as more than 20% of the population was not LN1-3.
82	Agendia	3.11, page 16	The Draft guidance states the following sentence: *"In RxPONDER, differences in 5-year invasive disease-free survival within the RS 0 to 25 group were reported according to ethnicity (White, 92%; Black, 87%; Asian, 94%), but no prognostic or predictive data were reported."* However in fact, the provided sentence about RxPONDER does show clear differential prognostic information of the ODx in relation to ethnicities. Thus, the statement that no prognostic and predictive data were presented is only correct for the predictiveness as those specific prognostic values are presented within that sentence. **In both RxPONDER (for LN+ disease) and TAILORx (for LN0 disease) it is clear that Oncotype DX has poorer prognostic performance in Black women.**	Thank you for your comment, which the committee has considered. The EAG notes that the RxPONDER data stratified by ethnicity provides outcome data for only one genomic risk group (RS 0-25). Whether a test is prognostic in a particular group requires comparison of outcomes between different risk groups, which is not available from RxPONDER.

THEME: Implementation

Comment number	Name and organisation	Section number	Comment	NICE response
83 84 85	Web comment	General, 3, 7	This is a welcomed addition to the existing guidance. The tests require FFPE tissue produced and interpreted by Histopathologists but no Histopathologist seems to have been involved in the drafting of this guidance. Your Diagnostic Advisory Committee does not include Histopathologists and there is no Histopathologist among the Specialist Committee Members. This is a serious weakness of this guidance.	Thank you for your comment, which the committee has considered. The tests recommended in this piece of guidance are already recommended by NICE for the LN0 population (see recommendations 1.4 to 1.6) and it is likely that centres that would use these tests for people with LN1-3 breast cancer are already familiar with the appropriate sample preparation procedures.
86	Web comment	7.	It is important that Histopathologists are resourced into the specialist committee. Their contribution on technical matters and implementation are invaluable. The results of these tests will be discussed at the local Breast Cancer MDTs and Histopathologists will be needed to help interpretation, therefore consideration should be given on how to upskill the pathology workforce accordingly. These tests measure the relative proportion of mRNA in tumour tissue. The amount and quality of mRNA in the tissue is dependent on good pre-analytics as well as appropriate handling and processing within the laboratory. Relevant tumour tissue needs to be chosen from several possible tumour blocks. The successful implementation requires the input of competent histopathologist at the local level	Thank you for your comment, which the committee has considered. The tests recommended in this piece of guidance are already recommended by NICE for the LN0 population (see recommendations 1.4 to 1.6) and it is likely that centres that would use these tests for people with LN1-3 breast cancer are already familiar with the appropriate sample preparation procedures.
87	Web comment	2.12	The diagnostic tests – EndoPredict (Myriad Genetics) There is value in the possibility to do these tests in house or in any case not abroad. Economically, this creates more jobs int he UK. Logistically, we spend less packaging and sending tissue abroad and having it returned. Professionally, we can develop a more knowledgeable pathology workforce. Strategically, we can acquire know-how that can be used to deliver molecular tests in other tumour types. Clinical timelines would be reduced because of shorter TAT.	Thank you for your comment, which the committee has considered. The committee considered the effect of turnaround time, and concluded that all tests were likely to provide results within a useful timeframe (see section 3.5).

Comment number	Name and organisation	Section number	Comment	NICE response
88	Web comment	2.20	The diagnostic tests – Oncotype DX (Exact Sciences) The fact that this test needs to be done in the US is a disadvantage. Oncotype is a costs to the English taxpayer but does not provide further employment in England. It does not help up skilling the histopathology workforce. Being a send away abroad, it adds to the decision making timeline and leave patients longer with no outcome.	Thank you for your comment, which the committee has considered. The committee considered the effect of turnaround time, and concluded that all tests were likely to provide results within a useful timeframe (see section 3.5).
89	Web comment	2.22	The diagnostic tests – Oncotype DX (Exact Sciences) Send away abroad adds to TAT. While this may not affect the start of chemotherapy, it does impact on patient well being since they are left longer without knowing whether they will require chemotherapy.	Thank you for your comment, which the committee has considered. The committee considered the effect of turnaround time, and concluded that all tests were likely to provide results within a useful timeframe (see section 3.5).
90	Web comment	2.13	The diagnostic tests – EndoPredict (Myriad Genetics) Differently from Oncotype, Endopredict has only two risk groups (Low and High). This provides an advantage over Oncotype, which retains the intermediate risk group. In practice, a number of cases with intermediate risk using NPI or Predict, remain intermediate after Oncotype, while Endotpredict will provide a clear Low/High risk steer.	Thank you for your comment, which the committee has considered. Both Oncotype DX and EndoPredict use 2 risk groups in this population (see sections 2.13 and 2.21). Prosigna does define an intermediate group (see section 2.25).
91	Web comment	2.21	The diagnostic tests – Oncotype DX (Exact Sciences) Oncotype has an intermediate risk group therefore a patient who is of intermediate risk using conventional parameters (NPI, Predict etc) may remain intermediate risk after Oncotype. This happens in a significant proportion of cases. This is a weakness of this test.	Thank you for your comment, which the committee has considered. Both Oncotype DX and EndoPredict use 2 risk groups in this population (see section 2.13 and 2.21). Prosigna does define an intermediate group (see section 2.25).
92	Web comment	3.15	Endopredict seems to have lower economical benefit per QALY. But it eliminates the indeterminate risk group. In addition, it can be performed in the UK providing economical advantage (new jobs) and contribute to workforce ups killing.	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			These elements should be also considered when weighing in the economical argument.	
93	Web comment	5	5. Implementation NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice. In addition, NICE will support this guidance through a range of activities to promote the recommendations for further research. Well good luck with that. Your considered opinion is that there is no certain answer - so think about it - how on earth are you going to implement it or indeed should you try to do so at this stage ? What former colleagues have told me is that once agreed by NICE (for example with OncotypeDx for node negative disease) there will be an aggressive strategy employed by Exact Science, who take your guidance and apply pressure to Cancer Alliances and thereby to Trust managers, and thereby directly to clinicians to use the test and change their practice routinely, on uncertain evidence. If doing the tests remains uncertain, even in your own considered opinion, then this is likely to cause considerable distress both to clinicians and patients.	Thank you for your comment, which the committee has considered. The committee has emphasised that tumour profiling tests should be used alongside consideration of clinical factors, and recommendation 1.8 has been added which states “An oncologist should explain to the person what their tumour profiling test results mean, and the risks and benefits of treatment options based on all available risk factors.”
94	NHSE Genomics Unit	General	DAP71 recommends the use on Oncotype DX and EndoPredict to guide adjuvant chemotherapy decisions in lymph node positive early breast cancer. These are propriety tests and predominantly delivered on a sendaway basis. Whilst this is the current practice the guidance references that EndoPredict, as well as Prosigna and MammaPrint (latter two not currently recommended) can be delivered in local laboratories. These are currently listed in the National Genomic Test Directory and are complex genomic tests which required specialist interpretation. We would like to ensure that if tumour profiling is to be delivered at a local level that it is within the framework of the Genomic Medicine Service and delivered by a Genomic Laboratory Hub where the skills to develop these tests are embedded into the NHS.	Thank you for your comment, which the committee has considered. When used for people with LN+ breast cancer, the tests will be processed in the same way that they are currently processed for people with LN-negative breast cancer.
95	Myriad	2.12, page 8	We want to emphasize that EndoPredict is performed in local laboratories and results are available short term, latest 5 days	Thank you for your comment, which the committee has considered.
96	Breast Cancer Now	1, page 3	We now hope the tests will be recommended in the final guidance published in January 2024 and once published, we must emphasise the importance of having the tests swiftly entered on to the National Genomics Testing Directory. This is important to ensure equitable rollout across Trusts and to ensure that all eligible patients have equal access to testing as soon as it is available. Given some Trusts already provide access to the tests in the eligible lymph node	Thank you for your comment, which the committee has considered. NICE is in contact with the NHS England Genomics Unit and are working to ensure the test directory

Comment number	Name and organisation	Section number	Comment	NICE response
			positive group, we now hope the guidance will provide for a greater standardisation of the pathway for this group of patients and reduce variability of care that currently exists. Therefore, it is important that the necessary actions are taken to ensure updating of the National Genomics Testing Directory does not hinder this and that the timelines align with the NICE guidance publication date.	is updated as soon as possible once the guidance is published.

THEME: Regulatory issues

Comment number	Name and organisation	Section number	Comment	NICE response
97	NHSE Genomics Unit	1.1, page 3	What regulatory approval is required for Oncotype Dx and what is the time frame for this. Can a final recommendation be made if use is dependent on regulatory approval?	Thank you for your comment, which the committee has considered. The relevant statement has been removed as the regulatory status of Oncotype DX has been confirmed. Further information on regulatory factors relating to Oncotype DX has been included in a box at the beginning of section 1 and in recommendation 1.6.
98	Veracyte	1.1, page 3	It is importantly noted that Oncotype DX can only be used once it has appropriate regulatory approval. Veracyte supports, that for patient safety it is essential that products recommended and used in England and Wales are safe, reliable, of good quality and registered appropriately. We question how NICE can recommend a test (Oncotype DX) that does not have the appropriate regulatory approval as stated by NICE. Veracyte find it of utmost importance that NICE expand on the regulatory issues that have been identified by NICE for Oncotype DX so that patients and healthcare staff are fully informed of the regulatory status of this test and the identified regulatory issues before it is recommended for broader use. Further, we urge NICE to	Thank you for your comment, which the committee has considered. The relevant statement has been removed as the regulatory status of Oncotype DX has been confirmed. Further information on regulatory factors relating to Oncotype DX has been included in a box at the beginning of section 1 and in

Comment number	Name and organisation	Section number	Comment	NICE response
			comment on how this influences DG34 recommendation of use of Oncotype DX in node negative patients since the regulatory issues identified will be relevant in this patient population. Veracyte places utmost importance on patient safety, regulatory compliance and ensuring a high degree of reproducibility and repeatability of any IVD device. To this end, Prosigna® is a fully CE marked test meeting all requirements of the UK MHRA. Prosigna is also FDA 510(k) cleared which is also not the case for Oncotype DX. Further, it should be noted that Prosigna® is also UK GDPR compliant as no patient sensitive information or biological materials are shipped outside the country and thereby do not exit the closed loop system and safeguarding of the NHS. Veracyte asks that UK GDPR compliance status is also mentioned for each of the assessed tests or services. The latter is highly relevant since it is noted that both Oncotype DX and MammaPrint, wholly or partly rely on shipment of human tissue and patient sensitive information to non-UK GDPR compliant territories (such as US).	recommendation 1.6. This states that Oncotype DX is processed in the US and laboratories processing the test must be CLIA-certified and be accredited to ISO15189 or ISO17025. Use of tests must be in compliance with UK General Data Protection Regulation (GDPR) and the Health and Social Care Act (2012). Additionally, laboratories processing the tests must take part in a UK national external quality assurance scheme.
99	Veracyte	2.18, page 9	It is noted that Oncotype DX is a CE marked assay. Veracyte is not aware that the assay for Oncotype DX is CE marked. In a report published in 2021: (https://www.tlv.se/download/18.7102c4617a75ed7acf77376/1630506397339/bed210602_Oncotype_dx.pdf) by another HTA agency, the Swedish TLV, it is noted in section 3.2.1 that the company has informed TLV that Oncotype DX is not a CE marked assay but has a self-declared CE mark for the sample collection kit and the software. Remarks on legal prerequisites for the use of Oncotype DX in a Swedish setting can also be found in the MTP Council report of 2022: https://janusinfo.se/download/18.510ef4417d14cc072fc7d8f/1669624210367/MTP-r%C3%A5dets%20rekommendation%20prognostiska%20plattformar.pdf Veracyte considers that it is very important for safety and decision making that patients, relatives and health care professionals are fully informed about the regulatory status of the different tests and particularly the most important element, the assay, and thereby validated and regulatory approved claims for the intended use. It is Veracyte's understanding that the entire IVD workflow should be CE marked (instrument, assay, and software). Veracyte asks that NICE seek documentation from each manufacturer of the CE marking and regulatory approval of its assay and not just for a sample collection kit or software. Furthermore, in the absence of such documentation, we ask that NICE clearly writes that such documentation has not been provided and that the test in question can, therefore not be considered a CE marked assay and is not in compliance with EU or UK (MHRA) regulations. If the assay is CE marked there should also be a	Thank you for your comment, which the committee has considered. The regulatory status of Oncotype DX has been confirmed. The descriptions of technologies in section 2 have been updated to ensure alignment with the instructions for use for each technology.

Comment number	Name and organisation	Section number	Comment	NICE response
			defined intended use statement in the package insert (see attached Prosigna package insert/instructions for use). Throughout the draft guidance documents there are statements that the manufacturer claims use in a certain population or claims prognostic or predictive value. All such statements can be removed and instead NICE can clearly refer to the intended use statement that comes as part of the CE marking of an assay. Again, if documentation has not been provided about the assays intended use, we believe the claim has no value and should be removed from the draft and final guidance. Examples of such statements for Endopredict (page 7, section 2.10 "...as well as the benefit of chemotherapy"; and for Oncotype DX page 9 section 2.21 "The company states that the recurrence score also estimates chemotherapy benefit". Such statements should only be included if they are clearly described in the package insert/intended use and supported by performance data summarized in the package insert as required under the CE IVDD (IVD Directive), CE IVDR (IVD Regulation) and by the UK MHRA. Veracyte confirms that the Prosigna® Breast Cancer Prognostic Gene Signature Assay is CE marked. The Assay consists of two separate IVD medical devices: 1. Prosigna® Breast Cancer Prognostic Gene Signature Assay Kit 2. Prosigna® Breast Cancer Prognostic Gene Signature Assay Software Module Both devices are CE marked and currently designated as Class C "legacy devices" in compliance with the IVDR (EU 2017/746). They were self-declared under the IVD Directive (see attached Declarations of Conformity) and are currently available under the EU IVDR transition legislation (EU 2022/112). It is planned to submit these devices for Notified Body review to obtain IVDR CE certification prior to the end of the transition period (May 25, 2026) to ensure long-term compliance and availability within the EU. Outside the EU, the Prosigna Assay is available as a fully registered IVD medical device in several countries including 3 MDSAP countries - Australia (TGA, Class 3), Canada (Health Canada, Class 3) and the USA (FDA, Class II, 510(k) cleared). Further, it should be noted that Prosigna® is UK GDPR compliant as no patient sensitive information or biological material are shipped outside the country and thereby do not leave the closed loop system and safeguarding of the NHS.	
100	Veracyte	2.21, page 10	Exact Sciences proposes a changed cut-off of 25 for prediction of chemotherapy benefit for Oncotype DX which according to NICE is different from the referenced instruction for use with cut-off for LN-positive cancer (below 18, between 18-30 and above 30). Throughout the DAP71 there has been referral to studies for Oncotype DX utilising different cut-offs. We question why the company's statement that is not derived from a regulatory approved intended use statement which would have precise description of cut-offs is relevant? We also question why a test is recommendable when its assays performance claims and assigned cut-offs have not been	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			reviewed and approved by the relevant regulatory body and where the necessary certification is required (CE or UKCA). This only serves to create confusion and support speculative claims of predictive effects of Oncotype DX. In the EAR report it was noted how there is uncertainty relating to the predictive value of Oncotype DX. We ask that NICE ensures that if Exact Sciences changes cut-offs it should also note that this then disqualifies previous studies and narrows the total body of evidence for Oncotype DX? Any significant change to a legacy CE marked device (including any change to the intended use or performance claims), requires submission and full IVDR Notified Body Review with resultant IVDR CE certification. The same applies under the UK MHRA transition arrangements, unless full UKCA certification has been obtained.	
101	Breast Cancer Now	1.1 & 2.21, pages 3 & 10	We note that Oncotype DX can only be used once it has appropriate regulatory approval. What timeline can be expected for regulatory approval for the company's suggested changes to the cutoff recurrence score for predicting no chemotherapy benefit? Is this expected to align alongside the publication of the guidance in January. It is important that this happens in a timely manner so that eligible patients are able to benefit from access to tests as soon as possible once the guidance is published.	Thank you for your comment, which the committee has considered. The regulatory status of Oncotype DX has been confirmed, and the relevant statement has been removed.
102	Exact Sciences	1.1, page 3	The Oncotype DX Breast Recurrence Score® Test was CE-marked under Directive 98/79/EC of the European Parliament and the Council of 27 October 1998 on in vitro diagnostic medical devices (IVDD) before the entry into application of the Regulation (EU) 2017/745 ('IVDR'). Therefore, the Test qualified for the transition period defined by article 110(4) and to Article 112 of such regulation and its subsequent extension by the European Commission. The Test has thus been compliant with the IVDR regulation at all times during NICE guidance evaluation timeline. The Oncotype DX Breast Recurrence Score® Test's Technical File was in the process of Technical Documentation assessment by the Notified Body, according to Annex IX, Chapter II of Regulation (EU) 2017/746 of the European Parliament and the Council of 5 April 2017 on in vitro diagnostic medical devices (IVDR). The assessment was successfully completed on October 30, 2023, and resulted in regulatory approval / CE marking under IVDR.	Thank you for your comment, which the committee has considered. The regulatory status of Oncotype DX has been confirmed, and the relevant statement has been removed.

Comment number	Name and organisation	Section number	Comment	NICE response
			Also, of note included within the current IFU, assessed by the Notified Body, is the clinical trial data from RxPONDER and SWOG-8814, which in totality covers the scope of the NICE assessment. The Oncotype DX Breast Recurrence Score® Test therefore has full regulatory approval, based on a very recently conducted assessment by a Notified Body, according to the new requirements for the In Vitro Diagnostic Regulations (IVDR). Exact Sciences requests to remove the statement: “Oncotype DX can only be used once it has appropriate regulatory approval” from the final NICE guidance, as the statement is a factual inaccuracy. We have enclosed the IVDR CE mark certificate.	

THEME: Hormone receptor positivity

Comment number	Name and organisation	Section number	Comment	NICE response
103	Web comment	1.1	Recommendations Selection criteria for the use of these tests is positivity for ER and/or PR. There is little controversy for those tumours showing good expression of these biomarkers. However a small proportion of patients may be difficult to identify since the lower positivity threshold for these two biomarkers is controversial (is set by some at 1% and by others at 10%), there is no concordance on acceptable staining intensity and localisation and the test performance depends on the specific antibody and staining platform of used and on a number of pre-analytical factors. While these factors will impact on patient selection for the use of these tests, they also have an impact on patient selection for the studies used to provide this NICE guidance.	Thank you for your comment, which the committee has considered. It is beyond the scope of this assessment to define standards for laboratory procedures for determining ER and PR status.

Comment number	Name and organisation	Section number	Comment	NICE response
			This NICE guidance is disadvantaged by the weakness of having an ill-defined patient cohort. NICE needs to define an agreed standard for the identification of the breast cancer patients allowed for testing.	
104	Web comment	1.5	More research is needed for the correct identification of the subgroup of breast cancer suitable for these tests. Regrettably, the UK has not embraced the molecular classification of breast cancer based on gene expression profiling and the later St Galen classification based on on slide biomarkers for which there is over 20years of published work. More recently, more detailed work using data from genomics and proteomics in addition to the transcriptomics data, has refined the molecular classification of breast cancer. There is undoubtedly a subcategory of breast cancer referred to as "low ER" which continues to represent a clinical problem, siting between TNBC and HR+ breast cancer. We need more clarity on subclassifications of breast cancer and more research should be focused on this topic.	Thank you for your comment, which the committee has considered. It is beyond the scope of this assessment to define subclassifications of breast cancer.
105	Web comment	2.3	We have a robust system for the identification of the Her2 status of a breast carcinoma, with IHC as first line test and ISH as a second test to be used for equivocal IHC result. The tests for ER and PR are IHC based only and do not have a reflex test using alternative technology.	Thank you for your comment, which the committee has considered.

THEME: Comments on wording

Comment number	Name and organisation	Section number	Comment	NICE response
106	Web comment	3.4	The tests assessed here are not genomic tests, they are transcriptomic tests. Is this a typographical error or would the panel benefit from further expert input? I would be happy to contribute.	Thank you for your comment, which the committee has considered. The term ‘genomic’ has been deleted.
107	Exact Sciences	2.21, page 10	The last paragraph in this section refers to 2.9% benefit from chemotherapy at 5 years for premenopausal women with RS 0-25. It could be noted that the benefit from chemotherapy in this patient group reported by Kalinsky et al 2021 in their SABCS presentation, based on 6.1 years median follow up, was 2.4% in terms of the distant recurrence (the DRFI) endpoint.	Thank you for your comment, which the committee has considered. The text here is based on the OncotypeIQ website and so is consistent with the publicly

Comment number	Name and organisation	Section number	Comment	NICE response
				available information provided by the company.
108	Exact Sciences	3.7, page 14	We request that NICE amend the wording of the following statement regarding the RxPONDER estimate for DRFI in postmenopausal patients: Within this group, the hazard ratio for the effect of chemotherapy was non-significant but favoured no chemotherapy for postmenopausal women, and the lower limit of the confidence interval suggested a small benefit of chemotherapy (HR 1.12, 95% CI 0.82 to 1.52). We consider this statement to be misleading, as it is not the correct interpretation of a confidence interval. The lower limit of the 95% CI does not suggest a small benefit of chemotherapy. A confidence interval provides the range of values that we can say with 95% certainty that contains the true effect. From biostatistical input, if RxPONDER was repeated 100 times, we would be 95% confident that the HR would fall within the range 0.82 – 1.52.	Thank you for your comment, which the committee has considered. The text has been amended to: "Within this group, the hazard ratio for the effect of chemotherapy was non-significant but favoured no chemotherapy for postmenopausal women (HR 1.12, 95% CI 0.82 to 1.52)."

THEME: Comments on process

Comment number	Name and organisation	Section number	Comment	NICE response
109	Agendia	General	For the reasons explained below, accompanied by the closed letter from the MINDACT collaborative group, we kindly request NICE to **restore the resolution stage of the DAP71 process.** Data from the MINDACT trial indicating the clear ability of MammaPrint to predict the absence of chemotherapy benefit in post-menopausal women (aged >50) with HR+/HER2-/LN+ breast cancer have not been considered in the assessment and consultation so far. These data, when discussed and included would likely significantly impact the Guidance document.	Thank you for your comment, which the committee has considered. The resolution process has been reinstated as requested.

Comment number	Name and organisation	Section number	Comment	NICE response
			To ensure proper considerations of these data, and issuing factual accuracy of the guidance for suitable recommendations to the NHS, together with the impact the DAP71 and reputable NICE evaluations have in the field of tumour profiling tests and more, Agendia believes it is essential to reinstate the resolution stage to the DAP71 to ensure that all elements have been considered and checked on factual accuracy prior to the delivering a definitive guidance to NHS. As mentioned above, alongside the submitted comments, a closed letter from [redacted] has also been submitted. We would greatly appreciate **if the letter could be sent to the Committee members.** The letter brings critical interpretation of the MINDACT trial data by experts familiar with the trial, i.e., the principal investigators. We understand that physicians in the UK may not be as familiar MammaPrint considering the absence of a commercial presence from Agendia, compared with other tests. We believed that this letter and submitted comments, will provide further confidence in the MINDACT data and assurance concerning MammaPrint's ability to answer the question asked through the DAP71 process. Of note, the PI's letter is both uploaded on the NICE Docs portal as a version where the DocuSign signature of the four physicians have been merged in to one file as well as the four original DocuSign documents to testify of the authenticity of the letter endorsement. Agendia sincerely hopes that NICE agrees on the importance of a diligent approach and will honor the request to reinstate the resolution stage.	

THEME: Further research

Comment number	Name and organisation	Section number	Comment	NICE response
110	Web comment		I had a comment about this sentence:	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			"The committee encouraged clinicians to continue to promote enrolment in OPTIMA so that it can meet its recruitment target". It seems strange to encourage a trial just to "meet a recruitment target". How about "The committee encouraged clinicians to continue to promote enrolment in OPTIMA to answer outstanding questions about the use of profiling in younger and higher risk patients, and to provide further information about the relative value of different tests".	The text has been amended to: “The committee recognised that OPTIMA may be able to address some of the uncertainty around the results for Prosigna, and encouraged clinicians to continue to promote enrolment in OPTIMA.”
111 112 113 114 115 116 117 118	Web comment	1.1, 1.2, 1.5, 3.9, 3.19, 4.2	More research is certainly needed before ANY of these tests can be used to PREDICT the chemotherapy response of the breast tumour. As a breast cancer patient, I would not be confident to rely on any of the current tumour profiling tests to guide any decisions about chemotherapy. The OPTIMA trial is absolutely essential to answer the question of the predictive value of these tests. This guidance will seriously undermine recruitment to this essential trial.	Thank you for your comment, which the committee has considered. The committee recognised the value of OPTIMA and encouraged clinicians to continue to promote enrolment in the trial. Please see section 3.23 for more detail.
119	Web comment	1.5	A further consideration is the identification of breast cancer harbouring actionable mutation such as PIK3CA, Her2 Ex20 ins and others. These patients would benefit more from biological or targeted therapy than from chemotherapy but the current test guidance makes no effort to identify these patients and concentrates only on benefits from conventional chemotherapy. The use of RNA expression tests such as Endopredict or Oncotype should be used to identify patients at risk of recurrence/distant disease and for these patients there should be further tests to determine whether conventional chemotherapy or targeted therapy would be more effective. The current arrangement where the calculation of benefit and QALY is limited to conventional chemotherapy is a weakness of this guidance and more work should be done to understand if patients with high risk (or intermediate risks) disease would be better served with personalised treatment.	Thank you for your comment, which the committee has considered. Use of tumour profiling tests to inform treatment other than adjuvant chemotherapy is beyond the scope of this assessment.
120	Web comment	4	Future research to be considered: 1. A project of concordance between Oncotype and Endopredict in pre and post menopausal, with separate consideration for the LN(-) and LN(+) patients. 2. Role of these tests in the so called "ER Low" breast cancer. 3. Establishment of strict criteria for the identification of HR+ breast cancer.	Thank you for your comment, which the committee has considered.

Comment number	Name and organisation	Section number	Comment	NICE response
			4. Role of targeted therapy on breast cancer patients identified as high risk by Endopredict or Oncotype; would the health economy and the patients benefit from upfront screening for actionable mutation for this group of patients who require adjuvant therapy?	
121	Web comment	3.20	3.20 The OPTIMA Trial The committee encouraged clinicians to continue to promote enrolment in OPTIMA so that it can meet its recruitment target. This is paradoxical advice. If Oncotype Dx is given the go ahead for guidance for use in the NHS in patients with this tumour profile (ER+ve, PR+ve, HER2NEG) with 1-3 positive nodes, then the assumption from clinicians will be that it is a proven predictive test, and this is not the case. If Oncotype Dx is approved then it is very likely that recruitment to OPTIMA which would provide randomised evidence both of the test and it's implementation, will be slowed and grind to a halt. Recruitment from the ANZ group which is about to start would be called into question, and might not go ahead. NICE needs to recognise it's considerable influence around the world as a body that produces excellent, independent appraisal of the evidence and then cost-effective guidance. It would be a considerable reputational risk for guidance, which is not supported by the evidence (as stated in your own report), were to be put out now. It would be much more sensible and reasonable to allow the OPTIMA trial to complete recruitment, which will produce definitive, grade A evidence to support or otherwise multigene testing in this group of breast cancer patients. To hide behind shared-decision-making with the patient does not work; at present the evidence that Oncotype Dx and EndoPredict provide robust evidence for prediction of chemotherapy benefit remains uncertain. A large body of opinion from 'economics' suggests that confronting uncertainty is important in setting out to make guidance decisions, and that planning with incredible (in other words unbelievable) certitude can be harmful. From the evidence that is available and documented in the report, it seems to me that this is insufficient at present to lead to evidence-based approval of Endopredict and Oncotype Dx, as tests predictive of response to adjuvant chemotherapy in ER+,PR+,HER2neg, early breast cancer.	Thank you for your comment, which the committee has considered. The committee acknowledged the uncertainty in the evidence for predictive ability of Oncotype DX. However, it concluded that it was likely that Oncotype DX has some predictive ability for chemotherapy benefit, even if the size of the difference in chemotherapy benefit between risk groups was overestimated. A scenario in which the size of this difference was reduced did not have a large effect on the cost effectiveness estimates (see sections 3.9, 3.10 and 3.18). There was no evidence identified for the predictive ability of EndoPredict in a mostly LN+ population, so it was assessed as a prognostic test. Considered in this way, the committee concluded that it was likely a cost-effective use of NHS resources (see sections 3.7 and 3.16). The committee recognised that these recommendations could impact recruitment to OPTIMA, however it felt that there was sufficient evidence to recommend

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				EndoPredict, Oncotype DX and Prosigna.
122	Web comment	General	NICE guidance consultation clearly outlines the evidence for the different genomic tumour profiling in node positive patients. It supports the use of these assays for node positive post menopausal patients and this is a welcome confirmation of their use in this group. Post-menopausal women with 1 – 3 nodes positive (limited nodal involvement) do not benefit from chemotherapy with a recurrence score (RS) of 0 – 25 compared with pre-menopausal women where there is substantial clinical benefit (2.9% at 5 years). As we endeavour to personalise treatments for our patients and with careful consideration of both the positive and adverse effects of chemotherapy, this additional information is helpful. Studies have demonstrated that the results help decision making for these patients., for both clinicians and patients themselves. The challenge with pre-menopausal patients is that the evidence has less clarity. The papers included in the guidance demonstrate a 2.9% improvement in survival with chemotherapy in node positive pre-menopausal patients with an oncotype DX score of 0 to 25. The numbers of patients in the smaller subsets within this scoring group makes further analysis inappropriate. However, the complex decisions regarding risk benefit in this group of patients requires all the supportive information possible. While there is no clear cut off below which chemotherapy has no benefit, there is evidence of genomic scoring giving additional prognostic information to support decision making. We would encourage further data gathering in this population, alongside a recommendation to offer testing only in those patients where it would influence patients decision making.	Thank you for your comment, which the committee has considered. Another stakeholder highlighted the ongoing OFSET trial which will assess the effect of chemotherapy compared to ovarian function suppression in premenopausal women with an RS of 0-25: https://clinicaltrials.gov/study/NCT05879926
123	Breast Cancer Now	1.5, page 4	We welcome that the Committee has identified two further areas of research for tumour profiling tests for lymph node positive early breast cancer patients. We would like to understand when the Committee will take additional research into consideration when updating guidance, how they will take this into account and how they will review this new research once it is available. Additionally, we would like to understand whether there is a timeframe in which we can expect this research will be undertaken.	Thank you for your comment, which the committee has considered. Guidance can be reviewed at any time if there is reason to do so, including changes in the evidence base (for full detail please see the CHTE programme manual section

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				8). When notified by stakeholders or through NICE's own surveillance activities that there is relevant new information that could affect guidance, NICE will do a short surveillance review to establish whether the guidance should be amended, updated, withdrawn or not updated. If the new data is likely to have a material effect on the recommendations then NICE will do an update of the guidance, using a similar process to the current evaluation.
124	Breast Cancer Now	3.20, page 21	The Committee has recognised that the OPTIMA trial may be able to address some of the uncertainty around the results for Prosigna. When these results are published, we would be keen to understand whether NICE will reconsider the guidelines and how NICE will review the evidence, taking into consideration what the OPTIMA trial results show.	Thank you for your comment, which the committee has considered. Guidance can be reviewed at any time if there is reason to do so, including changes in the evidence base (for full detail please see the CHTE programme manual section 8). When notified by stakeholders or through NICE's own surveillance activities that there is relevant new information that could affect guidance, NICE will do a short surveillance review to establish whether the guidance should be amended, updated, withdrawn or not updated. If the new data is likely to have a material effect on the recommendations then NICE will do an update of the guidance, using a

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				similar process to the current evaluation.
125	UCL Cancer Institute	3.20, page 21	NICE states “The committee encouraged clinicians to continue to promote enrolment in OPTIMA so that it can meet its recruitment target.” This is a worthy but unrealistic sentiment. No clinician wishing to recruit postmenopausal 1-3N+ patients into the trial will be able to do so in the face of an endorsement of the predictive hypothesis by NICE. Pressure from patients, from MDT members not wholeheartedly committed to the trial, from management eager to reduce chemotherapy suite workload, and from the test manufacturers will be irresistible. This will jeopardise completion of the trial and deprive breast cancer community not to mention NICE itself of the high high-quality evidence on test efficacy and cost-effectiveness that is currently lacking from other sources.	Thank you for your comment, which the committee has considered. The committee recognised that these recommendations could impact recruitment to OPTIMA, however it felt that there was sufficient evidence to recommend EndoPredict, Oncotype DX and Prosigna.
126	UCL Cancer Institute	3.15 - 3.18, 4, pages 18-20, 21 And DAR 4.3, page 108 ff	The single most disappointing aspect of the cost-effectiveness analysis is the lack of comparison between the various scenarios considered with optimal decision making using existing tools, particularly PREDICT. It is entirely possible that use of PREDICT would reduce current chemotherapy use but no such data appear to be available. Comparisons between PREDICT tool and the profiling tests was a research recommendation in DG34 and arguably should also be included as a research recommendation in the current guidance. The committee should also be aware of the work of Chowdhury and collaborators who have assessed the impact of adding tumour profiling test results to PREDICT. The report is almost certainly outside the scope of the current assessment as it uses "in silico" test results to model results but nevertheless it does reach interesting conclusions and may be a way forwards. Reference: Chowdhury et al., Breast Cancer Res 2023, PMID: 36755280	Thank you for your comment, which the committee has considered. The comparator for this assessment was decision-making for adjuvant chemotherapy prescribing without the use of tumour profiling tests. This may include PREDICT. The EAG did not identify any studies comparing PREDICT to tumour profiling tests.
127	UCL Cancer Institute	DAR: 3.2.2, page 46	Ongoing prospective RCT of Prosigna: OPTIMA The OPTIMA statistical design has been revised; it will now assess invasive breast cancer free survival (IBCFS) in place of IDFS. Additional secondary endpoints have been added. Reference: Stein et al 2023, doi: 10.1158/1538-7445.SABCS22-OT3-32-01	Thank you for your comment, which the committee has considered.

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128	UCL Cancer Institute	DAR: 3.2.2	For completeness, the OFSET trial (NRG BR009, NCT05879926) has recently commenced recruitment. OFSET will examine the utility of a tumour profiling test (Oncotype DX) in premenopausal women using a randomised design of chemotherapy and endocrine therapy vs endocrine therapy alone. Chemotherapy-induced premature ovarian insufficiency is controlled for through the use of ovarian function suppression. Initial results are anticipated around 2030. Reference: https://classic.clinicaltrials.gov/ct2/results?cond=&term=NCT05879926&cntry=&state=&city=&dist=	Thank you for your comment, which the committee has considered.