Evaluation proposal for the Danish Health Technology Council regarding the Oncotype DX® test for guiding adjuvant chemotherapy treatment decisions in early-stage hormone receptor positive breast cancer

Instructions for the applicant

This template is used for submitting evaluation proposals to the Danish Health Technology Council in connection with the request of an assessment of new or existing health technology. Evaluation proposals are completed by the applicant and aim to provide the Danish Health Technology Council with a background for launching evaluations. Applicants are recommended to engage in a dialogue with the Danish Health Technology Council's secretariat to receive guidance for proper completion.

The template covers the following main topics:

- Information about the applicant
- Information about the health technology
- Information about the evidence base for the health technology

The Danish Health Technology Council defines health technologies broadly as any use of medical devices, procedures, or processes applied in the treatment or diagnosis of patients. Evaluations of health technologies by the Danish Health Technology Council are always conducted with the consideration of four perspectives: Clinical Effectiveness and Safety, the Patient Perspective, Organizational Implications, and Health Economics.

Evaluation proposals that are considered by the Danish Health Technology Council will be published on the Danish Health Technology Council's website. If there is confidential information in the evaluation proposal, it must be clearly marked using yellow text highlighting ("example").

The evaluation proposal should be kept as concise as possible and be in either Danish or English. At the end of the document, there is an example of a completed evaluation proposal that applicants can use for inspiration.

If questions arise during the preparation of the evaluation proposal, applicants may contact the Danish Health Technology Council's secretariat for elaboration or clarifications.

In addition to the evaluation proposal, companies, regions, and hospital administrations can complete and include a cost outline that provides an overview of the total costs associated with the use of the health technology. The Danish Health Technology Council's secretariat provides a cost outline template that can be accessed on the Danish Health Technology Council's website.

The completed evaluation proposal is the applicant's product.

Information about the applicant

Name of the applicant (company name or the name of the hospital/region)*:

Exact Sciences International Gmbh.

The Oncotype DX test is performed by Exact Sciences wholly owned subsidiary Genomic Health Inc.

* If you are a public applicant, the Danish Health Technology Council refers to the requirement that the evaluation proposal in its entirety must be approved by the hospital or regional management.

Contact person (name, position):

Lars Holger Ehlers. Director of Nordic Institute of Health Economics.

Date of submission of the evaluation proposal:

5th July 2024

Information about the health technology

Briefly describe the health technology to be evaluated:

The Oncotype DX Breast Recurrence Score® test (the Oncotype DX® test) is a non-invasive diagnostic test to guide adjuvant chemotherapy treatment decisions for individuals with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), early-stage (I-IIIa) invasive breast cancer. The test provides two pieces of information: 1. the recurrence risk and 2. the benefit of adding chemotherapy in order to reduce the risk.
The test analyses the expression of 21 genes in breast tumour tissue based on RT-PCR. It does not require additional tumour material beyond the surgically excised tissue.

Provide a rationale for why it is relevant to conduct an evaluation of the health technology:

Adjuvant treatment planning in this patient group seeks to reduce the risk of cancer recurrence and mortality. Most patients receive hormone therapy, and a course of chemotherapy is also added beforehand unless its omission is not expected to affect mortality.

Adding chemotherapy only improves outcomes for a small proportion (**4-8%)** of patients in this group (EBCTCG. Lancet. 2012). However, currently a much larger proportion of patients are assigned to chemotherapy based on current treatment guidelines, meaning there may be substantial over-treatment (DBCG). TLV (Sweden) and NIPH (Norway) assessments indicate **38%-63%** of node-negative & positive patients receive chemotherapy without the Oncotype DX test (TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023).

This is because with the current approach it is not possible to identify the individuals who will benefit, or a smaller subgroup most likely to benefit. Instead, the current approach identifies a subset of patients estimated to have the lowest risk of mortality, based on the presence of lower risk tumor characteristics (such as tumors of smaller size and/or lower grade), for whom chemotherapy is omitted (Ejlertsen et al. 2014;

DBCG). The remaining large proportion of patients classified as 'intermediate risk' or 'high risk' are likely to receive chemotherapy (DBCG).

This means with the current approach many patients may be exposed to short and long-term chemotherapy side-effects without gaining a benefit, negatively impacting quality of life and leading to greater healthcare resource, capacity and budget consumption.

Additionally, a smaller proportion of patients for whom chemotherapy is currently omitted based on lower risk tumour characteristics, may experience a cancer recurrence that could have been prevented with chemotherapy, leading to higher mortality, and higher costs and resource consumption associated with the management of late-stage cancer and end of life care.

Two pieces of information are crucial for precisely targeting chemotherapy treatment to the right patients:

- **the baseline risk of cancer recurrence or mortality without chemotherapy** (available with the current approach)
- **the extent to which adding chemotherapy would reduce the risk** (not available with the current approach)

The Oncotype DX test is designed and validated to both refine the baseline risk estimate, but crucially also to directly determine whether and by how much this risk would be reduced by adding chemotherapy (Paik et al, 2004, Paik et al, 2006; Albain et al, 2010; Sparano et al, 2018; Kalinski et al, 2021). This allows patients to make informed treatment decisions by identifying:

- ~80% of lymph node-negative (N0) and postmenopausal lymph node-positive (N1) patients for whom adding chemotherapy would have no benefit, independent from clinical risk (Sparano et al, 2018; Kalinski et al, 2021).
- ~20% of patients most likely to benefit from chemotherapy (74% and 41% relative risk reduction from chemotherapy among lymph node-negative and node-positive patients with high Recurrence Score results) (Paik et al, 2006; Albain et al, 2010; Sparano et al, 2018; Kalinski et al, 2021)

Use of the Oncotype DX test leads to a large proportion of patients avoiding either over or undertreatment with chemotherapy, and greatly reduces the overall proportion of patients receiving chemotherapy, without negatively impacting recurrence or mortality rates (TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023; NICE DG34/DG58). A European decision-impact study involving 2,471 patients, reported that use of the Oncotype DX test resulted in a 43% reduction in overall chemotherapy use (Barni et al. 2018).

Therefore, introducing the Oncotype DX test to help guide adjuvant chemotherapy treatment decisions with greater precision for pre- and postmenopausal N0 and postmenopausal N1 patients may be a cost-saving and health gaining alternative to the current chemotherapy decision-making approach in Denmark, as has been reported for other healthcare systems.

What is the classification of the health technology?

☐Medical device, which is CE marked*

☐ Class I

☐ Class IIA
☐ Class IIB
☐ Class III

☒Diagnostic technology, which is CE marked**

☐ Class A
☐ Class B
☒ Class C
☐ Class D

☐Procedure (workflow related to diagnostics, treatment, rehabilitation, and/or with a preventive purpose)

If the procedure involves the use of one dominant health technology, describe it, and provide its CE marking and classification

* The Danish Health Technology Council only evaluates medical devices that are CE marked or otherwise meets the legal requirements for medical devices.
** Diagnostic technology utilizing medical equipment for *in vitro* diagnostics.

☒ the applicant hereby declares under penalty of perjury that the above information is accurate and complies with the relevant legislation concerning CE marking.

Briefly describe the current status of the use of the health technology in Denmark and abroad.

The Oncotype DX test is not currently routinely conducted in Denmark, but is routinely conducted for both lymph node-negative (pre and postmenopausal) and lymph nodes-positive (postmenopausal) patients in many other European and other Western countries. To date, more than 1.5 million Oncotype DX tests have been conducted in more than 90 countries.

Proposed PICO specification (Population, Intervention, Comparator, Outcome) for framing the evaluation question:

Population – The patient group in/for which the health technology is utilized and which the evaluation focuses on, including the annual number of patients in Denmark:	The patient population includes individuals with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), early-stage (I-IIIa) invasive breast cancer. Data from Globocan reveals that in 2022, there were 5,259 new breast cancer cases in Denmark. Approximately 90% are stage I-IIIa, 69% are HR+ & HER2-, 95% are N0 or N1 (excluding N2), 80% are N0 / 20% are N1, 80% of N1 are postmenopausal, and 94% are assumed to be candidates for chemotherapy, meaning approximately **2,700** lymph node-negative and postmenopausal lymph node-positive patients eligible for the Oncotype DX test.

	Two separate patient subgroups are suggested for health economic analysis: • **lymph node-negative (N0) patients (pre- and postmenopausal)** • **postmenopausal lymph node-positive (N1) patients**
Intervention – The specific health technology to be evaluated:	The Oncotype DX Breast Recurrence Score® test (the Oncotype DX® test)
Comparator – The health technology or treatment that is natural to compare with and currently used as the best and most widely adopted alternative to the intervention in Denmark (I):	The most widely adopted alternative is chemotherapy treatment decision-making using **traditional risk assessment based on tumour characteristics** (DBCG). The **PAM50/Prosigna** test is also used for a specific subset of post-menopausal patients and so could be a relevant comparator (subject to feasibility based on comparative data availability).
Outcome – The clinical effectiveness measures that would be relevant to assess the health technology compared to the comparator are:	Relevant clinical effectiveness measures: • **Relative risk reduction from chemotherapy by test result category.** • **Impact on chemotherapy treatment decisions.** • **Expected lifetime QALYs** • **Expected life years gained (mortality)** • **Expected recurrence rate** • **Expected chemotherapy treatment rate** Please note: measures of sensitivity and specificity do not apply to multi-gene panel tests as they do for single biomarker tests reporting binary results i.e., the ability to correctly detect the presence (sensitivity) or absence (specificity) of a biomarker. Clinical validity and utility are more relevant for multi-gene panel tests. Clinical validation of a multi-gene panel test designed to predict treatment effect involves demonstrating a correlation between test result and treatment-dependent effect i.e., lack of treatment effect for patients with a 'low' score and

	large effect (risk reduction) for patients with a 'high' score. Clinical utility of a multi-gene panel test focuses on the impact of the test on treatment decisions (so-called decision-impact studies) i.e., treatment changed for patients with a low test result to avoid unnecessary treatment, and changed for patients with a high test result to avoid missing out on effective treatment.

* PICO is a tool utilized by the Danish Health Technology Council to formulate precise issues and is crucial in the planning and execution of an evaluation by the Danish Health Technology Council. PICO is further detailed in the Danish Health Technology Council's methods guide, available on the Danish Health Technology Council's website.

Provide a brief description of the proposed comparator and whether the suggested health technology (intervention) is suggested to replace or to be an add on to the current alternative:

Chemotherapy treatment decision-making using the current traditional risk assessment approach (based on clinical tumour characteristics) was selected as the comparator in multiple health technology assessments in several other countries, including the TLV in Sweden, NIPH in Norway and NICE in the UK (TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023; NICE DG34/DG58).

This is also the most widely adopted approach to chemotherapy treatment decision making in Denmark. Gene expression profiling using PAM50/Prosigna is currently only conducted for a small subset of patients (postmenopausal patients estimated to have intermediate-low risk) (DBCG guidelines).

It is important to note that the Prosigna test is not the same as the Oncotype DX test, and the tests are not interchangeable. The Prosigna test measures a different panel of genes and does not provide the same type of information, as acknowledged in multiple international clinical guidelines and health technology assessments across Europe. The Prosigna test is for prognostic risk assessment only (as per the traditional clinical approach) and is not currently validated to determine chemotherapy benefit (NCCN Guidelines Insights: Breast Cancer, version 4.2022; Andre et al. J Clin Oncol 2022; Burstein et al. Ann Oncol. 2021; Curigliano et al. Ann Oncol. 2023; Cardoso et al. Ann Oncol 2019; Loibl et al. Annals of Oncology 2024; TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023; NICE DG34/DG58).

We suggest the most appropriate comparator therefore remains current chemotherapy treatment decision-making based on traditional clinical risk assessment.

The Oncotype DX test is intended to be used alongside traditional risk assessment to help target adjuvant chemotherapy treatment with greater precision. However, use of the Oncotype DX test is not intended to be restricted to the narrow 'risk-stratified' patient group in which the PAM50/Prosigna test is used.

Is the health technology mentioned in professional clinical guidelines from institutions like the Danish Health Authority or medical scientific societies? Specify which ones:

The Oncotype DX test is not currently included in Danish clinical guidelines.

The Oncotype DX test is included in several international breast cancer clinical guidelines:

National Comprehensive Cancer Network (NCCN), 2022[1]:

- The Oncotype DX test is the only test recognized by NCCN guidelines to predict adjuvant chemotherapy benefit.
- The Oncotype DX test is the only test classified as the "preferred" test in both N0 and post-menopausal N1 patients with HR-positive, HER2-negative breast cancer.
- Specific recommendations regarding the interpretation of the Recurrence Score result for patient subpopulations, based on the TAILORx and RxPONDER studies.

European Society for Medical Oncology (ESMO), 2019[2]:

- The Oncotype DX test may be used to gain additional prognostic and/or predictive information, based on Level 1A evidence to complement pathology assessment.
- The Oncotype DX test may be used to predict the benefit of adjuvant chemotherapy.

St Gallen International Consensus Panel, 2023[3]:

- Test strongly endorsed for vast majority of N0 and N1, HR+, HER2- early-stage breast cancer patients, TAILORx and RxPONDER cutoffs to guide treatment decisions.
- The 2023 St Gallen guidelines update highlighted the need to test premenopausal patients with the Oncotype DX test, as not all of these patients require chemotherapy.

American Society of Clinical Oncology (ASCO), 2022[4]:

- The Oncotype DX test is the only test strongly recommended for all N0 and postmenopausal N1 patients with ER+, HER2- early breast cancer.
- Recommendation is irrespective of clinical risk.
- Recommendation is based on "high" evidence quality.

References:

1. NCCN Guidelines Insights: Breast Cancer, version 4.2022.
2. Loibl et al. Annals of Oncology 2024.
3. Curigliano et al. Ann Oncol. 2023.
4. Andre et al. J Clin Oncol 2022.

Has the health technology been evaluated by other HTA institutions (e.g. NICE, Nye Metoder)? Specify which ones:

The Oncotype DX test has been positively evaluated by several HTA institutions.

NICE, UK:

- Diagnostics Guidance 58 (DG58) published 9 May 2024.
    - Updated Diagnostics Guidance 34 (DG34) published 19 December 2018, which made a positive recommendation for certain individuals with lymph node-negative and micro-metastatic breast cancer.

- Recommendation for lymph node-positive early breast cancer: Use EndoPredict, Oncotype DX or Prosigna as options alongside consideration of clinical risk factors to guide adjuvant chemotherapy decisions.
- Recommendation for Lymph node-negative and micrometastatic early breast cancer: EndoPredict, Oncotype DX or Prosigna can be used (under certain conditions) for patients if they have an intermediate risk of distant recurrence using a validated tool such as Predict or the Nottingham Prognostic Index.

Nye Metoder/NIPH, Norway:

- Single technology assessment of the Oncotype DX test, published October 2023.
- Concluded that the Oncotype DX test seems to be more effective and less costly compared to no gene-profiling test.
- Concluded that the Oncotype DX test predicts chemotherapy benefit in patients with ER+ HER- early-stage breast cancer who were node negative (regardless of menopausal status) or postmenopausal and node positive (1-3 lymph nodes).

TLV, Sweden:

- Health economic assessment of Oncotype DX test, published in June 2021.
- Concluded that the Oncotype DX test is expected to be more effective and less costly compared to no gene-profiling test.
- The results were largely driven by the product's ability to predict the expected relative benefit of chemotherapy (predictive ability) and thus reduce both under- and over-treatment.

HIQA, Ireland:

- A rapid health technology assessment of gene expression profiling tests for guiding the use of adjuvant chemotherapy in early-stage invasive breast cancer, published February 2023.
- Oncotype DX® is currently the only Gene Expression Profiling test that is reimbursed by the Health Service Executive in Ireland.
- HIQA concluded that the available evidence supports the continued use of Oncotype DX® among N0 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 N+ patients.

IQWIG, Germany:

- A multi-technology assessment published in 2018.
- IQWIG concluded that with the results of TAILORx, only Oncotype DX® has sufficient evidence to guide adjuvant chemotherapy decisions in patients with early stage, node-negative, invasive breast cancer.

Provide the names of manufacturers/suppliers of the health technology, if relevant:

The Oncotype DX test is performed by Exact Sciences wholly owned subsidiary Genomic Health Inc.

Information about the evidence base for the health technology:

Indicate whether the health technology (compared to the current alternative) aims to improve treatment~~/diagnosis~~ of the patient group as perceived from one or more of the following perspectives (indication of the primary impact of using of the health technology):

☒ Clinical effectiveness and safety	☒ Patient preferences and experiences
☒ Organizational aspects, such as changes to workflows	☒ Costs associated with treatment/diagnostics

*For the evaluation of health technologies, the Danish Health Technology Council employs four perspectives: Clinical Effectiveness and Safety, the Patient Perspective, Organizational Implications, and Health Economics. For further elaboration on these perspectives, refer to the Danish Health Technology Council Council's methods guide for the evaluation of health technologies, available on the Danish Health Technology Council Council's website.

State the expected impact of the health technology within the indicated perspectives above:

Clinical effectiveness and safety:

The literature on Oncotype can demonstrate a significant and clinically meaningful reduction in the number of patients assigned to chemotherapy and that patients avoiding chemotherapy based on a low RS result can do so without affecting recurrence or survival outcomes (Holt et al, 2024; NICE DG34/DG58; Paik et al, 2006; Albain et al, 2010; Sparano et al, 2018; Kalinski et al, 2021).

The proposed effect of the intervention is as follows:

- The ability to identify patients who do not benefit from chemotherapy, leading to more patients being able to be safely switched from CET to ET treatment, with RCT evidence proving no negative impact on distant recurrence or mortality.
- The ability to identify patients who are highly likely to benefit from chemotherapy treatment (with a substantially greater than average relative risk reduction from chemotherapy), for whom chemotherapy can be targeted more precisely to reduce the rate of recurrence.

The Oncotype DX test uses tissue samples that are routinely collected for this patient group, and so does not represent a safety concern.

Costs associated with treatment/diagnostics:

The Oncotype DX test does not require additional tumour material beyond the surgically excised tissue and does not require additional resources and expenditure beyond the all-inclusive purchase price for the test, as it is offered as a full testing service including shipping costs.

Use of the Oncotype DX test to reduce over and under-treatment is expected to lead to the following cost-savings:

- **Reduction in adjuvant chemotherapy treatment-related costs**: including drug acquisition costs, costs of administering and monitoring treatment, and costs of managing short and long-term side-effects resulting from chemotherapy treatment.
- **Reduction in advanced/metastatic cancer-related costs**: including high acquisition cost of metastatic treatments e.g., CDK4/6 inhibitors, and end of life care (TLV, Hälsoekonomisk bedömning av

Oncotype DX Breast Recurrence Score Test, 2021; NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023; NICEDG34/DG58).

Health economic evidence can demonstrate cost-effectiveness and costs savings (please see further information below). It is important that a long-term time horizon is applied in health economic analysis to capture the full value of the Oncotype DX test in terms of reduced distant recurrence and mortality rates.

Organizational aspects, such as changes to workflows:

Reducing the number of patients receiving adjuvant chemotherapy can lead to decreased resource consumption and alleviate burden on specialized healthcare personnel (including Oncologists and nurses).

Reduced chemotherapy may decrease the demand for infusion services, including chemotherapy chair time.

Reducing the number of patients progressing to advanced/metastatic cancer can also lead to decreased resource consumption and alleviate burden on specialized healthcare personnel.

The Oncotype DX® test is carried out in a state-of-the-art central laboratory in the US. A dedicated quality control and assurance team, as well as testing of all samples in triplicate, and extensive lab process automation, provides precision & reproducibility of a highly standardised process, with ISO 15189 / CLIA / CAP accreditations.

Exact Sciences offers a secure online portal, fully compliant with the General Data Protection Regulation (GDPR) for test ordering, tracking and reporting. Strict measures are followed to secure data privacy and GDPR compliance will be assured with the implementation of Oncotype DX in Denmark. Personal data are encrypted and pseudonymized and the encryption key remains in Europe so in no case does the laboratory in the US have access to patient personal information when performing the test. The test is performed on a sample identified by a QR code and the test result is associated with patient info only when the result is returned to the ordering clinician via the secure online EU portal. The Encryption process follows a strict principle of minimization of data access based on a privacy by design approach with clear definition of responsibilities and authorizations. Full details of the patient data security measures in place for the Oncotype DX testing service will be shared with the full evaluation submission.

Patient preferences and experiences:

Shared treatment decision-making between a patient and their clinician is of vital importance, especially considering the important consequences of the decision whether to have chemotherapy treatment. Chemotherapy side-effects can be severe, for example potentially leading to infertility for premenopausal women, impacting family planning, or leading to long-term health problems.

With the current approach patients do not have access to information about how having chemotherapy would affect the chances of their cancer coming back. Patients are therefore having to make very difficult treatment decisions based on suboptimal information, which may lead to additional anxiety.

A recent study reported that patients who had access to their Recurrence Score result had increased confidence when making their treatment decision (Holt et al. 2024).

Furthermore, patients undergoing unnecessary chemotherapy treatment may experience debilitating and life-changing short and long-term side-effects, potentially requiring taking time out of paid employment for themselves and/or carers i.e. a reduction in productivity costs.

Provide references* for documentation of the health technology's effects (if possible, include up to 2 key references per perspective):

Clinical effectiveness and safety	1. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018;379(2):111-21. 2. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med. 2021;385(25):2336-47. The Oncotype DX test is supported by a wealth of additional data, including RCTs and large real-world datasets.
The Patient perspective	1. Holt, S., Verrill, M., Pettit, L. et al. A UK prospective multicentre decision impact, decision conflict and economic evaluation of the 21-gene assay in women with node+ve, hormone receptor+ve, HER2-ve breast cancer. Br J Cancer 130, 1149–1156 (2024). 2. Parsekar K, Howard Wilsher S, Sweeting A, et al. Societal costs of chemotherapy in the UK: an incidence-based cost-of-illness model for early breast cancer. BMJ Open. 2021 Jan 11;11(1):e039412.
Organizational Implications	1. TLV, Hälsoekonomisk bedömning av Oncotype DX Breast Recurrence Score Test, 2021 2. NIPH, Single Technology Assessment: Oncotype DX Breast Cancer Recurrence Score Test, 2023
Health Economics	1. Berdunov V, Millen S, Paramore A, et al. Cost-effectiveness analysis of the Oncotype DX Breast Recurrence Score test in node-positive early breast cancer. J Med Econ. 2022 Jan-Dec;25(1):591-604. 2. Berdunov V, Millen S, Paramore A, et al. Cost-Effectiveness Analysis of the Oncotype DX Breast Recurrence Score® Test in Node-Negative Early Breast Cancer. Clinicoecon Outcomes Res. 2022 Sep 19;14:619-633.

* Reference to published, ongoing, or unpublished data.

Indicate whether the health technology is expected to incur additional costs, cost reductions, or be cost-neutral compared to the current alternative. Briefly describe how the costs are expected to be distributed across sectors (hospital, general practice, municipalities, patients, etc.), and what is considered to drive the potential addition or reduction in costs. The Danish Health Technology Council encourages applicants to complete and include the Danish Health Technology Council's cost outline, accessible on the Danish Health Technology Council's website.

☐ Additional costs ☒ Cost reductions ☐ Cost-neutral

Health economic analyses of the Oncotype DX test estimate that use of the test leads to overall savings for the healthcare system (including after considering the cost of testing) due to reduced adjuvant chemotherapy treatment-related costs and reduced distant recurrence and end of life care costs.

A cost-effectiveness analysis of the Oncotype DX test in the node-negative patient subgroup in the UK estimated that testing was more effective (0.17 more quality-adjusted life years) at a lower cost (-£519) over a lifetime compared to clinical risk alone. This result was primarily driven by a reduction in distant recurrence among patients with a treatment change to add chemotherapy based on a high test result identifying significant treatment benefit (Berdunov et al, 2022).

A similar cost-effectiveness analysis in the node-positive patient subgroup in the UK, again estimated that testing was more effective (0.02 more quality-adjusted life years) at a lower cost (-£989) over a lifetime compared to clinical risk alone. Due to much higher pre-test chemotherapy treatment rates among N1 patients, cost savings in the N1 subgroup was primarily driven by a large reduction in chemotherapy treatment among patients with a low test result, identifying that chemotherapy would offer no benefit (Berdunov et al, 2022).

The latter analysis included both pre- and postmenopausal N1 patients. For the recently published NICE DG58 guidance recommending testing only postmenopausal N1 patients, the External Assessment Group published a cost-effectiveness subgroup analysis in their Technology Assessment Report, specifically for the postmenopausal N1 patient subgroup. The conclusion was again that testing is expected to be more effective (0.11 more quality-adjusted life years) at a lower cost (-£4,273).

TLV in Sweden and NIPH also concluded from their health technology assessments of the Oncotype DX test that testing is expected to be cost saving.

Free-text field (optional additional information, max 300 words):

Additional references

1. Geyer CE, Jr., Tang G, Mamounas EP, Rastogi P, Paik S, Shak S, et al. 21-Gene assay as predictor of chemotherapy benefit in HER2-negative breast cancer. NPJ Breast Cancer. 2018;4:37.
2. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer. N Engl J Med. 2021;385(25):2336-47.
3. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018;379(2):111-21.
4. Paik S, Shak S, Kim C, Baker J, Cronin M, Baehner R, et al. Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients - NSABP studies B-20 and B-14. 2003. S10-S1 p.
5. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer. New England Journal of Medicine. 2004;351(27):2817-26.

6. Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol. 2006;24(23):3726-34.
7. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 2010;11(1):55-65.
8. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.
9. Early Breast Cancer Trialists' Collaborative Group. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379(9814):432-44.
10. Holt, S., Verrill, M., Pettit, L. et al. A UK prospective multicentre decision impact, decision conflict and economic evaluation of the 21-gene assay in women with node+ve, hormone receptor+ve, HER2-ve breast cancer. Br J Cancer 130, 1149–1156 (2024).
11. Tao JJ, Visvanathan K, Wolff AC. Long term side effects of adjuvant chemotherapy in patients with early breast cancer. Breast. 2015;24 Suppl 2:S149-53.
12. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst. 2009;101(21):1446-52.
13. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2015;373(21):2005-14.
14. Stemmer SM, Steiner M, Rizel S, Geffen DB, Nisenbaum B, Peretz T, et al. Clinical outcomes in ER+ HER2 -node-positive breast cancer patients who were treated according to the Recurrence Score results: evidence from a large prospectively designed registry. NPJ Breast Cancer. 2017;3:32.
15. Stemmer SM, Steiner M, Rizel S, Ben-Baruch N, Uziely B, Jakubowski DM, et al. Ten-year clinical outcomes in N0 ER+ breast cancer patients with Recurrence Score-guided therapy. npj Breast Cancer. 2019;5(1):41.
16. Nitz U, Gluz O, Christgen M, Kates RE, Clemens M, Malter W, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat. 2017;165(3):573-83.
17. Barni S, Curtit E, Cognetti F, Bourgeois D, Masetti R, Zilberman S, et al, Real-life Utilization of Genomic Testing for Invasive Breast Cancer Patients in Italy and France Reduces Chemotherapy Recommendations. #194P, ESMO, 2018.
18. Berdunov V, Millen S, Paramore A, Griffin J, Reynia S, Fryer N, et al. Cost-Effectiveness Analysis of the Oncotype DX Breast Recurrence Score(®) Test in Node-Negative Early Breast Cancer. Clinicoecon Outcomes Res. 2022;14:619-33.
19. Berdunov V, Millen S, Paramore A, Hall P, Perren T, Brown R, et al. Cost-effectiveness analysis of the Oncotype DX Breast Recurrence Score(R) test in node-positive early breast cancer. J Med Econ. 2022:1-48.
20. McSorley LM, Tharmabala M, Al Rahbi F, Chew S, Evoy D, Geraghty JG, et al. Real-world analysis of clinical and economic impact of 21-gene recurrence score (RS) testing in early-stage breast cancer (ESBC) in Ireland. Journal of Clinical Oncology. 2021;38(15_suppl):540-.