Proposal for assessment of new health technologies

Important information – read this first!

- Submitted proposals for national health technologies (HTAs) will be published in full. If the proposer thinks there is information necessary for filling out the form, that should not be made public, please contact the secretariat (Nye Metoder) before submission.

  The proposer is aware that the form will be published in its entirety (tick): ☒

- Proposer has filled out point 19 below «Interests and, if any, conflicts of interest» (tick): ☒
- This form serves the purpose to submit proposals for health technology assessment (HTA) at the national level in Nye Metoder - the national system for managed introduction of new health technologies within the specialist health service in Norway. The form does not apply to proposals for research projects. A health technology assessment is a type of evidence review, and for this to be possible, documentation is required, e.g. from completed clinical trials. Lack of documentation may be one of the reasons why the Commissioning Forum (Bestillerforum RHF) does not assign a health technology assessment.
- If the proposal concerns a medical device, the proposer is familiar with the document «Guidance criteria for management of medical devices in the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway» (link) (tick): ☒

Contact information:

Name of the proposer (organization / institution / company / manufacturer)**:**

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24 June 2021. UK

1. Proposer's title on the proposal: *
   *This may be changed during the course of the process"

The Oncotype DX® test to predict chemotherapy benefit and help guide adjuvant treatment decisions in HR+, HER2- early stage invasive breast cancer.

2. Brief description of the health technology proposed to be considered:

The Oncotype DX® test is a multigene assay that is used to guide adjuvant chemotherapy treatment decisions for patients with HR+, HER2-, early stage breast cancer.

The Oncotype DX test quantitatively determines the expression of 21 genes (16 cancer-related genes and 5 reference genes) using reverse transcriptase polymerase chain reaction (RT-PCR). The cancer-related genes are associated with proliferation, invasion, HRs and HER2, and their expression is normalised using the 5 reference genes. Cancer-related gene expression levels are used to calculate a Recurrence Score® result (RS®) between 0 and 100 (Paik, Shak, & Tang, 2004). The RS result is defined as low (0 to 25) or high (26-100) and stratifies patients into two groups: the vast majority of patients whose outcome in terms of distant recurrence and overall survival would be unchanged by adding chemotherapy treatment to hormone therapy (i.e., those who would not benefit from chemotherapy treatment), and the group of patients most likely to benefit from chemotherapy treatment, respectively (JA Sparano, 2018) (Kalinsky K, 2020).

The Oncotype DX test is used alongside traditional clinical pathological factors, such as tumour size, tumour grade and nodal status, to provide independent information regarding the relative and absolute chemotherapy benefit and prognosis at the patient level, to inform adjuvant chemotherapy treatment decisions for patients with node-negative and node-positive (1-3 involved lymph nodes, or N1) disease.

Published evidence shows that incorporating the Recurrence Score® result into adjuvant treatment planning enables improved selection of patients for adjuvant chemotherapy treatment. Chemotherapy can be reserved for the minority of N0 and N1 patients likely to benefit from the treatment (JA Sparano, 2018) (Kalinsky K, 2020). The majority of patients, for whom chemotherapy will not improve their outcome, can be spared unnecessary harm from side-effects of chemotherapy (e.g., secondary cancer, neurological damage, cardiac complications) (Krishnali Parsekar, 2021).

Published evidence shows that incorporating the Oncotype DX test into the breast cancer pathway leads to changes in a substantial proportion of chemotherapy treatment decisions, resulting in an overall reduction in the use of chemotherapy among tested patients (Albanell J, 2016).

The avoidance of both over- and undertreatment has both clinical and economic downstream benefits. From the payer perspective, by reducing overtreatment, savings can be accrued via lower chemotherapy-related costs, including costs of agents and administration, as well as costs related to the management of chemotherapy-related short- and long-term adverse events. Additionally, on an organisational level, the Oncotype DX test enables resource use optimisation and reallocation by allowing chemotherapy use to be targeted to patients for whom the benefits outweigh toxicities. By reducing undertreatment, rates of distant recurrence may be reduced, improving survival and reducing the high treatment costs associated with metastatic breast cancer, including the use of CDK4/6 inhibitors, as well as end of life care costs.

Thereby, incorporation of the Oncotype DX test into the treatment pathway for N0 and N1 patients can help to avoid the clinical, humanistic, and economic burden associated with under- and over-treatment of chemotherapy.

The clinical utility of the Oncotype DX test is supported by multiple large studies of over 100,000 patients in total. This includes two large independent prospective randomised studies (level 1A evidence) including both node-negative and positive patients, with a combined total of over 15,000 patients included. The evidence base also includes multiple large real-world datasets demonstrating long-term outcomes of patients who’s treatment was guided by the Oncotype DX test (JA Sparano, 2018) (Kalinsky K, 2020) (Hortobagy G, 2018) (Nitz U, 2017) (Salomon M. Stemmer, 2019) (Stemmer S, 2017)

National and international clinical practice guidelines recognise the unique value of the Oncotype DX test for guiding chemotherapy decisions for people with HR+, HER2- early breast cancer and the test is reimbursed in a number of countries worldwide.

3. Brief description of current standard of care (SOC) (Which health technology (ies) are currently used. What is the status of the technology (ies)? Whether it provides curative treatment, life extension, etc.)
Will the proposed technology replace or be a supplement to today's SOC?

Current clinical practice in Norway is to use conventional clinical pathologic factors such as tumour size, tumour grade and nodal status in combination with patient factors to estimate prognosis to guide chemotherapy treatment decisions. The Oncotype DX® test is designed to be used alongside conventional clinical pathological factors to not only refine prognosis but, crucially, to assess relative and absolute chemotherapy benefit. Prognostic-only tumour profiling tests are available which have been validated to estimate risk of distant recurrence with hormone therapy alone (not the benefit of adding chemotherapy treatment). The Oncotype DX test is the only test validated to predict relative chemotherapy benefit and is recognized by NCCN guidelines as “preferred” for N0 and post-menopausal N1 patients (HR-positive, HER2-negative early stage invasive breast cancer).

4. This proposal concerns:

	Yes	No
A brand new and innovative health technology	☒	☐
Anew application, or a new indication for an established method	☐	☒
A comparison between several methods	☐	☒
A technology that is already in use	☐	☒
If yes – technology used in clinical practice	☐	☒
If yes – technology used in research/clinical trials	☐	☒
A re-evaluation of technology used in clinical practice	☐	☒
The technology is relevant for disinvestment	☐	☒

N/A

5. This health technology involves (Multiple ticks are possible)

Pharmaceutical	☐
Medical device/IVD medical device that is CE-marked*	☒

IVDR article 6 requires CE-marking for 'distance sales' devices like the Oncotype DX test. Oncotype DX will therefore be CE-marked in connection with the IVDR coming into application, planned in May 2022.

As an intermediate step toward an IVDR CE-mark by May 2022 for the Oncotype DX Breast Recurrence Score® test, Genomic Health, Inc. issued a declaration of conformity under the IVDD in January this year for the proprietary software used to calculate the assay result. The software thus bears the CE mark. Please see below summary information.

Name Device	Catalogue number Device
Oncotype DX Breast Recurrence Score® Computational Software	G0039

Medical device/IVD medical device that is not CE-marked ☐

Procedure ☐

Screening ☐

Highly specialized services / national offers ☐

Organization of the health services ☐

Other (describe) ☐

"If relevant, please include who should be responsible for developing the technology."

6. Application of the technology:

Prevention	☐
Assessment and diagnostics	☒
Treatment	☐
Rehabilitation	☐
Specialist health care	☐
Primary health care	☐

To help guide adjuvant chemotherapy treatment decisions in HR+, HER2- early breast cancer.

7. Responsibility for funding

	Yes	No
Is the specialized health service responsible for financing the technology today?	☐	☒
May the specialized health service become responsible for funding the health technology?	☒	☐

It is our understanding that the funding source for a predictive genomic test in breast cancer is yet to be established and we believe this will be an important step in the future reimbursement process.

8. Is the technology mentioned in the national guidelines or action programs prepared by the Norwegian Directorate of Health?

Yes	No
☐	☒

It is our understanding that the National action program with guidelines for diagnosis, treatment and follow-up of patients with breast cancer (Oslo 2019) would be the relevant guidelines for the Oncotype DX test.

9. Does the technology involve the use of radiation (ionizing/ non- ionizing)?

Yes	No
☐	☒

N/A

10. Which discipline(s) does the health technology apply to, and which patients are affected? (Could the health technology also affect other groups (e.g. health personnel or relatives)?)

The Oncotype DX® test is typically ordered by breast cancer specialists, including oncologists, surgeons and specialist nurses, or pathologists.

The Oncotype DX test is validated for patients with HR+, HER2-, node-negative and node-positive (N1), early stage invasive breast cancer.

The test provides genomic information about an individual's tumour and therefore has no impact on patients' relatives?

11. Which aspects are relevant to the assessment? (Multiple ticks are possible)

Clinical efficacy	☒
Safety/adverse effects	☐
Costs/resource use	☒
Cost-effectiveness	☒
Organizational consequences	☒
Ethical	☒
Legal	☐

12. Please suggest the main scope/objective for the health technology assessment, as well as secondary scopes/objectives (in compliance with question 10). For those familiar with "PICO" (Patient, Intervention, Comparator, Outcome) – please include tentative suggestions for PICO.

Patient:

HR+, HER2-, node-negative and node-positive (N1), early stage invasive breast cancer (adjuvant setting).

Intervention:

The Oncotype DX Breast Recurrence Score® test.

Comparator:

Current clinical practice (the use of conventional clinical pathologic factors alone to inform prognosis and guide adjuvant treatment decision-making)

Outcome:

Clinical effectiveness - clinical validity: the ability of the test to identify which patients will/will not benefit from adjuvant chemotherapy treatment

Relevant clinical endpoints include invasive disease–free survival (IDFS), distant DFS (DDFS), freedom from disease recurrence at a distant site, overall survival (OS).

*Please note, prognostic accuracy, whilst an important component, is not the only or even the main consideration in relation to the Oncotype DX test. The most important information reported by the Oncotype DX test is the identification of patients who are most likely / not likely to benefit from chemotherapy treatment (relative and absolute chemotherapy treatment effect). A test which is able to identify the patients most likely to benefit from chemotherapy treatment directly addresses the most relevant clinical question for the patient population in question in the adjuvant setting i.e., whether or not to have adjuvant chemotherapy treatment. Another way of considering this question is whether the risk:benefit ratio of chemotherapy is favourable for the individual patient based on the expected absolute chemotherapy benefit vs. the risk of short and long-term adverse events from the treatment. The Oncotype DX test is uniquely able to directly address this clinical question based on the validation of the test to predict the relative effect/benefit from chemotherapy treatment, via studies randomizing patients to hormone therapy alone vs chemo-hormone therapy (Paik S T. G., 2006) (Albain KS, 2009).

Clinical effectiveness - clinical utility: the impact of the test on chemotherapy treatment decision-making and patient outcomes i.e., the ability of the test to identify patients who can be safely spared chemotherapy treatment without an increase in distant recurrence rates (JA Sparano, 2018) (Kalinsky K, 2020)

Cost effectiveness

13. Please give a brief explanation of why it is important that the health technology assessment proposed should be conducted.

One of the remaining major challenges and unmet needs in the management of patients with early-stage breast cancer is the decision of whether to recommend adjuvant chemotherapy or not. The goal is to optimally target chemotherapy to patients who will benefit in order to avoid distant cancer recurrence and improve survival, and avoid treating those patients who will not benefit from this treatment but will be exposed to short and long-term side effects and toxicity of the agents used.

In Norway, decisions regarding chemotherapy treatment are currently being made based on clinical risk assessment only, without incorporating information about chemotherapy treatment effect, based on information about underlying tumour biology from the Oncotype DX test. It has been shown that clinical risk is not a predictor of chemotherapy treatment effect/benefit. Not all patients with higher clinical risk benefit from chemotherapy and some patients with lower clinical risk do benefit (JA Sparano, 2018).

Today, 35–40% of Norwegian patients (HR+/HER2-, node-negative) receive chemotherapy. In contrast, approximately <10% of this patient group are expected to benefit from chemotherapy treatment. Rates of chemotherapy treatment are typically even higher among node-positive patients, despite a similarly low proportion (<10%) of these patients deriving benefit from chemotherapy ((EBCTCG), 2012).

Therefore, using clinical risk alone to guide chemotherapy treatment decisions without incorporating information about tumour biology risks both over- and undertreatment. The implications of overtreatment is lowering patients' quality of life due to treatment-related toxicities, while for patients being undertreated there is the risk of overlooking life-saving treatment.

The Oncotype DX® test can be used to identify approximately 80% of node-negative and post-menopausal node-positive patients who can be safely spared chemotherapy treatment (JA Sparano, 2018) (Kalinsky K, 2020).

14. Please comment on the technology that is proposed to be assessed with regard to the following points:

The severity of the disease/condition the health technology targets

The Oncotype DX® test is designed for investigating a severe illness; breast cancer.

Whilst HR+, HER2- early stage breast cancer is associated with a more favorable prognosis compared to other molecular subtypes such as triple negative breast cancer, the consequences of over and undertreatment with adjuvant chemotherapy are severe for patients (Krishnali Parsekar, 2021).

Unnecessary chemotherapy treatment needlessly exposes breast cancer patients to debilitating short and long-term side-effects.

Failing to identify patients who will benefit from chemotherapy (i.e., those who would experience a distant cancer recurrence unless they receive chemotherapy treatment) results in patients missing out on potentially life-saving treatment and having reduced survival.

Expected effect

The Oncotype DX® test has a large potential benefit in Norway.

The Oncotype DX test can be used to identify approximately 80% of node-negative and post-menopausal node-positive patients who can be safely spared chemotherapy treatment (JA Sparano, 2018) (Kalinsky K, 2020).

Use of the Oncotype DX test has consistently been shown to change a substantial proportion of adjuvant chemotherapy treatment decisions. This includes patients switching from chemo-hormone therapy to hormone therapy alone and vice versa. Testing leads to an overall reduction in the use of chemotherapy among tested patients. The reduction in chemotherapy use is particularly pronounced for the node-positive patient subgroup, due to much higher chemotherapy treatment rates based on conventional risk assessment approaches (Albanell J, 2016).

Sparing chemotherapy treatment for patients who will not benefit improves patients' quality of life by avoiding short- and long-term adverse events.

Reductions in the use of chemotherapy based on low RS® results are achieved without an increase in the rate of distant recurrences, as supported by clinical study and real-world evidence (JA Sparano, 2018) (Kalinsky K, 2020) (Hortobagy G, 2018).

Targeting chemotherapy treatment to patients who will benefit may reduce rates of distant cancer recurrence and may improve survival (Paik S, 2006) (Albain KS, 2009).

Safety

There is low risk associated with the Oncotype DX® test.

As the Oncotype DX test is a diagnostic tool, it is not directly associated with a safety risk beyond that of routine biopsy.

Total number of patients in Norway the health technology is applicable to

In 2017, 3905 women were diagnosed with breast cancer in Norway.

The Oncotype DX test is validated for HR+, HER2-, node-negative and positive, early invasive breast cancer. We estimate that 2734 women would be diagnosed with this type of cancer per year in Norway.

This assumes that 90% of breast cancer patients have invasive disease, 95% have early and locally advanced disease, 91% are hormone positive, and 90% are HER2 negative.

Consequences for resource use in the public health service

The Oncotype DX® test is not expected to have major budgetary implications for the specialist health service. Use of the test is expected to be cost-saving or cost-effective.

Savings can be accrued via lower total costs for chemotherapy treatment due to the overall reduction in the number of patients receiving the treatment. This includes costs for drug acquisition, administration, monitoring, supportive treatments, and management of chemotherapy-related adverse events (short- and long-term).

Savings may also be realized as a consequence of reduced rates of distant cancer recurrence. With the introduction of CDK4/6 inhibitors into routine clinical practice in the metastatic setting, treatment costs in this setting have increased substantially.

Additionally, the reduction in patients receiving adjuvant chemotherapy treatment, as well as treatment for metastatic disease following distant recurrence, also leads to a reduction and optimization of resource use in the health service. This includes personnel time (e.g., oncologist and nurse appointments) and chemotherapy chair time / infusion services.

The acquisition cost of the Oncotype DX test includes administration, logistics (including shipping), analysis, customer support and reporting of test results. Hence, no additional costs are expected by using the Oncotype DX test.

Need for revision of existing national guidelines or preparation of new guidelines

Recommendations regarding the use of multi-gene assays for early breast cancer are needed and it is our understanding that these would be incorporated into the National action program with guidelines for diagnosis, treatment and follow-up of patients with breast cancer. Oslo: 2019

15. Please provide references to documentation of the health technology's effect and safety (i.e. previous technology assessments). (Up to 10 key references can be provided, please do not send attachments in this step of the process):

Please note that a HTA report by TLV in Sweden is expected in the coming days.

German Institute for Quality and Efficiency in Health Care (IQWiG), Biomarker tests in breast cancer: New study data indicate advantage for certain patients 2018.

German Institute for Quality and Efficiency in Health Care (IQWiG), Biomarker tests for decision-making on chemotherapy for breast cancer: No evidence of transferability 2020.

National Institute for Health and Care Excellence, Tumour Profiling Tests to Guide Adjuvant Chemotherapy Decisions in Early Breast Cancer. 2018.

National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Version 4.2021). 2021.

Andre, F., et al., Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: ASCO Clinical Practice Guideline Update-Integration of Results From TAILORx. J Clin Oncol, 2019. 37(22): p. 1956-1964.

Cardoso, F., et al., Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Ann Oncol, 2019. 30(8): p. 1194-1220.

Burstein, H.J., et al., Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Ann Oncol, 2019. 30(10): p. 1541-1557.

Hortobagyi GN, C.J., D'Orsi CJ, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, Weaver DL, Winchester DJ, Giuliano A. Breast. In: Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR AJCC Cancer Staging Manual. 2018, NY: Springer Publishing: New York. p. 589-628. AJCC® 8th Ed.

Sparano, J.A., et al., Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. New England Journal of Medicine, 2018. 379(2): p. 111-121.

Kalinsky et al, SABCS 2020 GS3-00 (RxPONDER)

16. Please provide the name of the marketing authorization holder/manufacturer/supplier of the health technology (if applicable/available):

Genomic Health Inc.

17. Marketing Authorization Status (MA) or CE-marking: When is MA or CE- marking expected? If possible, provide the time of planned marketing:

IVDR article 6 requires CE-marking for 'distance sales' devices like the Oncotype DX test. Oncotype DX will therefore be CE-marked in connection with the IVDR coming into application, planned in May 2022.

As an intermediate step toward an IVDR CE-mark by May 2022 for the Oncotype DX Breast Recurrence Score® test, Genomic Health, Inc. issued a declaration of conformity under the IVDD in January this year for the proprietary software used to calculate the assay result. The software thus bears the CE mark. Please see below summary information.

Name Device	Catalogue number Device
Oncotype DX Breast Recurrence Score® Computational Software	G0039

18. Additional relevant information (up to 300 words.)

We believe there is sufficient documentation on the technology available to allow an HTA to be performed.

Furthermore, since recent health technology assessments of the Oncotype DX® test were conducted, results from the RxPONDER study have been presented, providing prospective randomised evidence that a large proportion of post-menopausal patients with N1 breast cancer can be identified by the Oncotype DX test who do not benefit from chemotherapy, allowing these patients to be spared unnecessary treatment and side-effects (Kalinsky K, 2020). For this reason, the node-positive patient subgroup is an important part of our proposal for assessment of the Oncotype DX test.

19. Interests and potential conflicts of interests

Please describe the proposer's relationships or activities that may affect, be influenced by, or be perceived by others to be important for further management of the health technology that is proposed assessed. (E.g. proposer has financial interests in the matter. Proposer has or has had assignments in connection with the technology or to other actors with interest in the technology)

Proposer is an employee of Exact Sciences, the provider of the Oncotype DX test.