NICE draft scope and provisional stakeholder list consultation – 'Tumour profiling tests to guide adjuvant chemotherapy decisions in lymph node-positive early breast cancer'

	Comment	Page	Section	Comments	NICE response
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	1	Provisional stakeholder list	General	Wide and appropriate representation	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	2	4	2.2.3	Text seems to suggest ER- PR-, require clarity that additional information is provided by oncotype on the level of oestrogen and progesterone receptor expression.	Thank you for your comment. We note that there was some confusion with the use of hyphens in this document and so have removed them when referring to biomarker status such as ER positive.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	3	8	3.1	Please check deff of locally advance (present in lymph nodes not specific as factor)	Thank you for your comment. We have updated the description to: "Early breast cancer can be locally advanced; this means that the cancer has spread to the surrounding area such as the nearby lymph nodes, skin or chest muscle, but not to distant parts of the body." Source: Cancer Research UK
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	4	Appendix A Questions	1:	Sections are complete noting comments above.	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	5		2:	Yes	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	6		3:	St Gallen consensus	Thank you for your comment. A paragraph on the St Gallen consensus has been added to section 3.2.5.1.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	7		4:	It may raise threshold for treatment with chemo as Abemaciclib may be seen as a half way between AI and Chemo (no direct evidence for this as far as aware)	Thank you for your comment. 'Impact of test results on decision making' is an outcome specified in the scope (table 2) for the external assessment group to look for data on.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	8		5:	Yes, minimal evidence for use in 4> node pos cancer	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	9		6:	Yes	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	10		7:	Yes, minimal evidence for validation in Male breast cancer although some evolving for oncotype.	Thank you for your comment. We have included a paragraph about male breast cancer in section 7.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	11		8	No	Thank you for your comment.

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Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	12		9	Agree IHC4 problematic due to variation in Ki67 testing	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	13		10	Agree	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	14		11	yes	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	15		12	Nil to add	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	16		13	No	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	17		14	No	Thank you for your comment.
Newcastle upon Tyne Hospitals NHS trust (PRE-DX Trialists)	18		15	No	Thank you for your comment.
Peony Breast Cancer Unit	19	General	General	We approve of the scoping document. Recently this unit has completed a trial entitled, “A UK Prospective Multicentre Decision Impact, Decision Conflict Trial and Economic Evaluation of the use of Oncotype Dx® in 680 women with early Hormone Receptor positive, HER2 Negative breast cancer and 1 to 3 lymph nodes involved.” The initial data was reported in a poster at the 2022 San Antonio Breast Cancer Symposium (P6-01-11). A manuscript presenting greater detail is in preparation and will be submitted for publication shortly. We are prepared to offer this academic in confidence, with all the underlying data for your consideration, if requested.	Thank you for your comment. Please send any relevant information to NICE (diagnostics@nice.org.uk) and we will pass it on to the external assessment group (EAG). Please note that the EAG will set a deadline in the protocol for submission of new data. Any data submitted after this date may not be considered. The protocol is due to publish on the 14th April.
Agendia N.V.	20	1	Title	Suggestion to change the title to: Tumour profiling tests to guide chemotherapy decisions in early breast cancer with up to three lymph nodes. One, because the GEP-tests are not used for chemotherapy decision-making for patients with 4 or more lymph nodes, and two, the title suggestion allows room for re-assessment of LN- data.	Thank you for your comment. The current guidance is focusing on the lymph node-positive population in response to a specific request from NHS England. Focusing on this narrower population will allow guidance for the NHS and patients to be produced more quickly. Any review of the tests in the lymph node-negative population would happen separately to the currently ongoing assessment. The population in the final scope includes only people with 1 to 3 positive lymph nodes.

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Agendia N.V.	21	2	2.1	Addition in bold and underline to clarify type of risk: “The use of tumour profiling tests may improve the identification of people with lymph node-positive early breast cancer who may not benefit from having adjuvant chemotherapy because they have a **genomic** low risk of disease recurrence.”	Thank you for your comment. This addition has been made.
Agendia N.V.	22	3	2.2.2	Please add that the 70 cancer related genes in MammaPrint are normalized with 465 control genes.	Thank you for your comment. This addition has been made.
Agendia N.V.	23	4	2.2.2	This section states that the MammaPrint is offered as an off-site service performed in Agendia’s laboratory in Amsterdam, the Netherlands. This information is outdated. For UK, patient material will be shipped to Agendia Amsterdam where material will be accessioned for MammaPrint testing. The processing of the microarray test will be performed in Agendia’s central laboratory located in Irvine, California USA, which is EU CE-Marked as well as accredited by the American Association for Laboratory Accreditation and the College of American Pathologists.	Thank you for your comment. The text has been updated to reflect your comments.
Agendia N.V.	24	3 and 4	2.2.2	To add to the section where it is described that MammaPrint genes are associated with the 7 different parts of the metastatic pathway: A more recent study, that aimed to update the annotation of the 70 genes of MammaPrint to the extended version of the 10 hallmarks of cancer (HoCs), demonstrated that the MammaPrint gene signature represents and capture all 10 HoCs. This highlights how comprehensively MammaPrint captures biology of early-stage breast cancer. 1. Genome instability and mutation 2. Replicative immortality 3. Evading growth suppressors 4. Sustaining proliferative signaling 5. Resisting cell death 6. Inducing angiogenesis 7. Invasion and metastasis 8. Tumor promoting inflammation 9. Cellular energetics 10. Immune desctruction Reference: Haan J.C., et al. MammaPrint and BluePrint comprehensively capture the cancer hallmarks in early-stage breast cancer patients. Genes Chromosomes Cancer 2022; 61(3): 148-160	Thank you for your comment. We have noted this information but it has not been added to the final scope which only provides an overview of technologies.

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Agendia N.V.	25	4	2.2.2	Turnaround time is not reflected correctly. Please change into: The MammaPrint results are typically reported within 4 to 10 days after the sample is received at the laboratory, with an average turnaround time of <5 days.	Thank you for your comment. This correction has been made.
Agendia N.V.	26	4	2.2.2	When describing the MammaPrint index, please consider adding information about the Ultralow cut-off. Suggestion to insert right before the sentence about turnaround time: Within the MammaPrint Low Risk category, a MammaPrint result of >0.355 indicates Ultralow risk (>99% breast cancer specific survival at 8 years, and 97% breast cancer specific survival at 20-years with 2-5 years of Tamoxifen).	Thank you for your comment. This addition has been made.
Agendia N.V.	27	7	Table 1	Purpose box for MammaPrint, please consider changing to: “Distant metastasis risk and Chemotherapy benefit”	Thank you for your comment. To maintain consistency of language across the descriptions of technologies we have not changed the phrasing.
Agendia N.V.	28	7	Table 1	Description box for all tests, please considering adding the distinction between cancer genes and normalization genes. MammaPrint: 70 cancer related genes, 465 normalization genes. Oncotype DX, 16 cancer related genes, 5 normalization genes. EndoPredict, 8 cancer related genes, 3 normalization genes, 1 control gene. Prosigna, 50 cancer related genes, 8 normalization genes, 6 positive controls, 8 negative controls.	Thank you for your comment. We have updated the table to report the total count of genes tested consistently across tests.
Agendia N.V.	29	7	Table 1	Testing location for MammaPrint, please change to “Test service (the Netherlands, USA) Local laboratory possible using the NGS version of MammaPrint”	Thank you for your comment. This correction has been made.
Agendia N.V.	30	7	Table 1	Test result box for MammaPrint, please change to: “(Ultra)Low risk, High risk Chemotherapy benefit”	Thank you for your comment. This addition has been made.
Agendia N.V.	31	7	Table 1	Assumptions box for MammaPrint, please change to: Assumes no adjuvant therapy, though also validated with 5-years of endocrine treatment	Thank you for your comment. As the final MammaPrint score provided in the test report assumes no adjuvant therapy, we have not changed the text in this cell.
Agendia N.V.	32	12	Table 2	Scope now only limits to the ASCO recommendations. To get a better picture of guidelines recommendations, it would be most appropriate if the ESMO 2019 and NCCN 2023 guidelines are also displayed within the scope. For example, MammaPrint has level 1 evidence by ESMO (2019) and NCCN (2023) for all ages, 0 to 3 lymph nodes.	Thank you for your comment. ESMO guidelines were included in the draft scope in addition to the NICE and ASCO guidance. We have removed the ASCO guidance and added recommendations from the 2021 St. Gallen Consensus.

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Agendia N.V.	33	22	Appendix A	Regarding Question 5: The population outlined in the draft scope is not appropriate, as it is currently limited to 1 to 3 lymph nodes. Limiting the scope to 1 to 3 lymph nodes, detracts from the availability of accurate and up to date diagnostic guidance for all UK breast cancer patients who are candidate for genomic testing. The long-term follow-up of the MINDACT trial published in 2021 classifies as significant new evidence for both the LN- and LN+ population, as these results will change the findings of the previous Diagnostic Guidance. Besides, since the publication of DG34, other significant new evidence for the LN- population, such as two TAILORx publication for the Oncotype DX product, have become available. These reasons, but particularly the availability of new MINDACT data, make that limitation in the scope to 1 to 3 lymph nodes inappropriate. The scope should also consider breast cancer patients with lymph node negative disease, as patient access to MammaPrint for both LN- and LN+ patients should be guaranteed if the assessment of the long-term follow-up data from MINDACT represent a clinically- and cost-effective use of NHS resources.	Thank you for your comment. The current guidance is focusing on the lymph node-positive population in response to a specific request from NHS England. Focusing on this narrower population will allow guidance for the NHS and patients to be produced more quickly. The population in the final scope includes only people with 1 to 3 positive lymph nodes. Any review of the tests in the lymph node-negative population would happen separately to the currently ongoing assessment. NICE will consider launching an evidence review for this population.
Agendia N.V.	34	22	Appendix A	Regarding Question 7a: MammaPrint has a decentralized version of the test available using NGS technology.	Thank you for your comment. This has been noted in the scope.
Agendia N.V.	35	22	Appendix A	[redacted]	Thank you for your comment. Because this comment was submitted as commercial in confidence in entirety, we cannot provide a response without potentially revealing information disclosed in the comment.

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Agendia N.V.	36	22	Appendix A	Regarding Question 7b: The low incidence of male breast cancer limits the ability to conduct clinical trial specifically for this population. Research has been performed to assess utilization of MammaPrint in male breast cancer. Results of a poster presentation at San Antonio Breast Cancer Symposium, have shown that MammaPrint index distributions between tumors from male and female breast cancer patients were similar, indicating that MammaPrint results are not influenced by biological sex. Although further studies are needed to assess clinical outcomes, initial findings did confirm MammaPrint's consistent performance. Albeit it not with the same evidence base as for female breast cancer, this indicates that MammaPrint could be used as part of chemotherapy decision-making in case of an uncertain chemotherapy recommendation in male breast cancer as well. Poster available on: https://agendia.com/wp-content/uploads/2020/12/Male-breast-cancer-poster_FINAL.pdf Crozier J.A. et al. Differential gene expression and clinical utility of MammaPrint and BluePrint in male breast cancer patients. SABCS 2020; #PS14-11	Thank you for your comment. In section 7, the following text has been added: "Some tests may not be validated for use in men with breast cancer. Clinical and manufacturer advice is that the tests can be used for men with breast cancer, but could perform differently." Sex is also included as a subgroup to identify any evidence on results and outcomes in men with breast cancer.
Agendia N.V.	37	23	Appendix A	Regarding Question 10: Yes, NPI and PREDICT are the most appropriate comparators for the assessment.	Thank you for your comment.
Agendia N.V.	38	23	Appendix A	Regarding Question 11: Disease free survival as a clinical outcome for chemotherapy decision making is less relevant, as chemotherapy is administered to prevent distant recurrence. The utility inputs for the CE-model that was submitted by Agendia for DAP71 uses the relevant outcome measure Distant Metastasis Free Interval.	Thank you for your comment. The outcome 'distant recurrence free interval' has been added to the scope.

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Agendia N.V.	39	23	Appendix A	Regarding Question 12: The equality legislation legally protects people from discrimination in the workplace and in wider society. All though the forthcoming comments is not necessarily addressing any form of direct discrimination in the draft scope, it does fit the subject. As written in Chapter 7 of the draft scope, it is known that there are racial disparities in breast cancer, resulting in less favourable tumor characteristics at diagnosis for women with a South Asian, Black African or Caribbean family background. For these patients, it is equally important to have access to accurate diagnostic information using GEP-tests to guide chemotherapy. The only available Level 1A test for LN- disease through NHS funding (Oncotype DX) has showed poor prognostic performance in African American early-stage breast cancer, and the test is thus not warranting access to accurate diagnostic information for this group (Albain 2021, JNCI & Hoskins 2021 JAMA Oncology). For the only other Level 1A evidence GEP-test (MammaPrint), that is currently not available for LN- disease, there is no evidence for this apparent limitation that Oncotype DX has. A recent ASCO abstract compared genomic results for African American patients for whom both the MammaPrint and Oncotype DX result were available. This analysis has shown that of tumors with TAILORx intermediate RS (11-25), the majority (62%) classified as MammaPrint high risk. The high percentage of MammaPrint high risk patients, within the RS intermediate group might explain the observed poor prognostic performance of Oncotype DX. The data suggest that the majority of African American patients are more likely to receive a MammaPrint high risk results, which may capture the diversity of pathways driving tumor metastasis that is not being captured by Oncotype DX. Result of this abstract available on: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.e12568 As the current scope is limited to LN+ disease only, the exclusion of an update for LN- disease will result in African American patients being excluded for access to accurate diagnostic information of a Level 1A evidence GEP-tests, if the updated MINDACT results represent a clinically- and cost-effective use of NHS resources.	Thank you for your comment. Ethnicity is included as a subgroup to identify any evidence on differing outcomes for people from different family backgrounds. The current guidance is focusing on the lymph node-positive population in response to a specific request from NHS England. Focusing on this narrower population will allow guidance for the NHS and patients to be produced more quickly. The population in the final scope includes only people with 1 to 3 positive lymph nodes. Any review of the tests in the lymph node-negative population would happen separately to the currently ongoing assessment. NICE will consider launching an evidence review for this population.

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Agendia N.V.	40	24	Appendix A	Regarding Question 15: The inclusion of an update guidance for lymph node negative disease is lacking in the draft scope. As previously communicated via e-mail and iterated in comments #14 and #20, the inclusion of an update of LN- disease to the draft scope is a key point and is important and relevant to ensure accurate and up to date diagnostic guidance for all UK breast cancer patients. In brief, MammaPrint's clinical validity was approved by NICE in DG34, however, did not pass the cost-effectiveness threshold at the time. Of note, currently with updated follow-up from the MINDACT study, the clinical validity of MammaPrint is further strengthened. Furthermore, this data has been included in the cost effectiveness model that has been submitted by Agendia as part of this DAP71 and shows to positively affect the cost-effectiveness of MammaPrint in a UK setting. Of consideration, to include MammaPrint LN- patients as part of the cost-effectiveness assessment within the scope of DAP71.	Thank you for your comment. The current guidance is focusing on the lymph node-positive population in response to a specific request from NHS England. Focusing on this narrower population will allow guidance for the NHS and patients to be produced more quickly. The population in the final scope includes only people with 1 to 3 positive lymph nodes. Any review of the tests in the lymph node-negative population would happen separately to the currently ongoing assessment. NICE will consider launching an evidence review for this population.
Myriad International GmbH	41	2	2.1 2 nd paragraph	We strongly agree with the wording that "the use of tumour profiling tests may improve the identification of people with lymph node-positive early breast cancer who may not benefit from having adjuvant chemotherapy because they have a low risk of disease recurrence" since this statement also applies to new drugs beyond chemotherapy such as abemaciclib to be used in non-low risk patients	Thank you for your comment.
Myriad International GmbH	42	2	2.1 2nd paragraph, last sentence	We support the statement that "people with breast cancer and clinicians may also benefit from improved confidence in the appropriateness of the treatment they are having or recommending" since this was a clinical challenge before tumour profiling tests were available resulting in a "clinical intermediate risk group" in which a treatment decision was inconclusive. Increased confidence by physicians and patients in treatment decision by gene expression tests was shown in decision impact studies (e.g. Fallowfield L, Matthews L, May S, Jenkins V, Bloomfield D. Enhancing decision-making about adjuvant chemotherapy in early breast cancer following EndoPredict testing. Psychooncology. 2018 27:1264-1269).	Thank you for your comment.
Myriad International GmbH	43	3	2.2.1 First paragraph on this page	We suggest adding the following sentence after "1 control gene": "This information is used to calculate the 12-gene molecular score (also referred to EP score in the literature)." It is important to mention both terms (12-gene molecular score and EP score) since both are used synonymously in the literature.	Thank you for your comment. This addition has been made.

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Myriad International GmbH	44	3	2.2.1 2nd paragraph	Please note that we are no longer sending tests to the USA since we have established partnerships with labs in the UK using our CE marked kits. Therefore, the 2., 3. and 4. sentence of this paragraph ("The test can be done in a local laboratory or the Myriad Genetics pathology laboratory in the USA. It takes approximately 3 days to receive the test results if a local pathology laboratory is used. The turnaround time is longer if samples are sent away for testing.") should be changed to "The test can be done in local laboratories in the UK. It takes approximately 3 to 5 days (Müller BM, et al The EndoPredict gene-expression assay in clinical practice – performance and impact on clinical decisions. PLoS One. 2013; 8:e68252; https://www.clinicallabs.com.au/endopredict) to receive the test result from the lab after the sample is received at the laboratory."	Thank you for your comment. The text has been updated to reflect your comments.
Myriad International GmbH	45	3	2.2.1 Last paragraph	In the second sentence after "EPclin score" the following should be added ", the final test result." From a regulatory perspective it is important to point out that the EPclin score is the final test result (and not the EP score). In addition, in the last sentence of this paragraph "These categories can also be used to estimate absolute chemotherapy benefit" should be replaced with "The EPclin score can also be used to estimate absolute chemotherapy benefit" since the test provides an individual EPclin-dependent estimated chemotherapy benefit rather than the average benefit of the entire risk group.	Thank you for your comment. This addition has been made.
Myriad International GmbH	46	7	Table 1, row 4	In the EndoPredict column only "local laboratory" should be mentioned and "test service (USA)" should be removed. We are no longer sending tests from UK to the USA since we have established partnerships with labs in the UK running the test locally using our CE marked kits.	Thank you for your comment. This correction has been made.
Myriad International GmbH	47	7	Table 1, row 10 (test result)	In the EndoPredict column "risk of distant recurrence" should be added as third information in the row "test results" in addition to "low risk, high risk" and "chemotherapy benefit" since the result report of the test provides not only a low or high-risk class and an individual EPclindependent estimated chemotherapy benefit but also an EPclin-dependent risk of distant recurrence within 10 years with 5 years of endocrine therapy only without chemotherapy	Thank you for your comment. This addition has been made.
Myriad International GmbH	48	16	4, first paragraph, second sentence	Please consider adding "age, tumour grade, and Ki67" in the sentence starting with "Features may include the stage of the disease, nodal status, ER or PR status, HER2 status". Age tumour grade, and Ki67 are indeed important clinical/pathologic prognostic factors and are also included in risk assessment tools like PREDICT.	Thank you for your comment. These factors are noted in the description of the PREDICT tool, and we have also expanded the text in the first paragraph of section 4.
Myriad International GmbH	49	18	Table 3, row "interventions"	We agree that the combined clinical-pathological-molecular EPclin score is used for this assessment since it is the final and validated result provided on the result report of the test. It also has the highest diagnostic accuracy compared to the individual components of the EPclin score alone. Moreover, from a regulatory perspective EPclin is the final test result.	Thank you for your comment.

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Myriad International GmbH	50	18	Table 3, row "time horizon"	We suggest using a time horizon of at least 10 years. In ER+, HER2- primary breast cancer more than half of the distant recurrences occur after 5 years (Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, Peto R, Pritchard KI, Bergh J, Dowsett M, Hayes DF; EBCTCG. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med. 2017;377:1836-1846) so that it is important to cover also the time period between 5 and 10 years (or even up to 15 years).	Thank you for your comment. The scope notes (see table 3, 'Time horizon') that the time horizon to be used for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Myriad International GmbH	51	19	6.2	We agree that the use of tumour profiling tests for LN-positive disease during the COVID-19 pandemic is considered as we think that these tests could actually reduce the pressure on clinics	Thank you for your comment.
Myriad International GmbH	52	20	8.3	We fully agree with the statement that "training on interpretation of test results would be required to support safe adoption". Proper communication of risks, harms, and benefits to patients by physicians may reduce anxiety and increase confidence in treatment (Fallowfield L, Matthews L, May S, Jenkins V, Bloomfield D. Enhancing decision-making about adjuvant chemotherapy in early breast cancer following EndoPredict testing. Psychooncology. 2018 27:1264-1269). Also a professional selection of patients for tumour profiling tests by trained physicians can increase the impact of testing on treatment decisions (Dinh P, Graham JD, Elder EN, Kabir M, Doan TB, French J, Meybodi F, Hui R, Wilcken NR, Harnett PR, Hsu J, Stuart KE, Wang T, Ahern V, Brennan M, Fox SB, Dear RF, Lim E, White M, Mann GB, Pathmanathan N. Impact of the EndoPredict genomic assay on treatment decisions for oestrogen receptor-positive early breast cancer patients: benefits of physician selective testing. Breast Cancer Res Treat. 2022 191:501- 511).	Thank you for your comment.
Myriad International GmbH	53	27	Appendix C	Although "Goldhirsch et al 2013" (St Gallen expert consensus) is listed in the reference list, it is not referenced anywhere in the document. We would recommend taking this reference out of the list if it is not referenced in the document.	Thank you for your comment. This reference has been removed. The 2021 St Gallen recommendations have been added to section 3.2.5.1.
Association of Breast Surgery	54	8	3.1	• present in the lymph nodes in the armpit. Comment: this statement is too general to be correct, N2 makes it locally advanced	Thank you for your comment. We have updated the description to: "Early breast cancer can be locally advanced; this means that the cancer has spread to the surrounding area such as the nearby lymph nodes, skin or chest muscle, but not to distant parts of the body." Source: Cancer Research UK
Association of Breast Surgery	55	Appendix A		Care Pathway (responses to questions) 2. Is the care pathway as outlined in the scope accurate? Yes 3. Are there any other clinical guidelines for the management of early breast cancer that NICE should be aware of? No 4. Does the availability of abemaciclib affect adjuvant chemotherapy use for people with LN+ early breast cancer? Not suree	Thank you for your comment.

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Association of Breast Surgery 56		Appendix A		**Population** 5 Is the population outlined in the draft scope appropriate? yes a. Is limiting to people with cancer with involvement of 1 to 3 lymph nodes appropriate? It would be worth adding potential consideration of genomic profiling to patients with 4 or more positive nodes (in light of an ongoing trial, OPTIMA) and to aid decision for those wishing to avoid/refuse chemotherapy. This also becomes relevant as this group would be recommended abemaciclib. There needs to be a caution in the absence of evidence/validation in this group of patients but a cautious/considered approach in consultation with the oncologist would not be unreasonable until OPTIMA trial is reported. 6 Are the listed subgroups appropriate? Are there any other subgroups that should be included? Yes a. The presence of which comorbidities are most likely to influence decisions on whether to offer adjuvant chemotherapy? Cardiac, pulmonary, neurological disorders such as MS,	Thank you for your comment. The population in the final scope has been restricted to those with 1 to 3 positive lymph nodes. This is because clinicians advised that the currently available evidence does not support decision-making about chemotherapy based on tumour profiling test results in the 4+ positive node population. Clinical advice was also that abemaciclib would be offered after any adjuvant chemotherapy. Thank you for your comment about comorbidities. This has been clarified in section 3.3 and in table 2.
Association of Breast Surgery 57		Appendix A		**Interventions** 7. Are the descriptions of the technologies accurate? 1. Are there any other tools or methods that can be used alongside the test outputs to further inform decisions about treatment? yes 2. Can the tests be used for men with breast cancer? Yes 8. Are there any other technologies that should be included in this assessment? 9 The IHC4 and IHC4+C tests have not been included in this draft scope. This is because clinical experts have advised that uncertainty about the analytical validity of the test remains (for example about the reproducibility of test results as described in NICE diagnostics guidance 34). Any comments on this decision would be welcomed during the scope consultation. No comments	Thank you for your comment. In section 7, the following text has been added: “Some tests may not be validated for use in men with breast cancer. Clinical and manufacturer advice is that the tests can be used for men with breast cancer, but could perform differently.” Sex is also included as a subgroup to identify any evidence on outcomes in men with breast cancer.
Association of Breast Surgery 58		Appendix A		**Comparator** 10 Is this the most appropriate comparator for the assessment? Yes	Thank you for your comment.

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Association of Breast Surgery	59	Appendix A		13 Are there any potential barriers to implementation of tumour profiling tests in NHS clinical practice? For example, testing capacity, time for testing, interpretation of intermediate results. There will be undoubtedly an element of 'learning curve' especially with the intermediate test results that will require discussions and decision be made based on patient preference and likely risk-benefit profile for that patient. The test is being used routinely in some centres so there is expertise and experience available to help with dissemination of information and education.	Thank you for your comment. The issue of intermediate test results has been expanded on in section 8.3.
SCM applicant	60	22	Q5a)	1-3 is probably appropriate as it appears to be the criteria used for major studies in the field – e.g OncotypeDx Kalinsky 2021 NEJM. The review team should look out for any studies that include patients with more nodes and if identified this could be a separate subgroup.	Thank you for your comment. The population in the final scope has been restricted to those with 1 to 3 positive lymph nodes. This is because clinicians advised that the currently available evidence does not support decision-making about chemotherapy based on tumour profiling test results in the 4+ positive node population.
SCM applicant	61	19	7 Equality Issues	Tests in the scope are unlikely to be validated in men, however a systematic review of oncotypeDx shows that male breast cancer has a similar range of scores to female breast cancer – Davey 2022 The Breast. – I am wondering if testing could be opened up to Male Breast Cancer patients for research purposes and data collected though the SACT – similar to what is done with Cancer Drugs Fund Drugs.	Thank you for your comment. Sex has been included as a subgroup to identify any evidence on results and outcomes in men with breast cancer. Clinical and manufacturer advice is that the tests can be used for men with breast cancer, but could perform differently.

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Exact Sciences	62	22	Appendix A Care pathway Q3	In addition to ESMO and ASCO guidelines mentioning in the scoping document, the St Gallen international consensus guidelines and the National Comprehensive Cancer Network (NCCN) guidelines also include recommendations for gene expression profiling testing. Recent assessments of gene expression profiling testing has also been carried out by health authorities in different countries. The Oncotype DX test is recognized by the St Gallen Guidelines to predict adjuvant chemotherapy treatment benefit for N0 and postmenopausal N1 (1-3 positive nodes) patients. The St Gallen panel recommended against routine use of adjuvant chemotherapy in postmenopausal women with stage I and II (including 1-3 positive lymph nodes) breast cancers that had a Recurrence Score® result <25. The Panel also recognized that for some premenopausal patients with N1 disease there is also utility for the Oncotype DX test to help aid treatment decision making. As acknowledged in the NCCN guidelines, the Oncotype DX test is the only test to predict adjuvant chemotherapy benefit and to be recognized as "preferred" for N0 and post-menopausal N1 (1-3 positive nodes) patients. The Health Information and Quality Authority in Ireland published a rapid HTA in February 2023 of gene expression profiling tests for guiding the use of adjuvant chemotherapy in early-stage invasive breast cancer. The report acknowledged the predictive ability for the Oncotype DX test for both the lymph node negative and positive patient groups and concluded that, of the tests included in the review, "the available evidence supports the continued use of Oncotype DX among LN- patients and the evidence most strongly supports the continued use of Oncotype DX in postmenopausal women, based on available five-year follow-up data among LN+ patients". In July 2021, the TLV in Sweden published an assessment of the Oncotype DX test. The TLV's analysis showed that use of the Oncotype DX test was expected to lead to an improvement in patient outcomes alongside overall costs savings, for both lymph node-negative and lymph node-positive patients groups.	Thank you for your comment. A paragraph on the 2021 St Gallen recommendations has been added to section 3.2.5.1.

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Exact Sciences 63		22	Appendix A Population Q5.a.	Exact Sciences welcomes the review of gene expression profiling (GEP) testing for people with lymph node-positive (N1) breast cancer, as there is an urgent need to address the considerable over-treatment with adjuvant chemotherapy, as underscored by recent UK prospective multi-centre clinical study data (Holt et al. 2022). However, there is also an equally important need to review the use of GEP testing for patients with lymph node-negative disease. The NICE Diagnostics Guidance #34 published in 2018 was due for review in 2021. The assessment that was carried out for DG34 included both lymph node-negative and node-positive patient groups. Data for the Oncotype DX test relating to the node-negative patient group have also evolved since the publication of DG34 and the current recommendation for testing people considered to be at 'intermediate risk' based on NPI or Predict omits some people for whom the Oncotype DX test would offer considerable value, as observed in other healthcare systems across Europe and elsewhere around the world. For example, today women 70 years of age with LN-negative breast cancer with a Grade 2 tumour over 4cm (up to 42mm) can be classified as 'low risk' according to the Predict tool* and therefore denied access to GEP testing to help inform their decision whether or not to opt for adjuvant chemotherapy treatment. (*Predict tool estimate of benefit from chemotherapy of 2.9% based on the following criteria: 75 years of age at diagnosis, post-menopausal, Ki-67 unknown, screen detection, 3rd generation chemotherapy.) Many people with this type of breast cancer are likely not to be recommended adjuvant chemotherapy due to being classified as 'low risk'. However, evidence shows that a substantial proportion of these patients, when tested with the Oncotype DX test, have a high Recurrence Score result. This means that adding chemotherapy treatment would significantly reduce the risk for these people of developing metastatic cancer, as supported by additional analysis of key validation studies which has been conducted since DG34 publication. Many people every year in England, who's assessed clinical risk falls just below the current DG34 'intermediate risk' definition according to the Predict or NPI tools, may progress to advanced stage cancer as a result of not having chemotherapy, which could be prevented by having access to the Oncotype DX test. In line with the principle of 'consolidation' as part of NICE's proportionate approach to technology appraisals, Exact Sciences would therefore recommend including both lymph node-negative and node-positive patient groups in the planned review of GEP testing to ensure that the recommendation is up to date and supports optimal outcomes for people with breast cancer. Conducting a separate review at a later time of GEP testing for people with lymph node-negative breast cancer would be inefficient and delaying optimal care for breast cancer patients.	Thank you for your comment. The current guidance is focusing on the lymph node-positive population in response to a specific request from NHS England. Focusing on this narrower population will allow guidance for the NHS and patients to be produced more quickly. The process for updating NICE guidance has changed and there is no longer a set time period for review (see section 8 of the CHTE programme manual). If you believe there are changes to the evidence base or clinical practice that could change the recommendations in existing guidance, please send this information to nice@nice.org.uk (stating the guidance topic it relates to) for review by the team responsible for allocating surveillance reviews. As an initial step, NICE will assess the likely effect of the new evidence on the recommendations. NICE would then consider if a surveillance review is needed to make a decision about whether changes to existing guidance need to be made (as described in sections 8.3 and 8.4 of the programme manual). When this could be done would depend on when it could be scheduled into the work programme. For this type of communication, we would ask that you make clear what changes have occurred since the guidance was published, and how these are likely to change previously issued recommendations (for example, changes to cost effectiveness estimates from models used in the original assessment).

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Exact Sciences 64		22	Appendix A Population Q6	The proposed clinical risk subgroups (low, intermediate and high-risk groups) based on the Predict and NPI risk assessment tools are suboptimal for a number of reasons. The three risk groups are too broad and do not allow sufficient granularity in the health economic analysis. Patients falling just outside of the 'intermediate risk' group, for whom GEP testing may be highly beneficial and also cost-effective, are combined with patients at the extremes of clinical risk (very high or very low risk), making it infeasible to demonstrate cost-effectiveness. Furthermore, the clinical risk subgroups/threshold based on the Predict and NPI risk assessment tools are arguably somewhat arbitrary and/or are limited in clinical utility for determining who will or will not benefit from adjuvant chemotherapy treatment. Therefore, more caution should be given to ensuring that patients are not overlooked who could derive value from GEP testing. Simpler and more universal clinical pathological criteria should be used to define clinical risk subgroups for the assessment, based on supporting clinical evidence. Clinical risk subgroups should be defined based on clinical evidence and clinical expert input indicating expected clinical utility of GEP testing, instead of standard cut-offs for the risk assessment tools. Clinical utility is indicated, in part, by discordance between chemotherapy treatment rates based on current practice and test result groups e.g., patient group with high rates of chemo-endocrine therapy (without GEP testing) and high proportion with low GEP score (with GEP testing), should not be grouped in a 'high risk' group, but rather should be included in a 'treatment uncertain' group, making it more feasible for cost-effectiveness to be demonstrated. Other reasons for not defining risk subgroups based on standard thresholds for risk assessment tools: Inter-hospital variation in the use of tools (some hospitals use Predict, some use NPI, and others use other criteria) Lack of overlap between prognostic groups according to these tools means that the same patients are classified into different risk groups by the tools i.e., Predict <3%, 3-5% and >5% do not correlate with NPI ≤3.4, >3.4-5.4, >5.4. A NPI score of 3.4 is equivalent to as low as 1.2% according to Predict (based on an illustrative person who is 75 years of age at diagnosis, 1 positive lymph node, unknown ki-67, screen detection, 20mm grade 1 tumour).	Thank you for your comment. These proposed subgroups (which are not exhaustive, see below) were based on feedback from clinical experts and relate to currently used guides for decision making; for example, as described on page 16 of the draft scope, the Cambridge Breast Unit's use of the PREDICT tool outputs. Considering the recommendations for treatment stated based on the PREDICT score, the intermediate grouping would appear to match the description of a 'treatment uncertain group' (as described in the comment) as opposed to people with scores either side of this range for whom recommendations for chemotherapy use are stated (recommended or not recommended). The full subgroup description referred to in this comment is "People predicted to be in low, intermediate or high risk groups using a risk assessment tool (such as PREDICT or NPI), or using clinical and pathological features" (underlining added). The subgroups are therefore not restricted to those defined by the PREDICT or NPI tools and could include alternative definitions of low, intermediate and high risk groups if these can be defined and suitable data are available. We note that no such definitions of risk groupings or definitions of 'treatment uncertain' groups are proposed in this comment. The full population to be considered (as stated in table 3 of the draft scope) does not restrict by risk group, therefore recommendations for use of the tests in populations broader than defined by low, intermediate or high risk groups will be considered by committee.

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Exact Sciences	65	22	Appendix A Interventions Q7.b.	Retrospective analysis shows that Recurrence Score® (RS) result distribution in early HR+HER2-male breast cancer patients is similar to that of female breast cancer patients. There are currently a number of studies that analyse clinical outcomes in male breast cancer patients, these show that clinical endpoints for male breast cancer patients are correlated to their RS results. Retrospective studies on registries and patient cohorts showed very similar distribution of RS results between males and females with early HR+,HER2- breast cancer. Overall, treatment decisions show that in male breast cancer patients with higher RS results, an increase in chemotherapy prescription was observed. Overall, there is evidence of utilisation of the 21-gene expression assay in male early HR+, HER2- breast cancer patients. Results should be interpreted with the knowledge from these studies that risk thresholds may be different between male and female breast cancer patients.	Thank you for your comment. In section 7, the following text has been added: “Some tests may not be validated for use in men with breast cancer. Clinical and manufacturer advice is that the tests can be used for men with breast cancer, but could perform differently.” Sex is also included as a subgroup to identify any evidence on results and outcomes in men with breast cancer.
Exact Sciences	66	23	Appendix A Comparator Q10	Exact Sciences agrees that the comparator for this assessment should be decision making for adjuvant chemotherapy prescribing without use of the technologies being assessed. However, the proposed clinical risk subgroups (low, intermediate and high-risk groups) based on the Predict and NPI risk assessment tools are suboptimal for a number of reasons.	Thank you for your comment. Please see the response to comment 58.
Exact Sciences	67	23	Appendix A Outcomes and costs Q11	We suggest also including distant recurrence free interval (DRFI)	Thank you for your comment. This addition has been made
Royal College of Pathologists	68	2		A hyphen has been used after the words ER, PR and HER2 several times in the dopcument, for example "ER-, PR- positive". I would suggest to drop the hyphen as there is a potential risk of it being misread as a negative symbol.	Thank you for your comment. We have removed the hyphen in these contexts to avoid confusion with the minus symbol.
Royal College of Pathologists	69	24	Q 13.	I think specific consideration must be made in terms of testing process and impact it has on laboratories (local v send away). Currently labs in the UK are under significant pressures due to staff shortages.	Thank you for your comment. This has been noted in section 8.2.
University Hospitals Coventry and Warwickshire NHS Trust	70	16	4.1	There is no standardised methodology for assessing Ki-67 expression; testing for Ki-67 is not performed in every breast cancer unit.	Thank you for your comment. The following sentence has been added to section 3.2.2. “In some centres Ki67 is also tested for, although the methodology for this is not standardised.”

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University Hospitals Coventry and Warwickshire NHS Trust	71	19	6.2	Several centres use the Oncotype DX assay in post-menopausal women with 1-3 lymph nodes involved following publication of the interim results from the RxPONDER trial, which shows no benefit from additional chemotherapy to endocrine therapy where the Recurrence Score is 25 or less. There is no difference in outcomes at 5 years from omission of chemotherapy in this group of people.	Thank you for your comment. The use of Oncotype following the RxPONDER trial has been noted in section 2.2.3, and current use of the tests in section 6.2.
University Hospitals Coventry and Warwickshire NHS Trust	72	22	Q1	There has been no discussion of the RxPONDER data, the interim results of which were published in the New England Journal of Medicine. This data needs to be taken in to consideration as part of this consultation. The Prosigna Test is the subject of a Clinical Trial which is currently in the recruitment phase.	Thank you for your comment. We are aware of the RxPONDER and OPTIMA trials. Relevant evidence will be identified by an external assessment group, based on the scope for the assessment, and will be presented it in their report which will be used to support committee decision making. Please see section 5.6 of the CHTE Programme Manual for more information.
University Hospitals Coventry and Warwickshire NHS Trust	73	22	Q3	The St Gallen breast cancer consensus statement should be considered. The St Gallen meeting has recently been held and an update from the meeting is expected immenently	Thank you for your comment. A section on the 2021 St Gallen recommendations has been added to section 3.2.5.1.
University Hospitals Coventry and Warwickshire NHS Trust	74	22	Q4	No, abemaciclib in the adjuvant setting as extended treatment has no bearing on decision making pertaining to adjuvant chemotherapy	Thank you for your comment.
University Hospitals Coventry and Warwickshire NHS Trust	75	22	Q5	Yes. The OPTIMA trial, currently still in recruitment, is assessing the utility of the Prosigna Assay in breast cancer with involvement of 4-9 lymph nodes following surgery. There is no data to support the use of these assays in people with involvement of 4 or more lymph nodes currently,	Thank you for your comment.
University Hospitals Coventry and Warwickshire NHS Trust	76	22	Q6	Yes; the presence of co-morbidities influence the decision making process regarding the benefit of chemotherapy. This includes an assessment of the WHO Performance Status. In general terms adjuvant chemotherapy would not be considered in patients with a Performance Status on 2-4, or those with co-morbidities that would increase the potential risk of morbidity or mortality associated with adjuvant chemotherapy	Thank you for your comment. The text on comorbidities has been expanded in section 3.3.

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University Hospitals Coventry and Warwickshire NHS Trust	77	22	Q7	Male breast cancer is highly uncommon therefore it is challenging to conduct clinical trials of breast cancer treatment in men. In general terms, there appears to be no reason why the tools can not be utilised in men with breast cancer.	Thank you for your comment. In section 7, the following text has been added: "Some tests may not be validated for use in men with breast cancer. Clinical and manufacturer advice is that the tests can be used for men with breast cancer, but could perform differently." Sex is also included as a subgroup to identify any evidence on results and outcomes in men with breast cancer.
University Hospitals Coventry and Warwickshire NHS Trust	78	23	Q9	We agree with this assessment	Thank you for your comment.
University Hospitals Coventry and Warwickshire NHS Trust	79	23	Q10	The NHS Predict website has never been tested in the context of a randomised clinical trial. It is a population based tool which relies on clinico-pathological data to give an estimate of the benefit of chemotherapy and endocrine therapy. The genomic assays provide more "personalised" information as they assess the genomic constitution of the cancer cells. Therefore the PREDICT website and tool is not a direct comparator however, it is the tool most utilised to assist with discussion with patients regarding the benefits of adjuvant chemotherapy above and beyond endocrine therapy.	Thank you for your comment. The comparator for NICE assessments is typically established practice in the NHS (see the CHTE programme manual). As noted, the PREDICT tool is the most commonly used to help make chemotherapy decisions in discussion with people with early breast cancer, so would be covered by the comparator description: "Current decision making, which may include any tool, or clinical and pathological features, used to assess risk"
University Hospitals Coventry and Warwickshire NHS Trust	80	23	Q11	Treatment of adverse events should include any hospital admissions which have occurred as a direct result of chemotherapy related toxicity. Costs of treating breast cancer also needs to include CNS time dedicated to support through chemotherapy and beyond. Costs of treating breast cancer should also include the economic impact of these patients taking 6-12 months sick pay from work due to receiving chemotherapy. Cost of the tests should also include any administrative time involved in the pathology lab in processing and packaging samples.	Thank you for your comment. The reference case perspective on costs considered in NICE assessments is that of the NHS and personal social services. For more information see section 4 of the CHTE programme manual.
University Hospitals Coventry and Warwickshire NHS Trust	81	24	Q13	No	Thank you for your comment.

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University Hospitals Coventry and Warwickshire NHS Trust	82	24	Q15	We are not particularly good at recognising late side effects of chemotherapy (e.g. cardiac toxicity later in life), we treat many younger patients and should not be giving adjuvant chemotherapy where not appropriate due to impact later in life, this should be considered in addition to acute toxicities.	Thank you for your comment. The following text has been added to section 3.3: "Younger people may also have more reason to want to avoid chemotherapy because there is a risk of long-term side effects such as cardiac toxicity."

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Veracyte Inc. 83		4-7	2.2.3 & 2.2.4	**Concern about inclusion of non-CE marked tests and shipping of patient data and human tissue outside UK to non-UKGDPR compliant territories (e.g., US)** An increasing number of European HTA agencies and the Australian HTA agency have assessed Gene Expression Profile tests in early-stage breast cancer. Due to increasing focus on appropriate regulatory registration for IVD diagnostic tests as well as concerns about shipment of human tissue and patient data to non-GDPR compliant territories (e.g. US) after European Schrems II ruling in 2020 which at the time included the UK, the Swedish TLV/MTP Council who undertakes HTA assessment guidance nationally and the Australian MSAC authority have raised concerns about certain GEP tests and excluded certain tests from participation in the reimbursement assessment (Australia 2021) or added legal caveats to a recommendation (Sweden 2022). In Australia in 2021 the MSAC HTA authority opened for assessment of reimbursement for available tests but only if these were registered and could be processed locally in Australia. This meant that tests not processed in Australia as a local service were excluded from the reimbursement application until they obtained regulatory approval in Australia and could guarantee processing and handling in Australia. Prosigna, which is registered and can be processed in Australia was allowed to participate in the reimbursement process along with tests that could demonstrate the same. In Sweden in 2021/2022 the TLV/MTP Council assessed the use of GEP test in early-stage breast cancer and recommended Prosigna as a cost-effective test and since it is CE marked and all testing and processing is handled locally within the health care system in Sweden in full compliance with processing of patient data and handling of human tissue it received a recommendation without legal caveats. Other GEP tests were also recommended but with legal caveats. NICE has already in 2018 in section 3.12 of DG34 stated the following: “The assay (Oncotype DX) does not have a CE mark because it is provided as a service by Genomic Health (now Exact Sciences) in an accredited laboratory in the US”. We feel that NICE should consider how tests involved in this scoping process, that do not hold a CE mark could participate in this DAP assessment? Further clarification is requested on whether processing of clinical samples from patients in the UK in a CLIA certified laboratory in the USA (that does not hold UKAS accreditation) is compliant with the MHRAs’ regulations on IVD medical devices? Also questioned here is whether the requirement for legacy devices to be CE marked has been fulfilled by all stakeholder companies who are participating? Prosigna is a fully CE marked test and FDA 510K cleared and is registered with MHRA in the UK. We are concerned from a patient perspective if NICE open the assessment for tests that do not meet these requirements that are fundamental for patient safety and handling of human tissue especially when alternative test options are available that are more affordable and have been assessed as cost effective by NICE, can be processed locally within NHS with a faster turnaround time and are strongly backed by European medical guidelines (ESMO). NICE should note that the legal foundation for shipping of personal data and human tissue to third party countries has changed within the European Union (at that time including the UK) Schrems II ruling in July 2020. The ruling invalidated the EU-US privacy shield so it can no longer be relied on as a method for legitimizing third country data transfers We ask that it is clearly shown in the overview Table 1 if the test is CE-marked. If NICE intends to draw on American guidelines (ASCO) and not just the more relevant European guidelines (ESMO) then also add FDA 510k clearance status for each test (and not just a sample collection kit). Further we ask that it is made part of the scoping process to investigate how each test complies with UKGDPR requirements and biobank legislation, so it is clear for patients and healthcare staff before they use a certain test how patient data and human tissue is safely handled within the NHS or in the shipping process of human tissue and patient data to third countries.	Thank you for your comment. All tests included in the assessment currently hold a CE mark and are registered with the MHRA. The technology descriptions in section 2 refer to the regulatory status of each technology. Current guidance referred to in section 3.2.5 is for reference only. NICE is currently investigating the full regulatory requirements for the tests included in the assessment, including those relating to GDPR. As noted in the CHTE programme manual section 2.2.5, a technology is only evaluated if it has or is expected to have regulatory approval (or appropriate regulatory signal) by the planned draft or final guidance publication date. See also 5.3.16: NICE will not publish final guidance on a technology until UK regulatory approval has been granted and the technology's price is known or can be determined.

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Veracyte Inc.	84		Provisional Stakeholder List Research Groups	Veracyte believe that all stakeholders should be represented equally within the consultation process of this Diagnostic Assessment Programme scoping process. Undue bias and conflicts of interest need to be avoided but it is also critical that a fully informed decision can be made in relation to the outcome of the project. We would request that NICE ensures a fair representation of clinical experts in the stakeholder panel chosen for this scoping process. This will ensure that experts who have been involved with only one type of gene expression test are represented equally across the review panel.	Thank you for your comment. You can find information on how specialist committee members are selected for Diagnostics assessments in section 1 of the CHTE programme manual and in the relevant policies located here. Applicants must disclose any potential conflicts of interest which are then judged by the appointment panel as to whether these could prevent the applicant from being selected.
Veracyte Inc.	85	4-5	2.2.3	DG34 refutes any predictive claim for these technologies. (Section 5.5 The EAG explained that the only evidence available to show a relative treatment effect for chemotherapy across different risk groups was for Oncotype DX, and the evidence included in the diagnostics assessment report was weak because it was at high risk of bias from potential confounding). Within DAP71, it's stated that (sic.) designed to quantify the 9-year risk of distant recurrence and predict the likelihood of chemotherapy benefit. The primary endpoint of the RxPONDER study was the prediction of chemotherapy benefit, and this endpoint was not met. Please can you provide the evidence for the inclusion of this claim. We would ask that NICE carefully consider not to include the RxPONDER study as part of this review as the study failed its primary endpoint and the follow-up for post-menopausal women is not mature or reported.	Thank you for your comment. Section 2 of the scope provides a description of the technologies as defined by the manufacturers. The evidence to support these claims will be searched for by the external assessment group (EAG) as part of their review of the literature. This review will include a critique of identified studies. The final report will also be made available for stakeholders to comment on, and these comments will be considered by committee when making their recommendations.
Veracyte Inc.	86		General	The OPTIMA trial is specifically designed to answer the question of utility of genomic testing in higher risk populations, including Node positive, and has been designed and is conducted in the UK. Previous studies have not answered the question. Any alteration to the guidance may impact recruitment into this NIHR study, and the academic group responsible for the study should be consulted as part of this process.	Thank you for your comment. The current guidance is focusing on the lymph node-positive population in response to a specific request from NHS England. The committee can consider the potential risks for the OPTIMA trial when making recommendations on the technologies. We would encourage the academic group responsible for the OPTIMA trial to register as stakeholder to ensure they are kept up to date about opportunities to comment on the assessment report and draft guidance.
Veracyte Inc.	87	5-6	2.2.4	Prosigna is an FDA 510k cleared test/assay. This is not noted in the document, and provides a differential, and higher level of regulatory clearance than other technologies in the assessment.	Thank you for your comment. Regulatory status descriptions in the scope relate to use of the tests in the UK.

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Veracyte Inc.	88	5-6	2.2.4	The proliferation score is determined by evaluating multiple genes associated with the proliferation pathway. Prosigna does not routinely report an individual proliferation score, though it is an important constituent part of the overall ROR score. Please amend.	Thank you for your comment. We have updated the text as follows: “Prosigna classifies the risk of distant recurrence within 10 years, assuming 5 years of endocrine therapy, based on the PAM50 gene signature, breast cancer subtype, tumour size, nodal status and proliferation score (the proliferation score is determined by evaluating multiple genes associated with the proliferation pathway). The test gives an overall risk of recurrence score between 0 and 100.”
Veracyte Inc.	89	7	Table 1	As other technologies are not held to the same reproducibility and regulatory standards, they are able to claim efficacy in the pre-menopausal population. Prosigna has a broad utility in this population with a bibliography that supports its use, and in due course, a resubmission to the FDA may take place to amend the label. We assert that the premenopausal question remains unanswered for all the available technologies and is only answerable by further prospective studies which are still underway or yet to be designed. Prosigna also provides a Risk of Recurrence score as part of the test result and is also valid in HER2+ patients. We would ask NICE to consider the points we have made above.	Thank you for your comment. Section 2 of the scope provides a description of the technologies as defined by the manufacturers, including the populations the companies state they are intended for use in. Menopausal status is included as a subgroup (see table 2) and any evidence relating to people in these groups will be evaluated by the EAG. The extent of evidence identified for premenopausal women will be considered by the NICE diagnostics advisory committee when making its recommendations. We have amended Table 1 to include that Prosigna provides a score representing the probability of distant recurrence and that is can be used for people with HER2 positive disease (although please note that the population is limited to people with HER2 negative cancer).

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Veracyte Inc.	90	12	Table 2	Why is ASCO preferentially referenced over ESMO guidelines in terms of specific recommendations? [redacted] ESMO explicitly recommends that individual treatment decisions can be directed using intrinsic subtyping, which only Prosigna can provide. Moreover, the ESMO guidelines do not distinguish the utility of intrinsic subtype information based on lymph node status. We are in Europe and follow European guidelines. It is not fair to preferentially include discordant international guidelines which favour one technology. We would welcome the opportunity to discuss the evidence behind this discordance in the guidelines but would also like to see evidence that UK clinicians routinely utilise ASCO guidelines. Prosigna has a different label outside of the US and therefore these guidelines are explicitly not relevant to the UK and the scope of this review. We ask that NICE updates Table 2 to follow the more relevant European ESMO guidelines. In these guidelines Prosigna as a 2nd generation test is recommended in both node negative and node positive patients consistent with the regulatory label in Europe for Prosigna. For Prosigna the text included in Table 2 should therefore be recommended for "post-menopausal, 1-4+ positive nodes".	Thank you for your comment. The ESMO recommendations were included in the draft scope. We have also included the 2021 St. Gallen Consensus recommendations as another set of European guidelines.
Veracyte Inc.	91	13-14	3.2.5.2	"Explain to women that ovarian function suppression may be most beneficial for those women who are at sufficient risk of disease recurrence to have been offered chemotherapy " The key pieces of published evidence for the use of genomic testing in this population have not controlled for this confounding factor. Only the ongoing OPTIMA study does and can therefore definitively answer the question in this population.	Thank you for your comment.
Veracyte Inc.	92	14	3.2.5.5	Will the recommendation for Abemaciclib be extended during this DAP? OPTIMA include this molecule as a stratification factor.	Thank you for your comment. The NICE guidance for abemaciclib in HR+, HER2-, LN+ early breast cancer will not be changed by the outcome of this assessment.

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Veracyte Inc.	93	17	Table 3	Why is the scope of the review limited to only 1-3 positive nodes? Prosigna is validated in 4+. Intermediate outcome measures: please explain why ability to predict benefit from chemotherapy is included when DG34 (5.20) defines that no assay can predict chemotherapy benefit. Clinical outcomes: Please ensure these are validated by a representative body (e.g., UKBCG)	Thank you for your comment. The population in the final scope is people with 1 to 3 positive lymph nodes. This is because clinicians advised that the currently available evidence does not support decision-making about chemotherapy based on tumour profiling test results in the 4+ positive node population. Predicting benefit from chemotherapy is a core claim of many of the included tests. Statements in DG34 relate to the committee discussions of the evidence available at the time, and the evidence base may have changed since that assessment. Section 5.20 of diagnostic guidance 34 describes the committee's conclusion that Oncotype DX may be able to predict relative treatment effects for chemotherapy but that this is very uncertain. Clinical outcomes included in the scope were included as part of this consultation (question 11 in the draft scope) and stakeholders have been invited to comment.
Veracyte Inc.	94	19	6.2	"Veracyte would request that NICE includes clinical experts with experience in all the test areas under review as part of this scoping process.	Thank you for your comment. You can find information on how specialist committee members are selected for Diagnostics assessments in section 1 of the CHTE programme manual and in the relevant policies located here.
Veracyte Inc.	95	20	8.2	Please see earlier comments in relation to location of testing, especially overseas	Thank you for your comment. Please see response to comment 77.

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Veracyte Inc.	96	20	8.3	Clinical experts noted that intermediate risk results can be problematic as they introduce uncertainty about optimal treatment planning. This is the subjective view of unspecified clinical experts. Risk is a continuous variable, and many clinicians highly value the presence of an intermediate risk group, and their voice should be represented here. In fact, all the assays report a score that falls in a continuum risk range (e.g., Oncotype from 0-100, Endopredict from 1.1 to 6.2) and then assign this score to risk groups. Representations that the risk of recurrence is not a continuous function are more likely to lead to clinical management errors, particularly when applying a precise cut-point for predicting chemotherapy benefit.	Thank you for your comment. This section has been updated to the following: "Some clinical experts noted that intermediate risk results could be problematic as they could introduce uncertainty about optimal treatment planning, although intermediate risk groups could also indicate that the clinical decision should be particularly carefully considered."
Veracyte Inc.	97	General		DG34 stipulated that data would be collected as part of the initial approval of these technologies (5.29, 5.8). It also believed that it is necessary that data is collected as part of a national database, rather than by individual companies, to increase transparency, enable the data to be linked to clinical outcomes and ensure evidence is available that can be considered in future updates of this guidance. It therefore decided that its recommendations for EndoPredict (EPclin), Oncotype DX and Prosigna are conditional on data collection arrangements agreed with NICE being put in place. It is anticipated that arrangements will be made to collect timely and complete record-level test data, which can be submitted to the National Cancer Registration and Analysis Service, with the aim of linking test data to chemotherapy use, recurrence and survival outcomes. We would like to request an update on the status of data collection outlined in DG-34 since a review of DG-34 conducted in 2021 led to no further developments on how this data might be obtained and since it was central to the original DG-34 recommendation. In the group with LN-negative disease and a NPI of more than 3.4, the committee noted that in the base-case analyses Oncotype DX was dominated by the comparator. The committee concluded that Oncotype DX, when provided at the test cost stated in the access proposal, was likely to be cost effective in the group with LN-negative disease and a NPI of more than 3.4, but evidence on clinical outcomes will be important to confirm this.	Thank you for your comment. The outcome of this assessment will not update the recommendations in DG34 on the use of tumour profiling tests to help make chemotherapy decisions with people with LN negative disease. Data collection from DG34 is ongoing. NICE will consider if a surveillance review is needed to make a decision about whether changes to existing guidance need to be made (as described in sections 8.3 and 8.4 of the programme manual). When this could be done would depend on when it could be scheduled into the work programme.

	Comment	Page	Section	Comments	NICE response
Veracyte Inc.	98	20	8	It is mentioned in this section that, Oncotype DX, EndoPredict and Prosigna are all currently used in clinical practice in the NHS (see section 3.2.5.1). Any testing that is currently undertaken in the node positive population is outside of the DG34 recommendation. Therefore, it is unlikely that major adoption issues would occur if other tumour profiling tests were to be recommended for use, or if the population for use were to be expanded'. [redacted]	Thank you for your comment. Please see the response to comment 80.