Oncotype DX breast cancer recurrence score test: A single technology assessment

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Executive summary

Introduction

Early-stage breast cancer patients undergo surgery to remove the primary tumor. After surgery, patients characterized as estrogen reseptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2-) are routinely treated with endocrine therapy with or without chemotherapy to prevent recurrence. Chemotherapy causes side-effects and should ideally only be offered to patients who benefit from the treatment.

In this single technology assessment (STA), we have considered the gene-profiling test Oncotype DX. The test calculates a Recurrence Score (RS) between 0 and 100, and is intended to estimate the risk of recurrence, and to predict whether breast cancer patients will benefit from chemotherapy. Our assessment is based on documentation submitted by Oecona on behalf of the manufacturer of Oncotype DX, Exact Sciences.

Objective

The objective of the STA was to appraise the evidence addressing the following questions: (Q1) Can Oncotype DX predict chemotherapy benefit? (Q2) Does Oncotype DX provide prognostic information? (Q3) What is the distribution of RS in populations of breast cancer patients? (Q4) Can Oncotype DX reduce chemotherapy use?

We also appraised the cost-effectiveness and budget impact analyses provided by the submitter.

Method

***Clinical effectiveness**:* We performed a separate literature search to evaluate whether all randomized controlled trials (RCTs) addressing question Q1 were found and included by the submitter. We extracted data from the RCTs and critically appraised the risk of bias. Our confidence in the results was assessed using the GRADE approach. We also extracted data from RCTs and non-randomized studies to validate the submitted evidence for question Q2, Q3, and Q4.

Health economics: The health economic model provided by the submitter combined a decision tree and a Markov model to compare the Oncotype DX test strategy to assessment of traditional clinical parameters (no gene-profiling test). Patients were categorised as having low, intermediate or high RS, and in each RS group, patients received or did not receive chemotherapy. These groups were connected to a Markov model that

predicted lifetime QALYs and costs, considering the risk of distant recurrence. The submitter also performed sensitivity analyses and budget impact analyses.

Results

***Clinical effectiveness**:* The submitter identified four RCTs that investigated whether Oncotype DX can predict chemotherapy benefit in patients with ER+ HER- early-stage breast cancer. Two of the RCTs investigated patients with node negative disease and two investigated node positive disease (1-3 positive lymph nodes). Additional RCTs were not identified in our separate literature search.

For patients with node negative disease (regardless of menopausal status) and for postmenopausal patients with node positive disease, there was convincing evidence that:

- Patients with low or intermediate RS (0-25) have similar risk of recurrence regardless of whether they are treated with endocrine therapy plus chemotherapy or endocrine therapy alone (have no chemotherapy benefit). However, a small chemotherapy benefit was observed for node negative women below 50 years and a RS of 16-25.
- Patients with high RS (>25) treated with endocrine therapy plus chemotherapy have lower risk of recurrence than those treated with endocrine therapy alone (have chemotherapy benefit).

RCTs and non-randomized studies also demonstrated that Oncotype DX provides prognostic information. Distributions of RS suggested that approximately 75-90% of the patients with node negative and node positive disease have low or intermediate RS (0-25) and can omit chemotherapy. Decision-impact studies demonstrated that Oncotype DX reduced chemotherapy assignment by 16-27% for node negative patients and by 50-73% for node positive patients. The studies also illustrated that treatment decisions were not based entirely on the RS.

Health economics: The base case cost-effectiveness analysis indicated that Oncotype DX was dominant compared to assessment of traditional clinical parameters (no gene-profiling test) for both node negative and postmenopausal node positive patients (i.e., provided greater QALY gains at a lower cost). One way sensitivity analyses identified the primary sources of uncertainty in the model. These were the hazard ratio for the high RS group for node negative patients, and the hazard ratio for the low and intermediate RS group for postmenopausal node positive patients. Probabilistic sensitivity analyses showed that, with a willingness-to-pay threshold of 250,000 NOK per QALY, the Oncotype DX test had a probability of 99% and 100 % of being cost-effective (compared to no gene profiling test) for node negative and postmenopausal node positive patients respectively. Absolute shortfall of QALYs was calculated to be 1.83 QALYs.

Budget impact analyses showed net costs of implementing Oncotype DX (compared to no gene-profiling test) for node negative patients, and net savings for postmenopausal node positive patients, each of the five years following implementation. The budget impact analysis for the entire population showed net costs each of the five years. The analyses are associated with uncertainty.

Discussion

Four RCTs demonstrated that Oncotype DX predicted chemotherapy benefit for node negative and postmenopausal node positive breast cancer patients. The RCTs were well designed and risks of bias were deemed low. Together the four RCTs provided convincing evidence, and this represent a major strength.

The gene profiling test Prosigna was approved for node negative patients by the Norwegian Decision Forum in 2019, and is now implemented in clinical practice. Oncotype DX thus represents an alternative to Prosigna for node negative patients, but Oncotype DX was not compared with Prosigna in the submitted documentation or in this STA. No gene-profiling test is currently recommended for node positive patients in Norway. Oncotype DX may thus fulfill an unmet need for postmenopausal patients with node positive disease. Results from Oncotype DX may also be combined with traditional clinical parameters such as tumor grade, tumor size, proliferation status, and lymph node status, but it is not clear how the different parameters should be weighted in possible combinations.

The cost-effectiveness and budget impact analyses were conducted by integrating various sources of evidence and assumptions, which may have contributed to overall uncertainty in the model. The most important sources of uncertainty were regarding the distribution of RS, and that the different studies used different thresholds for which patients to offer adjuvant chemotherapy.

Conclusion

Oncotype DX predicted 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). In these groups, patients with low or intermediate RS (0-25) did not show chemotherapy benefit and could omit chemotherapy to reduce side-effects, whereas patients with high RS (>25) showed chemotherapy benefit and should be offered chemotherapy to reduce the risk of recurrence. The distribution of RS in breast cancer populations suggested that chemotherapy use can be substantially reduced. Decision-impact studies demonstrated that Oncotype DX can reduce chemotherapy assignment in clinical practice, but also illustrated that treatment decisions were not based entirely on RS.

Oncotype DX seems to be more effective and less costly compared to no gene-profiling test. Sensitivity analyses confirmed that Oncotype DX is probably cost-effective, also at low thresholds of willingness-to-pay. As the two tests were not compared, it remains unclear whether Oncotype DX is more cost-effective than Prosigna for node negative patients in Norway.

The budget impact analysis for node negative patients indicate incurred net costs in the five years after implementation, but this analysis is of limited relevance since Oncotype is compared to no gene-profiling test, rather than Prosigna. Implementation of Oncotype DX for postmenopausal lymph node positive patients seems to be cost saving the first five years.

Sammendrag (Norwegian summary)

Innledning

Pasienter med tidlig stadie brystkreft gjennomgår kirurgi for å fjerne primærtumoren. Etter operasjon blir pasienter som er østrogen reseptor positive (ER+) og human epidermal vekst faktor reseptor 2 negative (HER2-) rutinemessig behandlet med hormonterapi, med eller uten kjemoterapi, for å forhindre tilbakefall. Kjemoterapi forårsaker bivirkninger og bør derfor helst bare tilbys pasienter som har nytte av behandlingen.

I denne hurtige metodevurderingen har vi vurdert genprofileringstesten Oncotype DX. Testen beregner en risikoskår (Recurrence Score, RS) mellom 0 og 100, og er ment å estimere risiko for tilbakefall og predikere om brystkreftpasienter vil ha nytte av kjemoterapi. Metodevurderingen er basert på dokumentasjon levert av Oecona på vegne av produsenten av Oncotype DX, Exact Sciences.

Hensikt

Hensikten med metodevurderingen var å vurdere kunnskapsgrunnlaget for følgende spørsmål: (1) Kan Oncotype DX predikere kjemoterapinytte? (2) Gir Oncotype DX prognostisk informasjon? (3) Hva er fordelingen av RS i brystkreftpopulasjoner? (4) Kan Oncotype DX redusere bruken av kjemoterapi?

Vi har også vurdert innsenders analyser av kostnadseffektivitet og budsjettkonsekvenser.

Metode

Klinisk effekt: Vi utførte et eget litteratursøk for å vurdere om alle randomiserte studier (RCT-er) som omhandler spørsmål 1 var identifisert og inkludert av innsender. Vi hentet ut data fra RCT-ene og vurderte risiko for systematiske skjevheter. Vi brukte GRADE-tilnærmingen for å vurdere tilliten til resultatene. Vi hentet ut data fra RCT-er og ikke-randomiserte studier for å vurdere den innsendte dokumentasjonen for spørsmål 2, 3 og 4.

Helseøkonomi: Den helseøkonomiske modellen fra innsender kombinerte et beslutningstre og en Markov-modell for å sammenligne Oncotype DX test med tradisjonell vurdering av kliniske parametere (ingen genprofileringstest). Pasienter ble fordelt i tre RS-grupper med henholdsvis lav, middels eller høy RS, og i hver RS-gruppe fikk pasien-

ter enten kjemoterapi eller ikke. Gruppene ble tilknytteten Markov-modell som beregnet kvalitetsjusterte leveår (QALYs) og kostnader i en livslang tidshorisont, som hensyntok risiko for tilbakefall. Innsender utførte også sensitivitetsanalyser og budsjettkonsekvensanalyser.

Resultater

Klinisk effekt: Innsender identifiserte fire RCT-er som undersøkte om Oncotype kan predikere kjemoterapinytte for pasienter med ER+ HER- tidlig stadie brystkreft. To av RCT-ene undersøkte pasienter uten involverte lymfeknuter, og to undersøkte pasienter med 1-3 involverte lymfeknuter. Vi fant ikke flere RCT-er i vårt separate litteratursøk.

For node-negative pasienter (uavhengig av menopausal status) og for postmenopausale node-positive pasienter, fant vi overbevisende dokumentasjon for at:

- Pasienter med lav eller middels RS (0-25) har lik risiko for tilbakefall uavhengig av om de har blitt behandlet med hormonterapi pluss kjemoterapi eller hormonterapi alene (har ikke nytte av kjemoterapi). Det er imidlertid observert en begrenset gevinst av kjemoterapi blant node-negative kvinner under 50 år og RS på 16-25.
- Pasienter med høy RS (>25) som har blitt behandlet med hormonterapi pluss kjemoterapi har lavere risiko for tilbakefall enn de som har blitt behandlet med hormonterapi alene (har nytte av kjemoterapi).

RCT-er og ikke-randomiserte studier viste at Oncotype DX gir prognostisk informasjon. Fordelingene av RS tydet på at 75-90 % av pasientene med node-negativ og node-positiv sykdom har lav eller middels RS (0-25), og kan slippe kjemoterapi. Observasjonsstudier bekreftet at bruk av Oncotype DX reduserte kjemoterapibruk med 16-27 % for node-negative pasienter, og 50-73 % for node-positive pasienter. Studiene viste også at valg av behandling ikke utelukkende var basert på RS-verdier.

Helseøkonomi: Kostnadseffektivitetsanalysen indikerte at Oncotype DX var dominant sammenlignet med tradisjonell vurdering av kliniske parametere (ingen genprofileringstest) for både node-negative og postmenopausale node-positive pasienter (dvs. større QALY-gevinst til lavere kostnad). Enveis sensitivitetsanalyser viste at de viktigste kildene til usikkerhet i modellen var hazard ratio for høy RS-gruppen hos node-negative pasienter, og hazard ratio for lav og middels RS-gruppen hos postmenopausale node-positive pasienter. Om man antar en betalingsvillighet på 250 000 kroner per QALY så viste probabilistiske sensitivitetsanalyser at Oncotype DX hadde en sannsynlighet på 99 % og 100 % for å være kostnadseffektiv (sammenlignet med ingen genprofileringstest) for henholdsvis node-negative og postmenopausale node-positive pasienter. Absolutt prognosetap ble beregnet til 1,83 kvalitetsjusterte leveår.

Budsjettkonsekvensanalysene viste at sammenlignet med ingen genprofileringstest vil implementering av Oncotype DX gi netto merkostnader for node-negative pasienter og netto besparelser for node-positive postmenopausale pasienter i hvert at de fem første årene etter implementering. Budsjettkonsekvensanalysen for hele populasjonen viste netto merkostnader i hvert av de fem årene etter implementering. Analysene er forbundet med usikkerhet.

Diskusjon

Fire RCT-er viste at Oncotype DX predikerte kjemoterapinytte for brystkreftpasienter som er node-negative eller postmenopausale og node-positive. RCT-ene var godt designet og hadde lav risiko for systematiske skjevheter. Til sammen ga de fire RCT-ene overbevisende dokumentasjon, noe som er en stor styrke.

Beslutningsforum godkjente i 2019 genprofileringstesten Prosigna til bruk blant node-negative pasienter, og Prosigna er nå implementert i klinisk praksis. For node-negative pasienter representerer derfor Oncotype DX et alternativ til Prosigna, men Oncotype DX ble ikke sammenlignet med Prosigna i den innsendte dokumentasjonen eller i denne hurtige metodevurderingen. Når det gjelder node-positive pasienter foreligger per i dag ingen anbefaling om bruk av genprofileringstest i Norge, så for postmenopausale node-positive pasienter kan Oncotype DX fylle et udekket behov. Resultater fra genprofileringstester kan også kombineres med tradisjonelle kliniske parametere som tumorgrad, tumorstørrelse, proliferasjonstatus og lymfeknutestatus, men det er uklart hvordan de ulike parameterne eventuelt skal vektes i slike kombinasjoner.

Kostnadseffektivitets- og budsjettkonskevensanalysene ble utført ved å bruke ulike kilder og foutsetninger, noe som kan ha bidratt til generell usikkerhet i modellen. De viktigste usikkerhetskildene var knyttet til fordeling av RS, og at ulike studier har benyttet ulike terskelverdier for hvilke pasienter som tilbys adjuvant kjemoterapi.

Konklusjon

Oncotype DX predikerer kjemoterapinytte hos pasienter med ER+ HER- tidlig stadie brystkreft som er node-negative (uavhengig av menopausal status) eller postmenopausale og node-positive (1-3 lymfeknuter). Pasienter med lav eller middels RS (0-25) har ikke kjemoterapinytte og kan derfor slippe kjemoterapi for å unngå bivirkninger. Pasienter med høy RS (>25) har kjemoterapinytte og bør tilbys kjemoterapi for å redusere risikoen for tilbakefall. Fordelingen av RS i brystkreftpopulasjoner tyder på at bruken av kjemoterapi kan reduseres betydelig. Studier har vist at Oncotype DX kan redusere bruk av kjemoterapi i klinisk praksis, men også at valg av behandling ikke utelukkende ble basert på RS.

Oncotype DX synes å være mer effektiv og mindre kostbar enn ingen genprofileringstest. Sensitivitetsanalyser bekrefter at Oncotype DX sannsynligvis er kostnadseffektiv, også med lave terskler for betalingsvillighet. Ettersom de to testene ikke ble sammenlignet, er det uklart om Oncotype DX er mer kostnadseffektiv enn Prosigna for bruk blant node-negative pasienter i Norge.

Budsjettkonskevensanalysen for node-negative pasienter indikerer økte nettokostnader i de fem første årene etter implementering, men analysen har begrenset relevans siden Oncotype DX sammenlignes med ingen genprofileringstest heller enn Prosigna. Implementering av Oncotype DX for postmenopausale node-positive pasienter ser ut til å være kostnadsbesparende i de fem første årene.

Preface

The Division of Health Services at the Norwegian Institute of Public Health (NIPH) was commissioned in September 2021 to perform a single technology assessment of the gene-profiling test Oncotype DX for predicting chemotherapy benefit in women with early-stage invasive breast cancer classified as ER+ and HER2-. The single technology assessment was commissioned within the National System for Managed Introduction of New Health Technologies. The commissioner is comprised by the executive directors from the four regional health authorities in Norway.

In a single technology assessment, the technology (a pharmaceutical or a device) is appraised based on documentation submitted by the company owning the technology, or their representatives ("the submitter"). The submitter in this assessment is Oecona on behalf of Exact Sciences.

The submitter provided a submission file in August 2022. NIPH concluded that there were several shortcomings in the submission and requested further explanations and assessments. After some communication and clarification, NIPH offered the submitter to provide revised documentation that addressed a list of specific requirements. In February 2023, the submitter provided revised documentation and this was accepted by NIPH. A progress log that details the communication and progress is provided in Appendix 4.

Contributors
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- Jon-Vidar Gaustad (clinical effectiveness)
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Patient representative:

- Ellen Harris Utne, Chairman of the Board, the Norwegian Breast Cancer Association

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Conflicts of interest

All authors, external experts, and patient representative have completed a conflict of interest form, and no conflicts of interest have been reported.

The NIPH is solely responsible for the content of this report.

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Glossary/list of abbreviations

AML, acute myloid leukemia
AS, absolute shortfall
CI, confidence interval
ER, estrogen receptor
EC+D, epirubicin and cyclophosphamide plus docetaxel
EC+P, epirubicin and cyclophosphamide plus paclitaxel
EQ-5D-3L, EuroQol, five dimensions 3 levels
DFS, disease-free survival
DRFI, distant recurrence-free interval
DRFS, distant recurrence-free survival
DRG, diagnosis-related group
HER2, human epidermal growth factor receptor 2
HR, hazard ratio
HRQoL, health related quality of life
HTA, health technology assessment
ICER, incremental cost-effectiveness ratio
IDFS, invasive disease-free survival
LN0, lymph node negative disease
LN+, lymph node positive disease (1-3 lymph nodes)
NMB, net monetary benefit
NICE, National Institute of Health and Care Excellence
NIPH, Norwegian Institute of Public Health
NOK, Norwegian kroner
NoMA, Norwegian Medicines Agency
OS, overall survival
PR, progesterone receptor
RCT, randomized controlled trial
RFS (DL), recurrence-free survival (distant and local)
RS, recurrence score
SE, standard error
STA, single technology assessment
QALY, quality-adjusted life-year
SR Tool, SearchRefinery
WTP, willingness-to-pay

Background

Breast cancer

Breast cancer is the most common type of cancer in women and constitutes 23% of all diagnosed cancers among females in Norway (1). Since the 1950s the incidence rate of breast cancer has doubled, and there has been an increase also the last 10 years. In 2022, 4224 women were diagnosed with breast cancer in Norway (1). Breast cancer primarily affects women above the age of 50, and the median age at diagnosis is 62 years (1;2). The five-year relative survival for women with breast cancer is 93% when all stages are considered, but only 39% if the cancer has spread to other organs (stage IV breast cancer) (1).

Early-stage breast cancer patients undergo surgery (mastectomy or breast conserving surgery with or without neoadjuvant treatment) to remove the primary tumor. Subsequently, some patients are treated with hormone therapy, chemotherapy, radiation therapy or a combination of these to prevent future breast cancer recurrence. The identification of certain biomarkers expressed by the tumor cells are important in determining the best treatment for individual patients (2). For this purpose, the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) are routinely assessed to classify patients (2). Early-stage breast cancer patients that are classified as ER+ and HER2- are routinely treated with hormone therapy with or without chemotherapy, after surgery (2). Chemotherapy leads to short and long-term side-effects that can severely reduce quality of life, and should ideally only be offered to patients that benefit from the treatment.

Traditionally, the choice of adding chemotherapy has been made based on clinical pathological parameters such as tumor grade, tumor size, proliferation status (Ki-67-score), and lymph node status. Lately, several gene profiling tests have been developed to provide decision support for breast cancer, including Oncotype DX, Prosigna, EndoPredict, MammaPrint, and IHC4 (3). In 2019 NIPH conducted a single technology assessment (STA) of the Prosigna test (4). The STA found convincing evidence of a correlation between the risk stratification score generated by the Prosigna test and the actual observed risk of recurrence, implying that the Prosigna test provided prognostic information. Evidence that patients classified as having a high risk by the Prosigna test, actually benefitted from chemotherapy was not provided. Nevertheless, the National System for Managed Introduction of New Health Technologies in Norway recommended using the Prosigna test for ER+ HER2- breast cancer patients with lymph node negative disease. Furthermore, national clinical practice guidelines have been made for

breast cancer patients with a Prosigna test score, as well as for breast cancer patients without a Prosigna test score (2).

Oncotype DX

Oncotype DX is a gene profiling test intended to estimate the risk of recurrence, and to predict whether breast cancer patients will benefit from chemotherapy. The test calculates a Recurrence Score (RS) between 0 and 100, and classifies patients as having low (0-10), intermediate (11-25), or high RS (>25).

The intended populations for the Oncotype DX test are:

1. Early stage breast cancer patients classified as ER+ HER2- with lymph node negative disease, regardless of menopausal status.
2. Early stage breast cancer patients classified as ER+ HER2- with lymph node positive disease (1-3 lymph nodes), who are postmenopausal.

According to the submission file, the RS has been shown to reflect the risk of distant recurrence in these populations, and it has been demonstrated that only patients with a high RS benefit from chemotherapy. The Oncotype DX test is thus intended to identify patients that will not benefit from chemotherapy (patients with low or intermediate RS). These patients can avoid chemotherapy and chemotherapy-induced side-effects without increasing the risk of recurrence (reduce overtreatment). The Oncotype DX test is also intended to identify patients that will benefit from chemotherapy (patients with high RS). These patients should receive chemotherapy to reduce the risk of recurrence (avoid undertreatment).

The Oncotype DX test quantitatively measures the expression of 21 genes (16 cancer-related genes and five reference genes) using reverse-transcriptase polymerase chain reaction (RT-PCR) technology. The expression of the 21 genes is used to calculate the RS. The Oncotype DX test is performed on paraffin-embedded, formalin-fixed tumor tissue that has been removed during the original biopsy or surgery. The manufacturer requires that the tissue is shipped to a commercial laboratory located in the US for analysis. According to the submission file, results are provided on a secure online portal on average 7-10 days after the order has been sent. Specific information about the patient is also required, including name, date of birth, sex, diagnosis, and pathological information (lymph-node status, estrogen receptor status, and other information from the post-surgery pathology report). According to the submission file, strict measures are followed to secure privacy, including the GDPR compliance program and regulations for transfers of patient data outside the EU. NIPH has not evaluated these measures or considered possible legal and ethical issues related to the transfer of patient data and patient tissue outside Norway.

Objectives

The submission file described four questions that were investigated:

1. Can Oncotype DX predict chemotherapy benefit?
2. Does Oncotype DX provide prognostic information?
3. What is the distribution of RS in populations of breast cancer patients?
4. Can Oncotype DX reduce chemotherapy use?

We also evaluated cost-effectiveness and budget impact analyses provided by the submitter.

The objective of the current report was to appraise the evidence provided in the submission file addressing these questions, and to evaluate the cost effectiveness and budget impact analysis. Because the Oncotype DX test is intended to aid decisions on whether to add chemotherapy, the most important question was whether the test can predict chemotherapy benefit (question 1).

Literature search

Inclusion criteria

The submission file included studies investigating adult patients (older than 18 years) with early-stage invasive breast cancer (stage I-III), either unspecified in nature or histologically confirmed ER+ HER2-. Both patients with node negative disease (no positive lymph nodes) and patients with node positive disease (1-3 positive lymph nodes) were included.

Randomized controlled trials (RCTs) and observational studies addressing the research questions listed in Table 1 were included.

Table 1. *Research questions investigated in the included studies*

Research questions
Q1. Can Oncotype DX predict chemotherapy benefit?
Q2. Does Oncotype DX provide prognostic information?
Q3. What is the distribution of RS in populations of breast cancer patients?
Q4. Can Oncotype DX reduce chemotherapy use?

The performance of Oncotype DX was compared with that of standard practice for chemotherapy decision-making, including but not limited to combinations of clinical pathological parameters (such as tumor grade, tumor size, proliferation status, and lymph node status) and clinical pathological risk tools (such as PREDICT and the Nottingham prognostic index (NPI)).

Different outcomes were assessed for the different research questions. For question Q1 and Q2, various survival outcomes were included (such as distant recurrence-free survival, distant recurrence-free interval, invasive disease-free survival, disease-free survival, breast cancer specific survival, and overall survival). Only survival outcomes following a follow-up period of at least three years were included. For question Q3 and Q4, studies reporting distributions of RS and chemotherapy use were included.

Literature search and selection of studies in the submission file

The National Institute of Health and Care Excellence (NICE) evaluated five gene profiling tests (Oncotype DX, Prosigna, EndoPredict, MammaPrint, and IHC4) in an HTA published in 2019 (3). This HTA was based on a systematic literature search conducted in 2017. According to the current submission file, the NICE search broadly had two sets of terms: (1) synonyms of "breast cancer", and (2) synonyms of the gene profiling tests "Oncotype DX", "Prosigna", "EndoPredict", "MammaPrint", and "IHC4". The NICE search identified 2330 references, and 153 of these were included in the NICE HTA.

The search constructed by the authors of the NICE HTA was repeated twice for the current submission file (April 2020 and July 2022). The following databases were searched: Medline, Embase (OvidSP), Cochrane Database of Systematic Reviews, Epistemonikos Database, Cochrane CENTRAL Register of Controlled Trials, NIH Clinicaltrials, and WHO International Clinical Trials Registry Platform. Detailed search strings for the Medline searches are shown in Appendix 1. The submitter identified 3586 references and included 358 references that were published after the NICE HTA. The total number of included references was thus 511 (153 + 228 + 130; Figure 1).

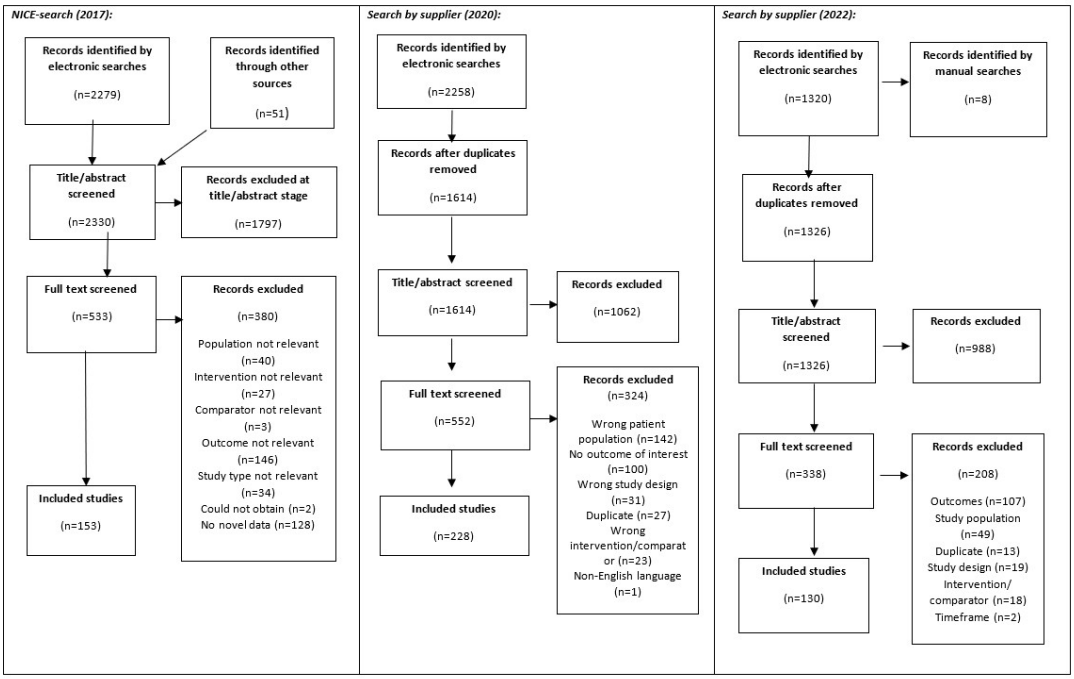

Figure 1. *Flow charts of the literature search performed by NICE (left side), and the two updates of the search performed by the submitter (middle and right side). The illustration is taken from the submission file.*

After the initial selection, the submitter used a hierarchy to rank references according to the strength of the evidence. The hierarchy was used in a second selection, i.e., to select studies to be described in the submission file. For instance, for research question Q1 (Table 1), phase III prospective RCTs were considered to provide the highest level of evidence (Criteria level 1a), and studies that reported RS ranges according to the novel RS thresholds were chosen rather than studies that used old RS thresholds (Criteria level 1b). The full hierarchy for question Q1 is shown in Figure 2.

Criteria level 1a: Study design	1. Phase III (prospective RCT) study
	2. Phase II (prospective/retrospective RCT) study
	3. Prospective national-level real-world registry
Criteria level 1b: RS ranges	1. RS ranges in line with Phase III study
	2. RS ranges similar to Phase III study
	3. RS ranges in line with Phase II study
Criteria level 2a: Geographical region	1. Europe
	2. Ex-US
	3. US
Criteria level 2b: Sample size	1. Largest sample size
Criteria level 2c: Year of publication	1. Most recent

Figure 2. *Hierarchy used to rank references according to the strength of the evidence. This hierarchy was used to rank references addressing question Q1 (Table 1) and the illustration was taken from the submission file.*

After ranking the included references, the submitter selected and described 33 references. Unfortunately, this second selection is poorly described in the submission file. Lists of the included references with brief explanations of whether (or not) the references were selected for description were provided by the submitter. However, there are multiple discrepancies between the number of references in these lists and the numbers stated in the submission file text and flow charts. Taken together, it is hard to evaluate whether all relevant references have been identified and selected in the two selection processes.

Oncotype DX is intended to aid decisions on whether to add chemotherapy. The most important question is thus whether the test can predict chemotherapy benefit (Q1; Table 1). The submitter included and described four RCTs addressing this question. To evaluate whether all relevant RCTs addressing this question were identified and selected for description, NIPH performed a separate literature search as described below.

NIPH's literature search and selection

NIPH used the SearchRefinery tool within Systematic Review Accelerator (5) to create a simple search string that identified all the RCTs found by the submitter. Five references (6-10) describing the four included RCTs were used as seed articles in the SearchRefinery tool. An initial search string was constructed based on the submitter's literature search strategy, and this search string was optimized within the SearchRefinery tool to reduce the number of irrelevant references without losing any of the seed articles. After several iterations, a simple search string consisting of the terms "breast cancer", three synonyms for the Oncotype test ("oncotype", "oncotype dx", and "21-gene"), and the term "recurrence score" was chosen, and a simple literature search was performed (Search string: ("breast cancer"[af]) AND (oncotype[af] OR "oncotype

dx"[af] OR "21-gene"[af]) AND ("recurrence score"[af])). The literature search was performed in April 2023 and identified 667 references.

EPPI-Reviewer (11) was used to screen the identified references. Two reviewers screened the references independently, and disagreements were solved by discussion. 641 references were excluded based on titles and abstracts, and 12 references were excluded after full text review (Figure 3). Eight references were included after full text review (6-10;12-14). All these references described the four RCTs found by the submitter. Consequently, no additional RCTs were identified in NIPH's separate search. NIPH thus consider that it is likely that all RCTs addressing research question Q1 (Table 1) have been identified and included.

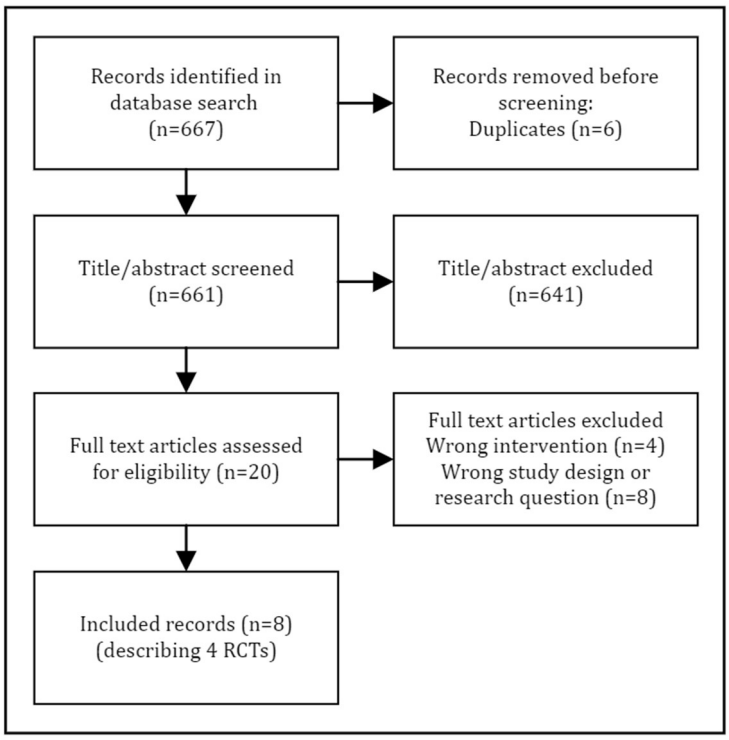

Figure 3. Flow chart of the literature search and selection performed by NIPH.

Evaluation of clinical effectiveness

Description of included studies

Populations in the included RCTs

The four included RCTs investigated women with early-stage breast cancer (grade I-III or histologic grade low-high). Two RCTs (NSABP B-20 and TailorX) investigated women with node negative disease, and two RCTs (SWOG-8814 and RxPONDER) investigated women with node positive disease (1-3 positive lymph nodes). The tumors were ER+ and/or PR+, and HER- (Table 2). Three RCTs (NSABP B-20, TailorX, and RxPONDER) included both pre- and postmenopausal women, whereas one RCT (SWOG-8814) included postmenopausal women. All RCTs included broad age groups, and the mean or median age of the included women varied from 51 to 60 years (Table 2). The women had previously had their primary tumor removed by surgery in all RCTs.

Table 2. *Description of the included RCTs (n = 4)*

Study (Reference)	Population	Intervention	Comparison	Outcome
Node negative disease				
NSABP B-20 (6)	Breast cancer, grade I-III, ER+, HER-, median age 51 years (range 28-74), pre- and postmenopausal, pretreatment: surgery +RT	Tamoxifen + chemotherapy** (n = 365)	Tamoxifen (n = 204)	10-years DRFS
TailorX (8)	Breast cancer, histologic grade low-high, ER+ and/or PR+, HER-, median age 55 years (range 23-75), pre-and postmenopausal, pretreatment: surgery	Endocrine therapy* + chemotherapy** (n = 3312)	Endocrine therapy* (n = 3399)	5- and 9-years DRFS, IDFS, RFS(DL), OS
Node positive disease				
SWOG-8814 (9)	Breast cancer, grade I-III, 1-3 pos. nodes, ER+ and/or PR+, HER-, mean age 60.4 years (SD 7.5), postmenopausal, pretreatment: surgery	Tamoxifen + chemotherapy** (n = 219)	Tamoxifen (n = 148)	5- and 10-years DFS, OS, BCSS
RxPONDER (10)	Breast cancer, histologic grade low-high, 1-3 pos. nodes, ER+ and PR+, HER-, median age 57.5 years (range 18.3–87.6),	Endocrine therapy* + chemotherapy** (n = 2487)	Endocrine therapy* (n = 2497)	5-years IDFS, DRFS

	pre-and postmenopausal, pretreatment: surgery		

*, more than 80% of postmenopausal women received aromatase inhibitor and about 80% of premenopausal women received tamoxifen alone or tamoxifen followed by aromatase inhibitor; **, chemotherapy regimens varied between the RCTs and are detailed below;
Abbreviations: SD, standard deviation; RT, radiotherapy; DRFS, distant recurrence-free survival; IDFS, invasive disease-free survival; RFS (DL), recurrence-free survival (distant and local); OS, overall survival; DFS, disease-free survival; BCSS, breast cancer specific survival.

Intervention and comparison in the included RCTs

Women were randomized to endocrine therapy plus chemotherapy (intervention group) or endocrine therapy alone (comparison group), in all RCTs (Table 2). The chemotherapy regimens varied between the RCTs. Cyclophosphamide, methotrexate, and fluorouracil, or methotrexate and fluorouracil was used in NSBAP B-20. Anthracycline with or without taxane, or taxane and cyclophosphamide was used in TailorX. Anthracycline-based chemotherapy was used in SWOG-8814, and the preferred chemotherapy regimen was anthracycline and taxane for premenstropausal women and taxane and cyclophosphamide for postmenopausal women in RxPONDER. Endocrine therapy involved tamoxifen in NSABP B-20 and SWOG-8814 (Table 2). In TailorX and RxPONDER, more than 80% of postmenopausal women received aromatase inhibitor and about 80% of premenopausal women received tamoxifen alone or tamoxifen followed by aromatase inhibitor.

Outcomes in the included RCTs

Overall survival was reported in two RCTs (TailorX and SWOG-8814), and distant recurrence-free survival was reported in three RCTs (NSABP B-20, TailorX, and RxPONDER). TailorX and RxPONDER also reported invasive disease-free survival, and SWOG-8814 also reported disease-free survival and breast cancer specific survival (Table 2).

Methodological quality

Methodological quality in RCTs

The methodological quality of RCTs was assessed using the RoB 2 checklist (15) in the submission file. The assessments were made on a study level rather than for individual outcomes. NIPH repeated the assessments for individual outcomes which is the recommended approach according to Cochrane (16). The assessments were identical for several outcomes of interest, and the overall risk of bias assessed by NIPH differed little from the overall risk of bias assessed by the submitter. Below, the assessments made by NIPH are presented.

The included RCTs had low risk of bias in most domains (Figure 4). However, the randomization process was insufficiently described in NSABP B-20 and RxPONDER, which led to some concerns in domain 1 for these studies. Furthermore, patients and carers were aware of the treatment group, or the blinding was insufficiently described in all RCTs. One can argue that it is hard to blind patients and carers in studies investigating

chemotherapy, because chemotherapy is delivered intravenously and results in easily recognized side effects. Nevertheless, the lack of blinding led to some concerns in domain 2 for TailorX (Figure 4). Lack of blinding may also lead to risk of bias in measurement of outcomes (domain 4). However, we consider that knowledge of treatment groups probably did not influence assessment of outcomes in the included RCTs, because the evaluated outcomes were various survival outcomes that are objective rather than subjective judgements. NSABP B-20 described a study protocol, but no reference to the protocol was provided in the papers, and the protocol was not found on "clinicaltrials.gov". Consequently, we were unable to evaluate whether NSABP B-20 reported all planned outcomes, which led to some concerns in domain 5. SWOG-8814 and RxPONDER did not report toxicities and/or overall survival which were listed outcomes in the study protocols, and thus also had some concerns in domain 5 (Figure 4).

The largest and most recent RCTs (TailorX and RxPONDER) were funded by the National Cancer Institue and other governmental sources, whereas the smaller RCTs (NSABP B-20 and RxPONDER) were partly funded by National Cancer Institue and partly by Genomic Health Inc. (the former manufacturer of Oncotype DX). We have not assessed that the partial funding by the industry pocess additional risk of bias.

Study (Reference)	Outcome assessed	Domain 1: Risk of bias arising from the randomization process	Domain 2: Risk of bias due to deviations from the intended interventions	Domain 3: Risk of bias due to missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result	Overall risk of bias
NSABP B-20 (6)	DRFS						
TailorX (8)	DRFS, IDFS, RFS(DL), OS						
SWOG-8814 (9)	DFS, OS, BCSS						
RxPONDER (10)	IDFS, DRFS						

Figure 4. *Risk of bias in the included RCTs. Green indicates low risk, and yellow indicates some concerns. None of the studies had high risk of bias in any domains (which would have been indicated by red color). Abbreviations: DRFS, distant recurrence-free survival; IDFS, invasive disease-free survival; RFS (DL), recurrence-free survival (distant and local); OS, overall survival; DFS, disease-free survival; BCSS, breast cancer specific survival.*

Methodological quality in non-randomized studies

The submission file included risk of bias assessment of non-randomized studies according to the ROBINS-I-checklist (17). NIPH assessed that the submitted ROBINS-I profiles included many errors and methodological shortcomings. Hence, the submitted ROBINS-I profiles for non-randomized studies were not used as a basis for our further work.

Q1. Can Oncotype DX predict chemotherapy benefit?

RCTs investigating node negative disease

NSABP B-20

NSABP B-20 originally enrolled 2363 patients with node negative breast cancer who were randomly assigned to endocrine therapy plus chemotherapy or endocrine therapy alone. Blocks containing sufficient cancer tissue were available for 670 patients, and RS-score was obtained in 651 patients. Distant recurrence-free survival for patients with low, intermediate, and high RS according to the original RS-thresholds were reported by Paik et al. (7). Later, Geyer et al. (6) excluded patients with HER+ tumors and reanalyzed the remaining 569 patients using both the original RS-thresholds as well as the new RS-thresholds that were introduced in the TailorX study (8). Here we present results obtained using the new RS-thresholds. Patients with low RS (0-10) and intermediate RS (11-25) showed similar 10-years distant recurrence-free survival regardless of whether they were treated with endocrine therapy plus chemotherapy or endocrine therapy alone (Hazard ratios: 1.19, 95% CI 0.41-3.51 (low RS) and 0.61, 95% CI 0.26-1.35 (intermediate RS); Table 3). For patients with high RS (>25), 10-years distant recurrence-free survival was higher for patients that were treated with endocrine therapy plus chemotherapy compared to patients that were treated with endocrine therapy alone (Hazard ratio: 0.27, 95% CI 0.12-0.62; Table 3). These data demonstrate that patients with high RS benefitted from chemotherapy whereas patients with low and intermediate RS did not. The same conclusion was reached also when the original RS-thresholds were used (6).

Table 3. *10-years distant recurrence-free survival for patients with low, intermediate, and high RS treated with endocrine therapy plus chemotherapy or endocrine therapy alone in NSABP B-20.*

	10-years DRFS (%)		
RS	**Chemoendocrine**	**Endocrine**	**Hazard ratio (95% CI)**
0-10	95 ± 3	98 ± 4	1.19 (0.41–3.51)
11-25	94 ± 2	95 ± 3	0.61 (0.26–1.35)
>25	88 ± 4	62 ± 13	0.27 (0.12–0.62)

Abbreviations: DRFS, distant recurrence-free survival; CI, confidence interval

TailorX

In TailorX, breast cancer patients were assigned to treatment based on their RS. Patients with intermediate RS (RS 11-25, n = 6711) were randomized to receive endocrine therapy alone or endocrine therapy plus chemotherapy. The patients in these treatment groups showed similar survival rates. This applied for various survival outcomes assessed at both 5- and 9-years (9-years survival rates are shown in Table 4). These results demonstrated that patients with intermediate RS did not benefit from chemotherapy.

Furthermore, several exploratory analyses were performed to investigate whether any subgroup within the patients with intermediate RS had any chemotherapy benefit. In-

terestingly, 74% of these patients were at low clinical risk and 26% were at high clinical risk, but neither of the groups showed chemotherapy benefit. This finding demonstrated that the clinical risk did not predict chemotherapy benefit in this patient group. However, the exploratory analyses demonstrated that the benefit of chemotherapy varied with the combination of RS and age and found some chemotherapy benefit in women ≤ 50 years and RS 16-25 (8).

All patients with low RS (RS 0-10, n = 1619) were treated with endocrine therapy alone, and all patients with high RS (RS > 25, n = 1389) received endocrine therapy plus chemotherapy. The study was thus not designed to investigate possible chemotherapy benefit in patients with low or high RS.

Table 4. *9-years survival rates for patients with low, intermediate, and high RS treated with endocrine therapy plus chemotherapy or endocrine therapy alone in TailorX.*

		9-years survival (%)		
	RS	**Chemoendocrine**	**Endocrine**	**Hazard ratio (95% CI)**
DRFS	0 -10	-	96.8 ± 0.7	-
DRFS	11 -25	95.0 ± 0.5	94.5 ± 0.5	1.10 (0.85–1.41)
IDFS	11 -25	84.3 ± 0.8	83.3 ± 0.9	1.08 (0.94–1.24)
RFS(DL)	11 -25	95.0 ± 0.5	94.5 ± 0.5	1.11 (0.90–1.37)
OS	11 -25	93.8 ± 0.5	93.9 ± 0.5	0.99 (0.79–1.22)
DRFS	>25	86.8 ± 1.7	-	-

Abbreviations: DRFS, distant recurrence-free survival; IDFS, invasive disease-free survival; RFS (DL), recurrence-free survival (distant and local); OS, overall survival; CI, confidence interval; NI, no information

Meta-analysis

The submission file did not combine results from NSABP B-20 and TailorX in meta-analysis. NIPH performed a meta-analysis for the patient groups with intermediate RS using the fixed effect model as recommended when few studies are included in meta-analysis. A forest plot displaying the hazard ratios for distant recurrence-free survival is shown in Figure 5.

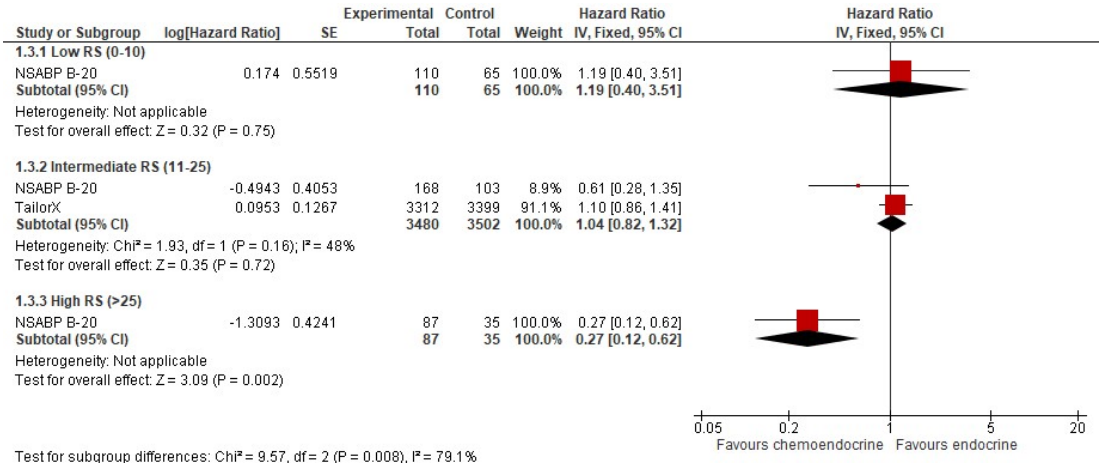

Figure 5. *Hazard ratios for distant recurrence-free survival in breast cancer patients with low, intermediate or high RS, and node negative disease.*

RCTs investigating node positive disease

SWOG-8814

SWOG-8814 investigated postmenopausal women with node positive breast cancer. The patients were randomized to receive chemotherapy plus endocrine therapy or endocrine therapy alone. RS-score was retrospectively obtained in 367 patients in which sufficient tumor tissue was available (40% of the original study population), and the patients were classified according to the original RS-thresholds. Patients with low RS (0-17) showed similar disease-free survival regardless of whether they were treated with chemotherapy plus endocrine therapy or endocrine therapy alone, implying that these patients did not benefit from chemotherapy (Hazard ratio: 1.02, 95% CI 0.54-1.93; Table 5). In the high RS group (>30), patients that were treated with chemotherapy plus endocrine therapy showed higher disease-free survival than those that were treated with endocrine therapy alone, implying that the high RS patients benefitted from chemotherapy (Hazard ratio: 0.59, 95% CI 0.35-1.01; Table 5).

Table 5. *10-years survival rates for patients with low, intermediate, and high RS treated with endocrine therapy plus chemotherapy or endocrine therapy alone in SWOG-8814.*

		10-years survival (%)		
	RS	**Chemoendocrine**	**Endocrine**	**Hazard ratio (95% CI)**
DFS	0-17	64	60	1.02 (0.54–1.93)
	18-30	62	49	0.72 (0.39–1.31)
	>30	55	43	0.59 (0.35–1.01)
OS	0-17	77	76	1.18 (0.55–2.54)
	18-30	76	69	0.84 (0.40–1.78)
	>30	68	51	0.56 (0.31–1.02)

Abbreviations: DFS, disease-free survival; OS, overall survival; CI, confidence interval; NI, no information

A forest plot displaying the hazard ratios graphically is shown in Figure 6. Similar results were obtained for overall survival (Table 5) and breast cancer specific survival (9).

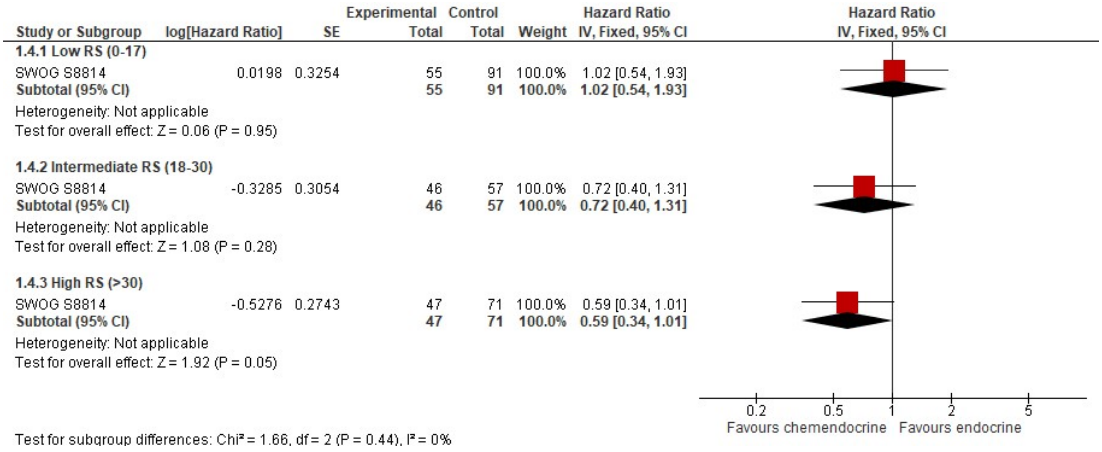

Figure 6. *Hazard ratios for 10-years disease-free survival in postmenopausal breast cancer patients with low, intermediate or high RS, and node positive disease.*

RxPONDER

In RxPONDER, patients with node positive disease and a low or intermediate RS (0-25) were randomly assigned to receive chemotherapy plus endocrine therapy or endocrine therapy alone. Both pre- and postmenopausal women were included, and separate analyses were performed for these groups. The study is still ongoing, but 5-years survival rates have been published (10). Postmenopausal patients showed similar 5-years survival rates regardless of whether they were treated with chemotherapy plus endocrine therapy or endocrine therapy alone (Table 6). Premenopausal patients treated with chemotherapy plus endocrine therapy showed higher survival rates than the premenopausal women that were treated with endocrine therapy alone (Table 6).

Table 6. *5-years survival rates for patients with low and intermediate RS treated with endocrine therapy plus chemotherapy or endocrine therapy alone in RxPONDER.*

	Menopausal status	RS	5-years survival (%)		Hazard ratio (95% CI)
			Chemoendocrine	Endocrine	
DRFS	Post	0-25	94.4	94.4	1.05 (0.81-1.37)
	Pre	0-25	96.1	92.8	0.58 (0.39-0.87)
IDFS	Post	0-25	91.3	91.9	1.02 (0.82-1.26)
	Pre	0-25	93.9	89.0	0.60 (0.43–0.83)

Abbreviations: DRFS, distant recurrence-free survival; IDFS, invasive disease-free survival; CI, confidence interval

A forest plot displaying the hazard ratios for distant recurrence-free survival is shown in Figure 7. Similar results were achieved for both distant recurrence-free survival and invasive disease-free survival (Table 6). The findings imply that postmenopausal woman did not benefit from chemotherapy, whereas premenopausal woman showed a small chemotherapy benefit.

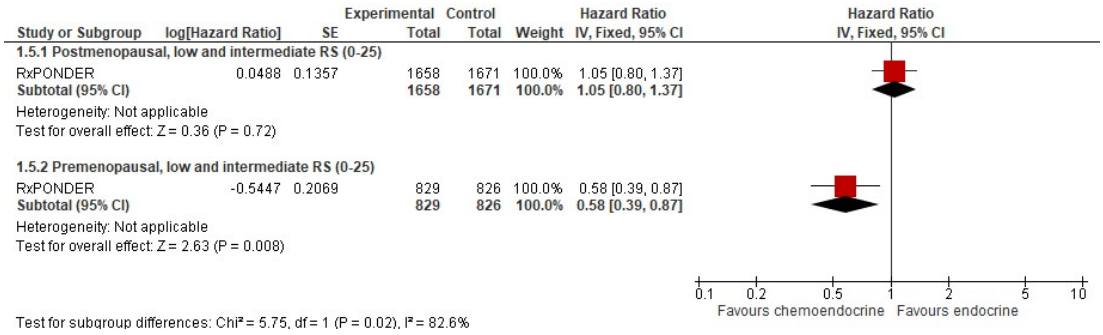

Figure 7. *Hazard ratios for 5-years distant recurrence-free survival in post- and premenopausal breast cancer patients with low and intermediate RS, and node positive disease.*

Meta-analysis

The submission file did not combine results from SWOG-8814 and RxPONDER in meta-analysis. These RCTs differ in outcome, RS-thresholds used, and follow-up (10- years vs 5-years). The submission file argues that it is not meaningful to combine these studies, and NIPH agree.

Non-randomized studies

The submission file also described a large registry-based study investigating whether Oncotype DX can predict chemotherapy benefit (18). This study included 89,402 breast

cancer patients with node negative disease from the SEER registry, USA. In a propensity score-matched analysis, patients with high RS (>25) treated with chemotherapy showed higher breast cancer specific survival than high RS patients who did not receive chemotherapy (hazard ratio = 0.78; 95% confidence interval, 0.62-0.99). In the low RS (0-10) and intermediate RS (11-25) groups, there were no significant differences in breast cancer specific survival between patients who received chemotherapy and those that did not. The study thus confirmed that patients with high RS have a chemotherapy benefit whereas patients with low or intermediate RS does not.

NIPH's certainty in the evidence

We used the GRADE approach (19) to assess certainty of the evidence addressing question Q1 (Can Oncotype DX predict chemotherapy benefit?; Table 1). The GRADE assessments are presented in Table 7.

Table 7. *GRADE evidence profile*

Outcomes	Certainty assessment				Relative effect** (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk of bias	Inconsistency	Indirectness	Imprecision			
Node negative disease							
10y DRFS, low RS (0-10)	not serious*	not serious	not serious	serious[a]	**HR 1.19** (0.40 to 3.51)	175 (1 RCT)	⨁⨁⨁◯ Moderate[a]
9&10y DRFS, IM RS (11-25)	not serious*	not serious	not serious	not serious	**HR 1.04** (0.82 to 1.32)	6982 (2 RCTs)	⨁⨁⨁⨁ High
10y DRFS, high RS (>25)	not serious*	not serious	not serious	not serious	**HR 0.27** (0.12 to 0.62)	122 (1 RCT)	⨁⨁⨁⨁ High
Node positive disease							
5y DFRS, low + IM RS (0-25), postmenopausal	not serious*	not serious	not serious	not serious	**HR 1.05** (0.80 to 1.37)	3329 (1 RCT)	⨁⨁⨁⨁ High
5y DFRS, low + IM RS (0-25), premenopausal	not serious*	not serious	not serious	not serious	**HR 0.58** (0.39 to 0.87)	1655 (1 RCT)	⨁⨁⨁⨁ High
10y DFS, high RS (>30)	not serious*	not serious	not serious	serious[a]	**HR 0.59** (0.34 to 1.01)	118 (1 RCT)	⨁⨁⨁◯ Moderate[a]

GRADE grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations: a, our certainty of the evidence was downgraded one level because the confidence interval was wide and included effect and no effect.

*, all RCTs had some concerns in the Risk of Bias assessment (Figure 1). However, we considered these concerns minor and have not downgraded our certainty of the evidence because of them.

**, absolute effects are shown in Table 3-6.

Abbreviations: DRFS, distant recurrence-free survival; DFS, disease-free survival; CI, confidence interval; HR, hazard ratio; IM, intermediate; y, years.

Q2. Does Oncotype DX provide prognostic information?

Node negative disease

The two RCTs NSABP B-20 and TailorX demonstrated that the Oncotype test provided prognostic information for breast cancer patients with node negative disease. Thus, survival rates decreased with increasing RS, both when patients were treated with endocrine therapy alone and when patients were treated with chemotherapy plus endocrine therapy. This is illustrated for distant recurrence-free survival in Figure 8 and the numerical values are provided in Table 3 and Table 4. Several non-randomized studies that demonstrated the prognostic value of Oncotype in node negative patients were also listed in the submission file (20-22).

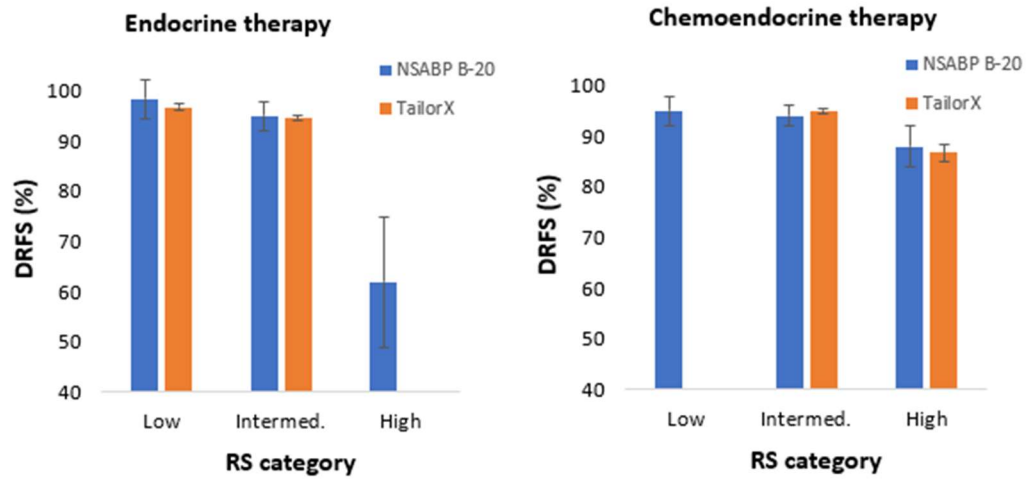

Figure 8. *Distant recurrence-free survival (DFRS) for breast cancer patients with node negative disease and low, intermediate, or high RS. The patients were treated with endocrine therapy alone (left panel), or chemotherapy plus endocrine therapy (right panel).*

Node positive disease

The RCT SWOG-8814 demonstrated that the Oncotype test provided prognostic information for postmenopausal breast cancer patients with node positive disease. Thus, survival rates decreased with increasing RS, both when patients were treated with endocrine therapy alone and when patients were treated with chemotherapy plus endocrine therapy. This is illustrated for disease-free survival in Figure 9 and the numerical values are provided in Table 5. Several non-randomized studies that demonstrated the prognostic value of Oncotype in node positive patients were also listed in the submission file (20;22-24).

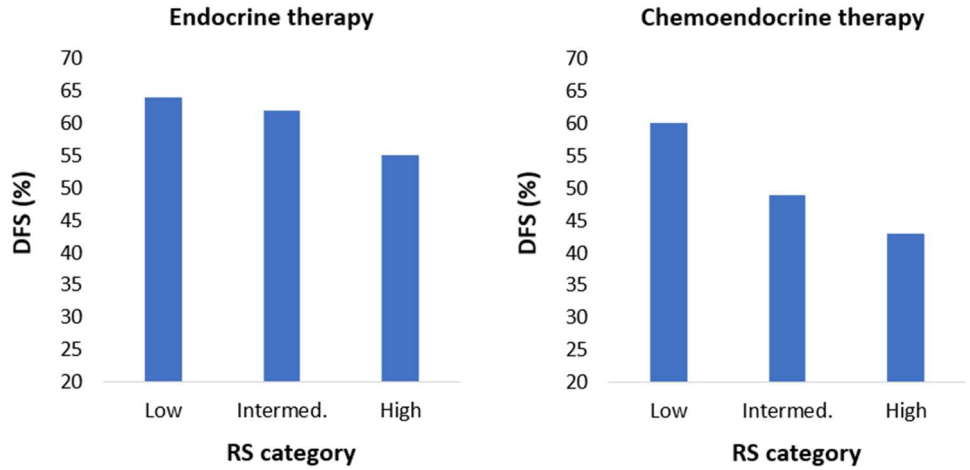

Figure 9. *Disease-free survival (DFS) for postmenopausal breast cancer patients with node positive disease and low, intermediate, or high RS. The patients were treated with endocrine therapy alone (left panel), or chemotherapy plus endocrine therapy (right panel).*

Q3. What is the distribution of RS in populations of breast cancer patients?

Node negative disease

The two RCTs NSABP B-20 and TailorX provided distributions of RS in breast cancer populations with node negative disease. In addition, the submission file listed distributions of RS found in non-randomized studies including large registry studies of breast cancer patients with node negative disease. Below we reproduce the list provided in the submission file (Table 8).

Table 8. *Distribution of RS in breast cancer patients with node negative disease*

	Distribution of RS, n (%)		
Study (reference)	**Low (0-10)**	**Interm. (11-25)**	**High (>25)**
RCTs			
NSABP-B20 (6)	176 (31%)	271 (48%)	122 (22%)
TailorX (8)	1,619 (17%)	6,711 (69%)	1,389 (14%)
Non-randomized studies			
Choi 2020 (18), SEER registry	18,736 (21%)	57,388 (64%)	13,278 (15%)
Ibraheem 2020 (20), N. Cancer Datab.	27,795 (23%)	73,951 (62%)	17,582 (15%)
Stemmer 2019 (23), Clalit registry	243 (18%)	853 (63%)	269 (20%)
Braun 2022 (25)	49 (15%)	206 (61%)	81 (24%)
Glasgow 2021 (26)	133 (22%)	361 (61%)	102 (17%)
Davey 2021 (27)	46 (12%)	294 (74%)	60 (15%)
Del Prado 2020 (28)	78 (23%)	207 (61%)	52 (15%)
Walter 2020 (29)	641 (20%)	2,053 (63%)	569 (17%)

SEER, cancer registry program of the National Cancer Institute (USA); Clalit, Clalit Health Services (Israel); N. Cancer Datab., National Cancer Database USA

Node positive disease

The RCT SWOG-8814 provided distributions of RS based on the original RS-thresholds rather than the novel thresholds. Furthermore, the RCT RxPONDER only included patients with low and intermediate RS (≤25) and thus did not provide the distribution of patients with high RS. However, the submission file listed distributions of RS found in non-randomized studies including a large registry study from the National Cancer Database, USA. Below we show the RS distribution in studies that applied the novel RS thresholds and reported data for breast cancer patients with node positive disease (Table 9). We have extracted the data from the original publications but have not evaluated the methodological quality of the studies. None of the studies reported separate data for postmenopausal women.

Table 9. *Distribution of RS in breast cancer patients with node positive disease*

	Distribution of RS, n (%)		
Study (reference)	**Low (0-10)**	**Interm. (11-25)**	**High (>25)**
Non-randomized studies			
Ibraheem 2020 (20), N. Cancer Datab.	5,936 (24%)	15,920 (64%)	3,173 (13%)
Petkov 2020 (30)	417 (16%)	1821 (70%)	350 (14%)
Kriegmair 2019 (31)	19 (16%)	83 (69%)	19 (16%)
Braun 2022 (25)	36 (17%)	150 (69%)	31 (14%)
Walter 2020 (29)	362 (25%)	922 (64%)	148 (10%)

N. Cancer Datab., National Cancer Database USA

Q4. Can Oncotype DX reduce chemotherapy use?

The Oncotype DX test is expected to reduce chemotherapy use in patients with low and intermediate RS (these patients can omit chemotherapy), and increase chemotherapy use in patients with high RS (these patients will benefit from chemotherapy). However, it is not obvious whether physicians will base assignments to chemotherapy entirely on the Oncotype test, or whether these test results will be considered together with other clinical parameters. Consequently, it is not obvious how the Oncotype test will change chemotherapy assignments, and it is not obvious whether the test will result in a net reduction of chemotherapy use in clinical practice.

The submission file listed three studies reporting chemotherapy assignment before and after Oncotype was applied (32-34). The three studies were multicenter prospective observational decision-impact studies. PONDx (32) and ROXANE (33) included both node positive and node negative patients and were conducted in Italy. Hassan 2022 (34) included node positive patients and was conducted in Canada.

Node negative disease

In PONDx (32), 44% of the node negative patients was assigned to chemotherapy before the Oncotype test result was known and 32% was assigned after the test result was revealed (Figure 10). This implies that chemotherapy assignment was reduced by 27% (Table 10). Furthermore, the authors estimated that only 23% of the patients would have been assigned to chemotherapy if assignments were based entirely on the

Oncotype test. This would have resulted in a 47% reduction in chemotherapy assignment.

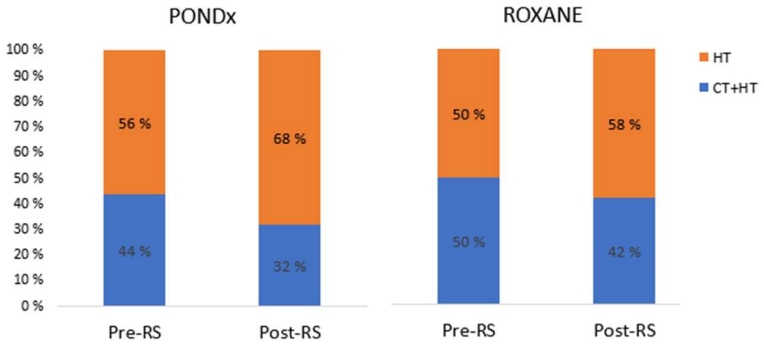

Figure 10. *Chemotherapy assignment before (pre-RS) and after (post-RS) the Oncotype test results were revealed for patients with node negative disease in PONDx (left panel) and ROXANE (right panel). HT, hormone therapy; CT +HT, chemotherapy plus hormone therapy.*

In ROXANE (33), 50% of the node negative patients were assigned to chemotherapy before the Oncotype test result was known and 42% were assigned after the test results were revealed (Figure 10). This implies that chemotherapy assignment was reduced by 16% (Table 10). ROXANE also reported separate data for subgroups with different RS. The subgroup data illustrates that treatment decisions were not based entirely on the RS because some patients with low and intermediate RS were assigned to chemotherapy. The study divided the intermediate RS group in two (11-17 and 18-25), and chemotherapy assignment was reduced in the 11-17 group and increased in the 18-25 group (Table 10).

Table 10. *Chemotherapy assignment before and after Oncotype test in breast cancer patients with node negative disease*

		Chemotherapy assignment, n (%)		
Study (ref.)	**Subpopulation**	**Pre-RS**	**Post-RS**	**Change (%)**
PONDx (32)	All (n=1160)	512 (44%)	374 (32%)	-27%
ROXANE (33)	All (n=152)	76 (50%)	64 (42%)	-16%
	Low RS (0-10, n=32)	18 (44%)	1 (3%)	-94%
	IM RS (11-17, n=nr)	nr (34%)	nr (10%)	-71%
	IM RS (18-25, n=nr)	nr (44%)	nr (54%)	+23%
	High RS (>25, n=38)	30 (79%)	37 (97%)	+23%

Abbreviations: IM, intermediate; RS, recurrence score; nr, not reported

Node positive disease

In PONDx (32), 62% of the patients with node positive disease were assigned to chemotherapy before the Oncotype test result was known, and 28% were assigned after the test result was revealed (Figure 11). This implies that chemotherapy assignment was reduced by 55% (Table 11).

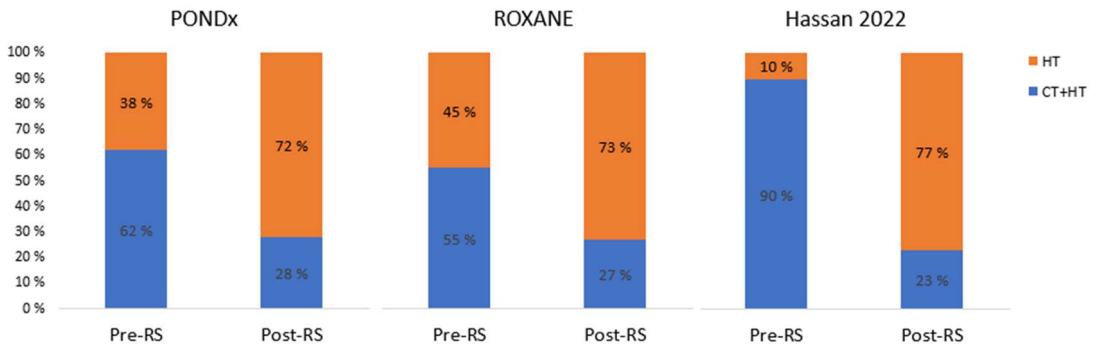

Figure 11. *Chemotherapy assignment before (pre-RS) and after (post-RS) the Ocotype test results were revealed for patients with node positive disease in PONDx (left panel), ROXANE (central panel), and Hassan 2022 (right panel). HT, hormone therapy; CT +HT, chemotherapy plus hormone therapy.*

In ROXANE (33), 55% of the patients with node positive disease were assigned to chemotherapy before the Oncotype test result was known and 27% were assigned after the test result was revealed (Figure 11). This implies that chemotherapy assignment was reduced by 50% (Table 11). ROXANE also reported separate data for subgroups with different RS. The subgroup data illustrates that treatment decisions were not based entirely on the RS because some patients with low and intermediate RS were assigned to chemotherapy. The study divided the intermediate RS group in two (11-17 and 18-25), and chemotherapy assignment was reduced in the 11-17 group and increased in the 18-25 group (Table 11).

In Hassan 2022 (34), 90% of the patients were assigned to chemotherapy before the Oncotype test result was known and 23% were assigned after the test results were revealed (Figure 11). This implies that chemotherapy assignment was reduced by 75% (Table 11). Hassan 2022 also reported separate data for subgroups with different RS. The subgroup data illustrates that treatment decisions were not based entirely on the RS because some patients with low and intermediate RS were assigned to chemotherapy (Table 11).

Table 11. *Chemotherapy assignment before and after Oncotype test in breast cancer patients with node positive disease*

		Chemotherapy assignment, n (%)		
Study (ref.)	**Subpopulation**	**Pre-RS**	**Post-RS**	**Change (%)**
PONDx (32)	All (n=414)	258 (62%)	110 (28%)	-55%
ROXANE (33)	All (n=99)	54 (55%)	27 (27%)	-50%
	Low RS (0-10, n=31)	19 (61%)	3 (10%)	-84%
	IM RS (11-17, n=nr)	nr (49%)	nr (20%)	-59%
	IM RS (18-25, n=nr)	nr (40%)	nr (45%)	+13%
	High RS (>25, n=7)	36 (100%)	44 (100%)	0%
Hassan 2022 (34)	All (n=70)	63 (90%)	16 (23%)	-75%
	Low RS (0-10, n=18)	14 (78%)	1 (6%)	-93%
	IM RS (11-25, n=48)	45 (94%)	11 (23%)	-76%
	High RS (>25, n=4)	4 (100%)	4 (100%)	0%

Abbreviations: IM, intermediate; RS, recurrence score; nr, not reported

Health economic evaluation

Methods

Methods for evaluating submitted cost-effectiveness models

The basic aim of any economic evaluation is to identify, measure and compare costs and consequences of the alternatives under consideration. This is done in an incremental analysis in which the differences in costs between an intervention and its comparator, are compared with differences in health consequences. Economic evaluations support decision making by informing the three criteria for priority setting in the Norwegian health care sector: 1) the benefit criterion, 2) the resource criterion, and 3) the severity criterion (35).

The primary objectives of health economic modelling are to provide a mechanism to determine the relative cost-effectiveness of the specified health intervention(s) compared to standard practice using the best available evidence, and to assess the most important sources of uncertainty surrounding the results. To make comparisons across different health interventions and multiple health outcomes, economic models typically measure health outcomes in terms of quality-adjusted life-years (QALYs). QALY is a variable designed to capture both life extension and health improvement. The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as:

$$(Cost_{Intervention} - Cost_{Comparator}) \,/\, (QALY_{Intervention} - QALY_{Comparator})$$

The intervention is to be compared with the appropriate comparator. The relevant comparator should ideally be the intervention currently used for the population or the intervention that will most likely be completely or partially replaced if the proposed intervention is implemented in clinical practice (36). It is important to use the right comparator in order to get reliable results.

There is no single correct way to build economic models estimating the cost-effectiveness of a specific health intervention. Modelling requires consulting with clinical experts to gain understanding of expected disease progression, and to determine the relevant population, comparators, health outcomes and adverse events connected to each relevant health intervention that will be compared to one another. This information informs the basic model structure and determines which clinical effect data are most important to retrieve in the systematic literature search. Once the

model structure is in place, systematic searches and evidence grading are used to assess the model input parameters and relevant cost and quality of life data that is needed for cost-effectiveness calculations.

A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include sufficient details to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying to answer. Appraisal of health economic model is primarily about determining whether the choices made by the submitter regarding model structure and treatment comparator are reasonable; whether baseline epidemiological data reflect the population in which the analysis is being performed; whether the interventions and subsequent treatment pathways compared in the model are relevant for current clinical practice; whether the clinical effect data used in the model have adequate quality; whether resource use and costs reflect the conditions of the healthcare system in question; whether there has been sufficient sensitivity and scenario analyses to determine the degree and sources of uncertainty in the model results; and whether the model displays external and internal validity.

In this report, we first described the health economic model and model inputs in the manufacturer's submission. We then provided our comments on these aspects. Subsequently, we presented the results generated by the model including sensitivity analyses to examine the extent of uncertainty in the model result. We also commented on the results. We further discussed the findings in the discussion section of this report.

Cost-effectiveness model structure provided by the submitter

The submitter introduced a decision analytic model to evaluate the cost-effectiveness of Oncotype DX compared to no gene-profiling test (assessment of conventional clinical parameters) in Norway. The model, constructed using Microsoft Excel, combines a hybrid decision tree and a Markov model.

The decision tree submitted consisted of two test strategies: 1) Oncotype DX test and 2) no gene-profiling test. Within the Oncotype DX test strategy the patients were categorized into high RS, intermediate RS, or low RS based on the test result. In the no gene-profiling strategy, patients were also categorized into corresponding hypothetical RS groups (i.e., the patients would have had high RS, intermediate RS or low RS if they had performed the Oncotype DX test). For each RS group there were two choices: 1) chemotherapy or 2) no chemotherapy. In the Oncotype DX test strategy, this choice was based on knowledge of the RS and consequently the probability of receiving chemotherapy differed between the RS groups. In the no gene-profiling test strategy, the probability of receiving chemotherapy was identical for the three (hypothetical) RS groups because the RS group status was unknown (since patients did not perform the Oncotype DX test). The (hypothetical) RS group status was thus not considered when treatment was chosen in the no gene-profiling test strategy.

These branches (chemotherapy and no chemotherapy) were connected to a Markov model (models 1-6) that predicts lifetime QALYs and costs, considering the patient's

risk of distant recurrence and whether they receive chemotherapy or not (see Figure 12).

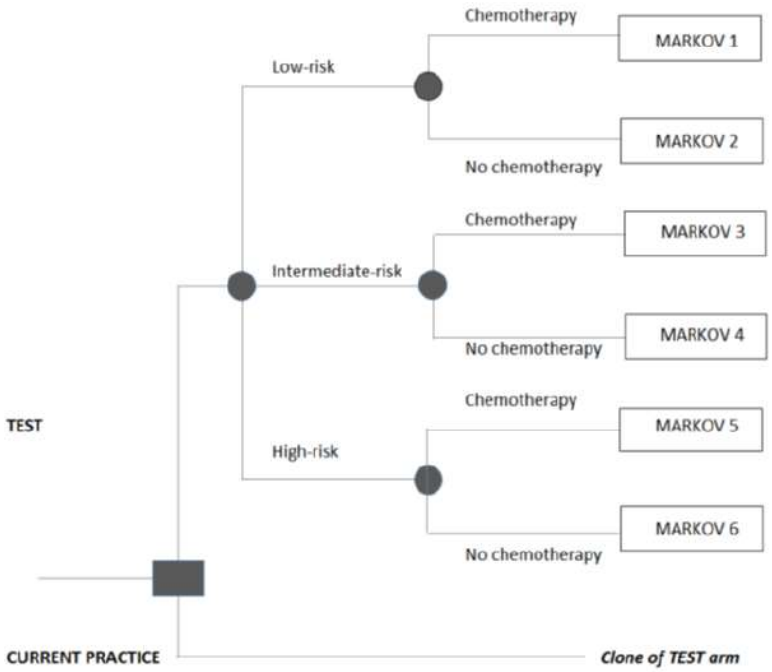

Figure 12. *Decision tree provided by the submitter*
Explanation: Test refers to Oncotype DX, current practice refers to no gene-profiling test, "low-risk" refers to low RS, "intermediate-risk" refers to intermediate RS, and "high-risk" refers to high RS.

The submitted Markov model uses 6-month cycles to track patients throughout their lifetime until they reach 100 years of age. The model comprises four health states: 1) recurrence-free, 2) distant recurrence, 3) acute myloid leukemia, and 4) dead (see Figure 13). The model does not include a separate health state for "local recurrence". The submitter included acute myloid leukemia because it can be a long-term adverse event following chemotherapy (37;38).

Each of the six Markov models varies based on the patient's risk of recurrence, which is determined by their risk classification (high, intermediate, or low RS) and whether they receive adjuvant chemotherapy, as depicted in Figure 12. Patients enter the model in the recurrence-free health state. During any 6-month cycle, patients who are recurrence-free may remain in their current health state, transfer to the acute myloid leukemia state, develop distant recurrence, or die. Patients in the distant recurrence state may stay in that state, transfer to the acute myloid leukemia state, or die. Patients in the acute myloid leukemia state are assumed to remain in that state. The "dead" health state includes patients who have died due to breast cancer, acute myloid leukemia, or other causes.

The submitted model follows the standard Markovian assumption that the prognosis of patients with acute myloid leukemia, as well as the costs and QALYs associated with the acute myloid leukemia state, are independent of whether the patient had previously developed distant recurrence from breast cancer. Once a patient develops acute myloid leukemia, the model assumes that this factor alone determines their survival prognosis.

Although congestive heart failure is a potentially relevant long-term adverse event related to chemotherapy, the submitter excluded it from the model due to a lack of evidence regarding the joint impact of congestive heart failure and metastatic breast cancer on survival.

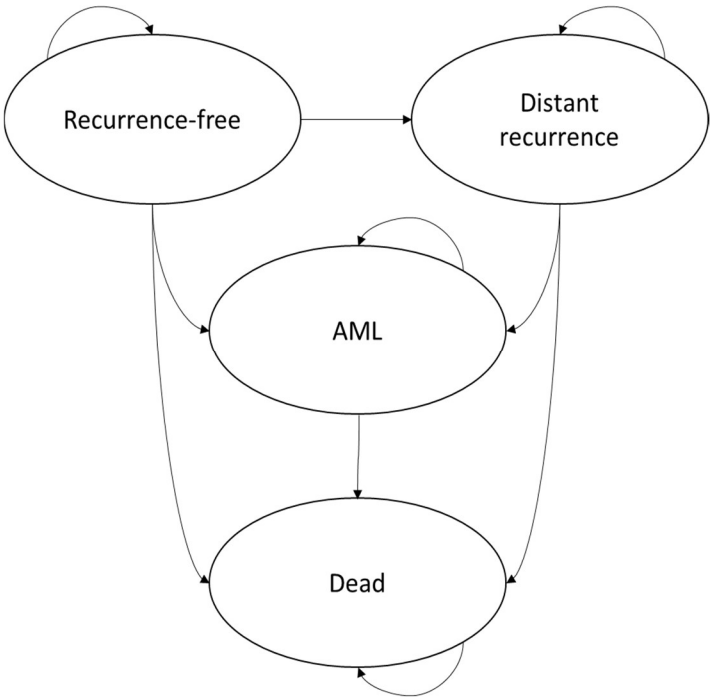

Figure 13. *Markov diagram provided by the submitter*
Abbreviation: AML, acute myloid leukemia

Although breast cancer is typically not classified as a chronic condition, the submitter of the model employed a lifetime time horizon in their analysis. This approach considers the risk of recurrence, which can persist throughout a patient's life.

In the submitted model, both costs and quality-adjusted life years (QALYs) were discounted at an annual rate of 4%. This discounting rate aligns with the guidelines set forth by the Norwegian Directorate of Health (39).

The established model underwent a thorough validation process following existing guidelines (40). The validation comprised the following steps:

1. Face validity: The model's design received input from a diverse advisory board consisting of experts in health economics and clinical practice. This multidisciplinary approach ensured that the model's structure and features were aligned with best practices in the field.
2. Internal validity: The input data and coding of the model were carefully verified by the vendor's staff responsible for designing the model. These staff members were independent from the development team and followed a pre-defined test plan to ensure the model's internal consistency and accuracy.
3. External validity: To assess the model's performance, its predictions were compared against outcomes from studies used to construct the model (dependent external validity). Additionally, comparisons were made with outcomes from studies that were not included in the model's development

(independent external validity). This evaluation allowed for an assessment of the model's generalizability and its ability to accurately predict outcomes beyond the specific studies it was built upon.

NIPH's comments on the model structure

The model appears reasonable, and is validated. It was developed by Ward et al. 2013 (37) and was used in a HTA for the NICE diagnostics guidance (3).

We had access to the health economic model constructed in Microsoft Excel, along with the underlying assumptions and parameters.

Patient population and time horizon in the submitted model

The start age in the submitted model is 57 years. This is the median age at diagnosis reported in Johansson et al. 2021 (41). The time horizon is 45 years (lifetime perspective), which means that it is assumed that all patients have died within 45 years.

The submitted cost-effectiveness model focuses on two groups of women:

1. Early stage breast cancer patients (stage I-III) classified as ER+ HER2- with lymph node negative disease (LN0), regardless of menopausal status.
2. Early stage breast cancer patients (stage I-III) classified as ER+ HER2- with lymph node positive disease (1-3 lymph nodes; LN+), who are postmenopausal.

NIPH's comments on the included patient population

The start age and time horizon used in the model appear reasonable and are in line with the Norwegian cancer register and Statistics Norway (41;42).

Efficacy input in the submitted health economic model

The model uses the distribution of RS in the relevant patient groups, i.e. the rate of patients with low, intermediate or high RS in node negative and postmenopaual node positive patients. Furthermore, the model applies probabilities of receiving chemotherapy within the Oncotype DX group and the no gene-profiling test group. Finally, the model uses distant recurrence rates and hazard ratios to calculate the probability of experiencing distant recurrence within the groups.

Below, we provide a more detailed description of the three factors considered in the submitted model: Distibutions of RS in breast cancer populations, probabilities of receiving chemotherapy, and distant recurrence rates.

Distribution of RS in populations of breast cancer patients

The distribution of RS in the relevant patient populations was obtained from TAILORx (8) and RxPONDER (10) and are shown in Table 12.

Table 12. *Distribution of Recurrence Score*

Patient population	Low RS	Intermediate RS	High RS	Reference
LN0	(RS 0-10) 17%	(RS 11-25) 69%	(RS 26-100) 14%	TAILORx (8)
LN+ (post-menopausal)	(RS 0-13) 39.9%	(RS 14-25) 49.1%	(RS 26-100) 11%*	RxPONDER (10) and assumption* (43)

Abbreviations: RS, Recurrence Score; LN0, lymph node negative; LN+, lymph node positive
*RxPONDER only included patients with low and intermediate RS (0-25). The distribution of patients with high RS (26-100) is based on an assumption/estimation (43).

Probability of receiving adjuvant chemotherapy

The submitted model included different probabilities of chemotherapy use. The chemotherapy use varied depending on the specific patient population of interest (LN0 or postmenopausal LN+). Table 13 presents the submitted probabilities of chemotherapy use for patients that performed the Oncotype DX test.

Table 13. *Probability of receiving chemotherapy conditional on Oncotype DX test*

Patient population	Low RS	Intermediate RS	High RS	Reference
LN0	(RS 0-10) 0%	(RS 11-25) 9.4%	(RS 26-100) 69.9%	Stemmer et al. 2019 (23)
LN+ (post-menopausal)	(RS 0-17) 5.2%	(RS 18-30) 18%	(RS 30-100) 77.3%	Stemmer et al. 2017 (44)

Abbreviations: RS, Recurrence Score; LN0, lymph node negative; LN+, lymph node positive

In the no gene-profiling test strategy, the submitter assumed that the hypothetical RS groups would have identical probability of receiving chemotherapy because the RS status was unknown and thus not considered when treatment was chosen. The probabilities of receiving chemotherapy for patients not tested with Oncotype DX were obtained from Harnan et al. 2019 (3), and was 27% for node negative patients, and 75% for postmenopausal node positive patients (regardless of RS group).

Distant recurrence rates

The probabilities of distant recurrence for LN0 patients undergoing endocrine therapy were obtained from two different sources (Table 14). For patients with low and intermediate RS, the probabilities were derived from TAILORx (8). For patients with high RS, probabilities were found in NSABP B-20 (6).

Regarding LN+ patients with RS ranging from 0 to 25, the rates of distant recurrence with endocrine therapy were sourced from RxPONDER (10). Since RxPONDER excluded patients with RS ranging from 26 to 100, the probability of distant recurrence for this particular patient group was obtained from the analysis reported in Harnan et al. 2019 (3). See Table 14 for the specific rates provided by the submitter.

Table 14. *10-year* DRFS for the Oncotype DX test arm by patient population and RS result group following endocrine therapy*

Patient population	Low RS (0-10)	Intermediate RS (11-25)	High RS (26-100)	Reference
LN0	96.8%	94.5%	62%	TAILORx (8) and NSABP B-20 (6)
LN+ (post-menopausal)	93.3%*		68.6%**	RxPONDER (10), TransATAC (45) and Harnan 2019 (3)

Abbreviations: RS, Recurrence Score; LN0, lymph node negative; LN+, lymph node positive; DRFS, distant recurrence-free survival

*Only 5-year survival data has been reported from RxPONDER thus far. The submitter has extrapolated RxPONDER data from 5 year DRFS to 10 year DRFS. The 5-year DRFS reported in RxPONDER was 94.4%.

**Reanalysis from TransATAC obtained from Harnan 2019 (3).

For LN0 patients who received endocrine therapy plus chemotherapy, the probability of distant recurrence was obtained in TAILORx (8) and NSABP B-20 (6). For postmenopausal LN+ patients who received endocrine therapy plus chemoendocrine therapy, the probability of distant recurrence was sourced from RxPONDER (10) and SWOG-8814 (9). The hazard ratios of distant recurrence following chemoendocrine therapy vs. endocrine therapy alone, for both LN0 and LN+ patients, can be found in Table 15.

Table 15. *Hazard ratio of distant recurrence (95% CI) following chemoendocrine therapy vs. endocrine therapy alone*

Patient population	Low RS (0-10)	Intermediate RS (11-25)	High RS (26-100)	Reference
LN0	1.19 (0.41, 3.51)	0.91 (0.71, 1.18)	0.27 (0.12, 0.62)	TAILORx(8) and NSABP B-20 (6)
LN+ (post-menopausal)	1.12** (0.82, 1.51)		0.59 (0.35, 1.01)*	RxPONDER (10) and SWOG-8814 (9)

Abbreviations: RS, Recurrence Score; LN0, lymph node negative; LN+, lymph node positive; CI: confidence interval

*SWOG-8814 reported disease-free survival (DFS) rather than distant recurrence-free survival and used the old RS thresholds (high RS: 31-100) (9).

**Data presented at San Antonio Breast Cancer Symposium 2021 (46)

The estimation of the probability of distant recurrence was based on the analysis of distant recurrence endpoints derived from pivotal trials involving endocrine and chemoendocrine therapy.

In the model, the distant recurrence-free survival (i.e. freedom from recurrence of breast cancer at a distant site, which corresponds "distant recurrence–free interval" (8) estimate was treated as a probability, where, for example, a 10-year distant recurrence-free interval of 0.96 corresponded to a 10-year probability of developing distant recurrence of 0.96. To incorporate these estimates into the model, transition probabilities were derived by converting the distant recurrence-free probabilities to the 6-month model cycle length, considering the assumed treatment effect of chemotherapy if applicable. Since the adjustment for cycle length and application of hazard ratios requires

hazard rates rather than probabilities, conversion from probabilities to hazard rates and vice versa was necessary. It was assumed that the hazards remained constant over time, following an exponential distribution. The conversion back to probabilities was essential for the utilization of these rates within the model engine. The conversion of transition probabilities was performed using standard formulas:

Conversion of a probability to a hazard rate:
r = -ln (1 - $p(t)$) / t

Conversion of a hazard rate to a probability:
$p(t)$ = 1 - e^(-rt)

Here, r represents the hazard rate, $p(t)$ represents the transition probability at time t.

The submitter calculated a 6-month probability of distant recurrence assuming a constant rate. For example, LN+ patients with RS 0-25 treated with endocrine therapy alone had a 10 years DRFS of 93.3% (Table 14) which resulted in a 6-month probability of distant recurrence of 0.0035 (1-exp(ln(0.933)*0.5y/10y)=0.0035). For patients treated with endocrine therapy plus chemotherapy, also the hazard ratio of 1.12 (Table 15) was applied. This resulted in a in a 6-month probability of distant recurrence of 0.0039 (1-exp(ln(0.933)/*1.12*0.5y/10y)=0.0039). The submitted 6-months distant recurrence probabilities following endocrine therapy alone are presented in Table 16, and the submitted probabilities following chemoendocrine therapy are presented in Table 17.

Table 16. *Calculated 6-months probability of distant recurrence with endocrine therapy (from submission file)*

Patient population	Low RS (0-10)	Intermediate RS (11-25)	High RS (26-100)	Reference
LN0	0.0018	0.0031	0.0287	TAILORx (8) and NSABP B-20 (6)
LN+ (post-menopausal)	0.0035		0.0187*	RxPONDER (10) and SWOG-8814 (9)

Abbreviations: RS, Recurrence Score; LN0, lymph node negative; LN+, lymph node positive
*SWOG-8814 reported disease-free survival (DFS) rather than distant recurrence-free survival and used the old RS thresholds (high RS: 31-100) (9).

Table 17. *Calculated 6-months probability of distant recurrence with chemoendocrine therapy (from submission file)*

Patient population	Low RS (0-10)	Intermediate RS (11-25)	High RS (26-100)	Reference
LN0	0.0021	0.0031	0.0078	TAILORx (8) and NSABP B-20 (6)
LN+ (post-menopausal)	0.0039		0.0111*	RxPONDER (10) and SWOG-8814 (9)

Abbreviations: RS, Recurrence Score; LN0, lymph node negative; LN+, lymph node positive
* SWOG-8814 reported disease-free survival (DFS) rather than distant recurrence-free survival and used the old RS thresholds (high RS: 31-100) (9).

Additionally, to incorporate the effects of chemotherapy treatment, the baseline probability of distant recurrence for both arms in the model was adjusted after 10 years. This adjustment was carried out based on the methodology employed in the analysis in the NICE guideline (47) and Ward et al. 2013 (37) to mitigate the risk of overestimating the duration of chemotherapy's effectiveness. From years 11 to 15, it was assumed that the risk of distant recurrence would be halved compared to the risk observed in the initial 10 years. Starting from year 16, an additional 50% reduction in risk was assumed to further reflect the declining baseline risk over time. This adjustment accounts for the potential long-term benefits of adjuvant treatment.

NIPH's comments on the efficacy input in the model

The submitter generally provides strong arguments for the selection of most clinical input data. However, there are some challenges associated with the categorization of recurrence score groups and certain reference choices.

Regarding the distribution of recurrence scores for postmenopausal node positive patients, these specific data are not reported in the original article of RxPONDER (10). The RxPONDER study (10) focuses only on low and intermediate RS (0-25), and excludes patients with high RS. However, the distribution provided by the submitter (percentage of patients with high RS) aligns reasonably well with the results from a large registry study (20) (see Table 9 in the chapter of evaluation of clinical effectiveness).

Another challenge is that the submitter uses different thresholds for low and intermediate RS for postmenopausal node positive patients compared to those identified for node negative patients. The thresholds for node negative patients are derived from TailorX (8) and appears to be the thresholds employed by most.

The probability values for receiving adjuvant chemotherapy are sourced from two registry studies, Stemmer et al. 2017 (44) and Stemmer et al. 2019 (23). However, a challenge arises as these studies applied different RS thresholds. Stemmer et al. 2017 emploied the old RS thresholds (low 0-17, intermediate 18-30, high >30), presenting yet another variation of thresholds. On the other hand, Stemmer et al. 2019 emploied the new RS thresholds (low 0-10, intermediate 11-25, high >25). However, we ran the model using alternative input data for chemotherapy use based on other references (23;44);(48) and the outcomes showed minimal changes.

The submitter did not show how they extrapolated 5-year survival data from RxPONDER to 10-year survival. The extrapolation constitute an uncertainty in the model. Moreover, the hazard ratio of distant recurrence (chemoendocrine therapy vs. endocrine therapy) for node negative patients with RS 11–25 used in the submitted model (0.91; Table 15) differs from the hazard ratio reported in TailorX (1.10; Table 4). It is not clear why the submitter have used another hazard ratio. Nevertheless, correcting this hazard ratio has minimal impact on the result.

Local recurrence rates

In breast cancer, women face the risk of both local and distant recurrence. The model does not provide an explicit estimation of the probability of local recurrence in each model cycle. Instead, it assumes that 10.5% of patients with a distant recurrence had experienced a local recurrence before the occurrence of distant recurrence. This assumption is based on the findings of de Bock et al. 2009 (49).

To account for the impact of local recurrence, a one-time cost of treatment, indirect cost, and utility decrement are applied in the model. These factors are considered to reflect the consequences of local recurrence on various aspects of the patients' well-being and overall quality of life.

NIPH's comment to local recurrence rate

It is unknown whether the proportion of patients experiencing local recurrence (10.5% of distant recurrence) is applicable to the Norwegien patient population. Also, the model does not take into account possible differences in occurrence of local recurrence without later distant recurrence.

Rate of adverse events of adjuvant treatment

Acute myloid leukemia
Within the model, a health state representing acute myloid leukemia was included as a long-term adverse event resulting from chemotherapy. Patients may develop acute myeloid leukemia in both the recurrence-free and the distant recurrence health states. The probability of acute myloid leukemia was obtained from a trial that examined anthracycline-based chemotherapy for primary breast cancer (50). This trial reported a probability of acute myloid leukemia of 0.6% after a 4-year follow-up period. A probability of 0.03% was applied in the model per cycle.

Short-term adverse events of chemotherapy
According to the submitter, the probability of short-term adverse events of chemotherapy was based on the rates of AEs obtained from the TACT trial for node negative patients. The TACT trial compared a taxane and anthracycline chemotherapy regimen (docetaxel, epirubicin, fluorouracil and cyclophosphamide, FEC-D) with an anthracycline-only regimen (without docetaxel) (53). The submitter assumed that these treatments reflect clinical practice in adjuvant chemotherapy in Norway. For the postmenopausal node positive patients, rates of adverse events were derived from the RxPONDER trial as the most recent reference available for this patient population (10).

NIPH's comment on short-term adverse events of chemotherapy
It may appear like adverse events are not included in the model in the way as previously indicated. Adverse events are included in two ways. First, as an one-off disutility for short-term adverse events and administration of chemotherapy applied in first cycle. Second, as an one-off cost for chemotherapy associated short-term adverse events in the first cycle.

Probability of death following distant recurrence

The submitter determined the survival prognosis of patients with distant recurrence by obtaining survival data from the MONARCH 2 trial (54). The median survival time after distant recurrence was reported to be 46.7 months in this study. To estimate the probability of death within 6 months, an exponential distribution was fitted with a median of 46.7 months. Using this approach, the estimated 6-month probability of death following distant recurrence was calculated as 0.085, assuming a constant rate. Since there was a lack of specific data for different subgroups or risk classifications, the submitted model assumes a constant rate of death due to distant recurrence across the three risk classification groups.

Probability of death following acute myloid leukemia

The submitter made an estimation of the average survival time after the onset of acute myloid leukemia based on the HTA by NICE of Liposomal cytarabine-daunorubicin for untreated acute myloid leukemia (55). The estimated mean survival time was approximately 9.6 months. Using this information, the 6-month probability of death following acute myloid leukemia was calculated as 0.353, assuming a constant rate of events.

Probability of death following other causes (life tables)

The submitter incorporated all-cause mortality, recurrence-related mortality, and acute myloid leukemia mortality into the model. The data source for this information was Statistics Norway, 2022 (42). The probabilities of death used in the model were specific to different age groups, and the probabilities for females were applied in the analysis. The baseline all-cause mortality for 57 year old women was 0.0015 (42).

Health-related quality of life

In the submitted model, health-related quality of life (HRQoL) was applied in two manners:

1. Multiplication of health state utility values by the duration spent in each health state, considering the number of cycles.
2. Incorporation of one-time reductions to capture the decline in HRQoL resulting from the administration of chemotherapy in early stage breast cancer, chemotherapy-related adverse events, and local recurrence.

The primary references for the utility values used in this study are Campbell et al. 2011 (56), Lidgren et al. 2007 (57), and Peasgood et al. 2010 (58). These studies provided EQ-5D-3L (EuroQol, five dimensions, 3 levels) values from the United Kingdom, which were obtained through the administration of a self-classifier to elicit the utility values.

In the study conducted by Lidgren et al. 2007 (57), utility values of 0.824 were reported for patients who were free of recurrent disease, while a utility value of 0.685 was associated with distant recurrence. For cases of local recurrence, it was assumed that there would be a one-time reduction in utility by 0.108, as indicated by Campbell et al. 2011 (56).

The utility level for acute myloid leukemia was obtained from the NICE appraisal of liposomal cytarabine-daunorubicin for untreated acute myloid leukemia (55). Furthermore, a utility decrement of 0.038, based on Campbell et al., was applied to all patients undergoing chemotherapy to account for the decrease in utility resulting from both treatment administration and treatment-related adverse events.

To account for background morbidity, health state utilities were adjusted using age-specific general population utilities in the UK, as indicated by Ara and Brazier 2008 (59). The health state utility values in the submitted model is presented in Table 18.

Table 18. *Health state utility values in the submitted model*

Health state	Health state utility value	CI (95%) or SE	Reference
Recurrence-free	0.824	(0.785, 0.857)	Lidgren 2007 (57)
Distant recurrence	0.685	(0.620, 0.375)	Lidgren 2007 (57)
AML	0.550	(SE 0.023)	NICE 2018 (55)

Abbreviations: AML, acute myloid leukemia; SE, standard error; CI, confidence interval

In the first model cycle, the utility decrement associated with adverse events was assumed to be applicable throughout the duration of chemotherapy treatment. To account for the loss of HRQoL resulting from specific chemotherapy-related adverse events, the submitter obtained utility decrements from a systematic review of health state utility values in breast cancer conducted by Peasgood et al. 2010 (58). These utility decrements specifically addressed neuropathy, infection, and edema.

For the decrement associated with febrile neutropenia, a study by Lathia et al. 2013 (60) analyzing the cost-effectiveness of filgrastim in lymphoma was referenced in the submitted documentation. The assumed duration for the decrease in utility due to febrile neutropenia was six months, after which utility values corresponding to the association in specific health states were applied.

The utility decrements in the submitted documentation is presented in Table 19.

Table 19. *Utility decrements in the submitted model*

Health state	Quality of life weighting	SE	Reference
Chemotherapy administration	-0.038	0.004	Peasgood (58)
Neuropathy (Chemo AE)	-0.085	0.063	
Infection (Chemo AE)	-0.228	0.009	
Edame (Chemo AE)	-0.017	0.755	
Febril neutropenia (Chemo AE)	-0.150	CI (0.05, 0.25)	Lathia 2013 (60)
Local recurrence*	0.108	0.04	Campbell 2011 (56)

*One-time QALY loss applied on transition to distant recurrence state
Abbreviations: AE, adverse events; chemo, chemotherapy; CI, confidence interval; EQ-5D: EuroQol 5 dimensions; SE, standard error

NIPH's comments on the utility values in the model

The utility values used in the submitted model are all based on EQ-5D utility scores. EQ-5D is the preferred instrument to measuring HRQoL in health economics and health care research according to Norwegian guidelines. To account for background morbidity, health state utilities were adjusted using general population in the UK. Utilities were thus not adjusted by using the Norwegian general population health state utilities.

The submitter stated in the submitted documentation report that they applied utility decrements for neuropathy, infection and edame and febril neutropenia. However, the model only seems to include a one time "chemotherapy utility decrement" of 3.038. This affects the results in favour of the no gene-profiling test strategy. They also stated that they used a health state utility for acute myolid leukemia of 0.550, but the value applied in the model is 0.26.

Costs and resource use input in the submitted health economic model

The submitter included the following costs in the model: drug acquisition costs, drug administration costs, costs due to adverse events, cost of Oncotype DX test, and surveillance. These are included in the relevant health states in the model. The health state cost is applied to the percentage of patients in the health state for each cycle. The health state costs, applied in 2022 NOK, are presented in Table 20.

Table 20. *Health state costs in the model*

Health state		Cycle cost (NOK)	Source
Recurrence-free	First year	29,695	Lidgren et al. 2007 (61)
	Years 2–5	1,869	DRG930A: one extra outpatient visit (62)
Local recurrence		164,704	Estimate by NIPH report (2019) (63) adjusted to year 2022
Distant recurrence		143,359	Estimate by NIPH report (2019) (63) adjusted to year 2022 and added costs for subsequent therapies
	Treatment cost	89,603	Varius, see cost explanation below and appendix 2.
	Disease management cost	53,756	Varius, see cost explanation below and appendix 2.
Acute myloid leukemia (one-off)		140,250	System for activity based financing of hospitals in Norway ("Innsatsstyrt Finansiering" (62)
Terminal care (14 days)		64,098	NoMA unit cost database V.1 (64)

Abbreviations: DRG, diagnosis related group; NoMA, Norwegian Medicines Agency

Cost of the Oncotype DX test

The Oncotype DX price in the model is NOK 32,341 per analysis of tumour specimen. This price includes ordering, shipping, and reporting of results. The test is analysed in the company's laboratory (the Genomic Health, Inc. laboratory in the US; part of Exact Sciences).

Cost of local recurrence

The cost used in the model, NOK 164,704, is based on costs reported in the Prosigna report by NIPH (4), and taken from Karnon et al. 2007 which is a UK-based patient-level costing analysis of breast cancer recurrence (65). This cost is applied as a once-only cost and include management local recurrence.

Cost of distant recurrence

The cost of distant recurrence has two components The first is drug costs which is a weighted average of endocrine therapy, chemotherapy and CDK4/6 inhibitors, in first, second and third line treatment. This was informed by expert opinion. Secondly, disease management cost which is taken from the HTA of Prosigna by NIPH from 2019 (4). The cost sums up to NOK 143,294 (NOK 89,537 for drug treatment + NOK 53,756 for disease management). This cost is applied in the 6 month cycles.

Drug and administration costs can be found in appendix 2. The drug prices used are without VAT and are publicly available.

<u>Drug regimen and costs of adjuvant chemotherapy acquisition and administration</u>

The submitter has included treatments according to the Norwegian guidelines (2). For ER+ HER- breast cancer patients and low risk profile, four EC90 (epirubicin + cyclophosphamide, 90 mg/m^2) courses are recommended. For higher risk profiles, four EC90 courses are recommended, followed by 12 weeks of taxane treatment. Based on this, the submitter assumed that 50% of patients receive EC90 × 4 and 50% get EC90 ×

4 followed by 12 weeks taxane treatment. The submitter has assumed no vial sharing in drug use, and used a body surface area of 1,75 m^2 for drug dosing based on mg per m^2. The costs of the drug regimens can be found in appendix 2.

Drug regimen and costs of endocrine therapy

The cost of endocrine treatment is a weighted average of Tamoxifen, Anastrozole, Letrozole, and Everolimus and Exemestane. The submitter has used assumptions for percentages of appropriate treatments in Norway, from the Prosigna report by NIPH (4). See the details on costs and percentages of patients receiving the drugs in table 1, 5 and 6 in appendix 2.

Cost of recurrence-free

Recurrence-free first year

Costs for first year recurrence-free was based on Lidgren et al. 2007 (61). The authors reported costs of treating breast cancer in Sweden including yearly cost per patient who are recurrence-free (after primary breast cancer/recurrence). These costs were converted into 2022 NOK and used in the model (Table 21).

Table 21. *Costs for first year local recurrence-free*

Cost item	Cost in Euro/NOK
In- and outpatient costs	€ 2,294
Drug costs	€ 65
Informal care costs	€ 238
Sum	€ 2,597
Sum costs 2022*	NOK 29,695

*The sum was converted to NOK by using the average exchange rate between EURO and NOK in 2005, and then the inflation from 2005 until 2022.

Recurrence-free year 2–5

For the second to fifth year, the recurrence-free cost is assumed to be one yearly outpatient oncologist visit. This cost was calculated using the reimbursement from the system for activity based financing of hospitals in Norway. The cost was calculated using the cost weight (for DRG 930A, outpatient consultation concerning malign breast tumor) multiplied by the unit cost for a DRG-point. This sums up to NOK 1,869 (0.040 × NOK 46,719) (62) .

Acute myloid leukemia

The cost of acute myloid leukemia is based on the abovementioned financing system, where DRG 473 (acute leukemia >17 years old) has been multiplied by the cost of a DRG-point (62). This sums up to 140,250 (3.002 × NOK 46,719).

Costs of adverse events

Adverse events costs in the model are related to chemotherapy. The applied unit costs are mostly based on the relevant DRG-codes and have been calculated as a weighted average of adverse event. The weighted unit cost applied is NOK 22,730 for each cycle. See appendix 2 for details and weighing of these costs.

Cost for terminal care

The cost of terminal is calculated in the same way as in the unit cost database by the Norwegian Medicines Agency (64). Here it is assumed that patients are in the end-of-life phase for up to 14 days and that they receive palliative care in this phase at home. The cost is based on DRG 959W (palliative day care under the auspices of palliative care centre) with a weight of 0.092 (62). The cost for terminal care then sums up to NOK 64,098 (14 days × 0.098 × 46,719).

NIPH's comments to costs and resource use in the submitted model

The costs included in the health economic seem in general comprehensive and reasonable for Norwegian clinical practice. They are mainly retrieved from Norwegian sources.

The drug prices used in the model do not involve possible discounts and may thus overestimate the actual prices. This would overestimate Oncotype's cost savings associated with treatment costs in the analysis.

The drug treatment of distant recurrence may not be fully in line with Norwegian clinical practice today. In the model it is assumed that 50 % receive EC90 and 50% receive EC90 plus taxane treatment. In Norwegian clinical practice these proportion are more likely to be 40% and 60% respectively, according to our clinical expert. The EC90 plus taxane treatment has a higher cost than EC90, however changing this input to 60% had minimal impact on the result.

The cost for follow-up of patients without recurrence was calculated based on a Swedish study. It is unclear whether it fully reflects Norwegian clinical practice and the population in the model. However, this has most likely minimal impact on the results of the analysis. Regarding follow-up of patients without recurrence at year 2–5, drug costs are not included. According to the clinical expert, patients may get endocrine treatment and zoledronic acid. Thus, this cost may be underestimated. This would be in favour of the no gene-profiling test strategy, but probably have little impact on the results of the analyses.

Calculation of severity – absolute shortfall

The submitter estimated absolute shortfall (AS) based on projections about life expectancies. The AS calculation follows the NIPH guidelines outlined in the guidelines for the submission of documentation for single technology assessments of medical devices and diagnostic interventions. These guidelines are based on the White Paper on Priority Setting, as well as a Norwegian life table and age-adjusted HRQoL data from a general Swedish population (35;42;66)

AS represents the difference between quality-adjusted life expectancies at a specific age (A) without the presence of the disease ($QALYs_A$), and the prognosis with the disease while receiving the current standard of care (P_A).

$$AS = QALYs_A - P_A$$

For the calculations, the submitter employed undiscounted numbers for $QALYs_A$ and P_A as indicators of prognosis. $QALYs_A$ represents the remaining quality-adjusted life years for patients receiving the standard of care in the absence of any intervention, considering the average age at diagnosis. QALY (A) refers to the overall quantity of remaining quality-adjusted life years for a healthy population at the average age at diagnosis.

One-way sensitivity analysis

The submitter conducted a series of one-way sensitivity analyses to explore the impact of individual parameter uncertainties on the cost-effectiveness outcomes. A list of parameters used for the one-way sensitivity analyses is presented in Appendix 3. One-way analyses were conducted on the net monetary benefit (NMB) metric, which is defined as the product of incremental quality-adjusted life years (QALYs) and the willingness-to-pay threshold (WTP), minus the incremental cost. The submitted analyses assumed a WTP value of 250,000 per QALY. The results of these analyses are illustrated in the form of a tornado diagram in the results chapter.

The tornado diagrams illustrate the variation in net monetary benefit for Oncotype DX as different parameter values are adjusted. The submitter derived plausible ranges for the parameters from 95% confidence intervals published in previous research or constructed using reported standard errors. In cases where no ranges or standard errors were available, the submitter assumed a deviation of ±20% from the expected value. The results of these analyses are illustrated in the form of a tornado diagram in the results chapter.

NIPH comments the one-way sensitivity analysis

It would be preferable if the tornado diagram also was shown in ICER in addition to NMB.

Probabilistic sensitivity analysis

The submitter employed 5,000 Monte Carlo simulations to generate probabilistic results, which encompass the uncertainties associated with multiple parameters in the cost-effectiveness model. The probability distribution functions for input parameters were defined using standard distributional forms: Dirichlet distribution (a distribution of categorical variables) was used for the distribution of the recurrence score, gamma distribution was used for costs and hazard rates of distant recurrence and beta distribution for utilities and for transition probabilities. A more detailed overview is presented in Appendix 3.

To illustrate the results, a scatterplot was presented, highlighting the range of probabilities that each modality would be considered optimal for various willingness-to-pay thresholds. Additionally, cost-effectiveness acceptability curves were provided to illustrate the probability of a modality being deemed optimal across different willingness-to-pay thresholds.

Budget impacts

Budget impacts are defined as additional costs, i.e. the total expenditure of introducing the technology minus the total costs of not doing so. Budget impacts for the specialist health services in a national perspective are to be calculated. The recommended time horizon for drugs is five years. For other products, the time horizon varies depending on the product's useful life or depreciation. The submitter has used a horizon of five years and calculated budget impacts for a scenarios where Oncotype DX is introduced in addition to no gene-profiling test.

Results

Base case cost-effectiveness results for node negative patients

According to the submitted cost-effectiveness analysis, the Oncotype DX test demonstrated dominance over no gene-profiling test, yielding greater QALY gains at a lower cost throughout a lifetime (Table 22).

***Table 22**. The submitted cost-effectiveness results for node negative patients*

Intervention	Total cost (NOK)	Incremental costs (NOK)	Effects (QALYs)	Incremental effect (QALYs)	ICER (NOK/QALY)
Oncotype DX	330,620	-15,453	12.11	0.18	Dominant
No gene-profiling test	346,974		11.95		

Abbreviations: QALY, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

One way sensitivity analysis for node negative patients

Figure 14 shows the findings of the submitted one-way sensitivity analysis for node negative patients. The hazard ratio in the high RS group appears as the primary source of uncertainty in the model. A list of parameters used for the one-way sensitivity analyses is presented in Appendix 3.

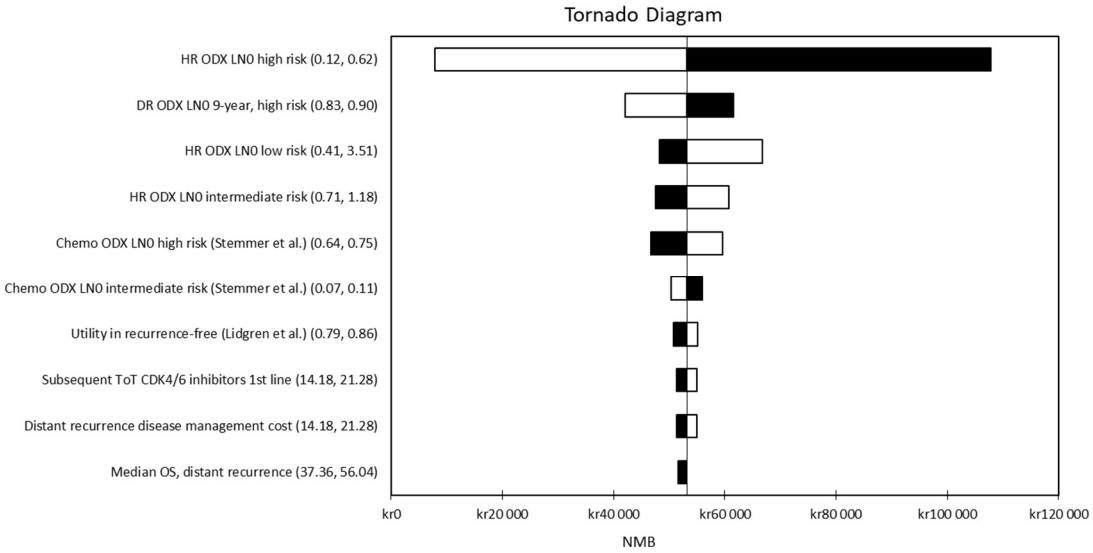

Figure 14. *The submitted tornado diagram for node negative patients*
Abbreviations: NMB, net monetary benefit (calculated as (incremental benefit × threshold) - incremental cost)); HR, hazard ratio; CDK4 inhibitors, cyclin-dependent kinase 4 and 6, (which are proteins involved in regulating cell division and proliferation), ODX, Oncotype DX; OS, overall survival. White bars indicate an increase in the parameter value, while black bars indicate a decrease.

Probabilistic sensitivity analysis for node negative patients

Figure 15 presents the findings of the submitted probabilistic sensitivity analysis for node negative patients. The scatter plot illustrates the combined parametric uncertainty in the model. The points are distributed across the upper right quadrant (indicating that the Oncotype DX test is more effective and also more costly than no gene-profiling test, and the lower right quadrant (indicating that the Oncotype DX test is both more effective and less costly). In 92% of the simulations, the Oncotype DX test demonstrated dominance.

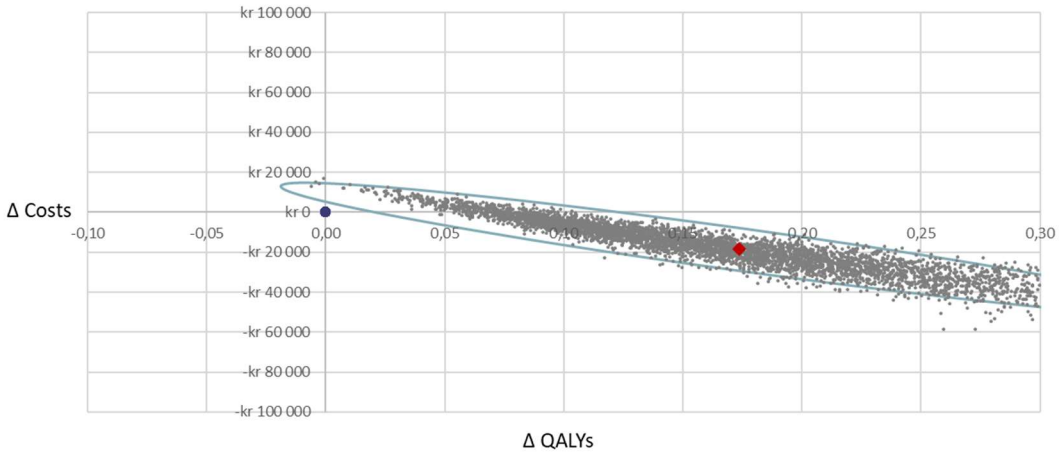

Figure 15. *The submitted incremental cost–effectiveness plot for node negative patients*

The submitted cost-effectiveness acceptability curve for node negative patients depicted in Figure 16 shows that the Oncotype DX test had a 99% probability of being cost-effective at a willingness-to-pay threshold of NOK 250,000 per QALY.

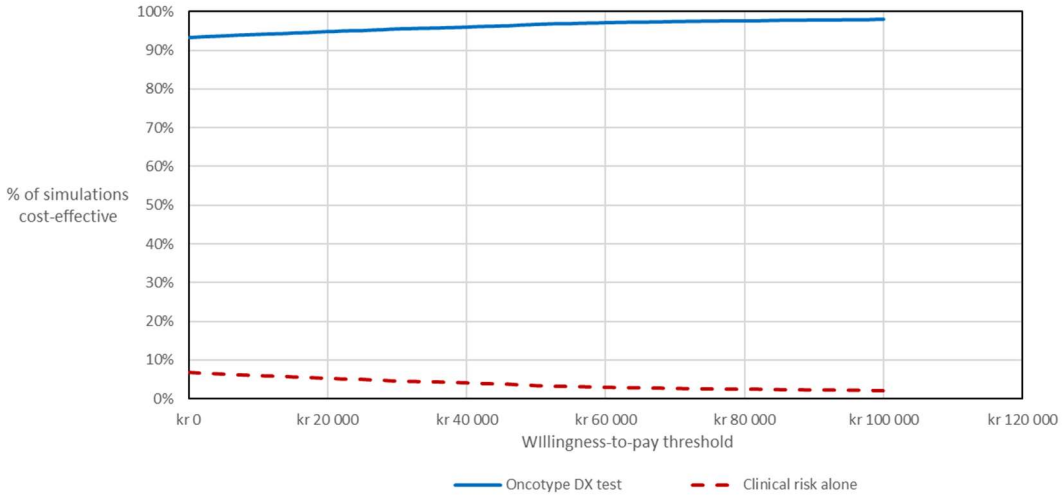

Figure 16. *The submitted cost-effectiveness acceptability curve for node negative patients*

Base case cost-effectiveness results for postmenopausal node positive patients

According to the submitter the Oncotype DX test demonstrated dominance over clinical risk alone for postmenopausal lymph node positive patients, as it provided more QALYs at a cost over a lifetime. See Table 23.

Table 23*. The submitted cost-effectiveness results for postmenopausal node positive patients*

Intervention	Total cost (NOK)	Incremental costs (NOK)	Effects (QALYs)	Incremental Effect (QALYs)	ICER (NOK/QALY)
Oncotype DX	385,189	-48,405	12.03	0.07	Dominant
No gene-profiling test	433,595		11.96		

Abbreviations: QALY, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio

One way sensitivity analysis for postmenopausal node positive patients

Figure 17 shows the submitted outcomes of the one-way sensitivity analyses for node positive, postmenopausal patients. The hazard ratio in the low and intermediate group apperas as the primary source of uncertainty in the model. A list of parameters used for the one-way sensitivity analyses is presented in Appendix 3.

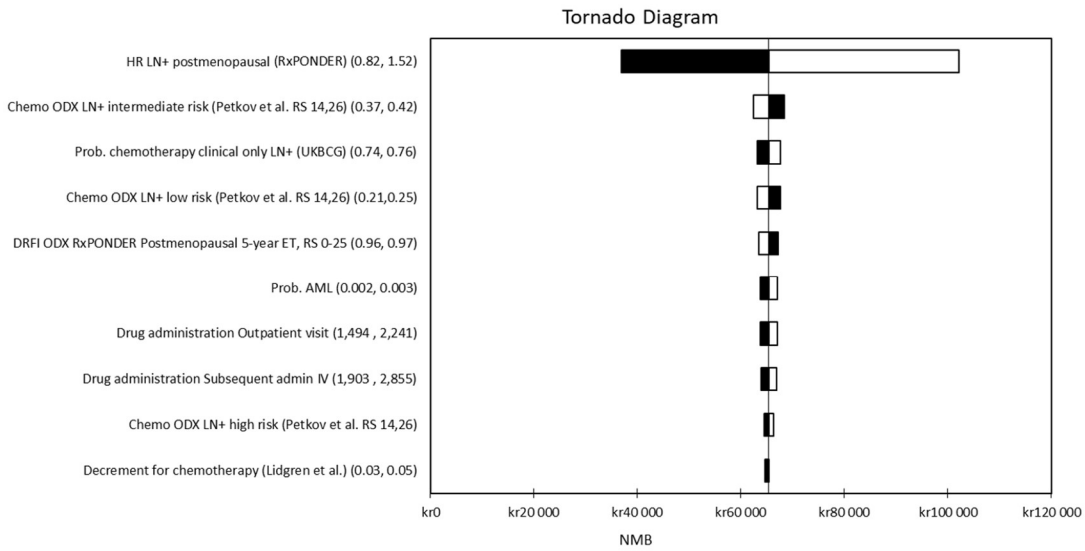

Figure 17. *The submitted tornado diagram for postmenopausal node positive patients*
Abbreviations: NMB, net monetary benefit (calculated as (incremental benefit × threshold) - incremental cost)); HR, hazard ratio; RS, Recurrence Score; ODX, Oncotype DX; DRFI, distant reccurence-free interval; AML, acute myloid leukemia; IV, intravenous; ET, endocrine therapy. White bars indicate an increase in the parameter value, while black bars indicate a decrease.

Probabilistic sensitivity analysis for postmenopausal node positive patients

Figure 18 presents the findings of the submitted probabilistic sensitivity analysis for node positive, postmenopausal patients. The scatter plot illustrates the combined parametric uncertainty in the model, with points distributed across the lower right quadrant (indicating that the Oncotype DX is more effective and less costly than clinical risk alone) and the lower left quadrant. Notably, 97.5% of the points fall within the quadrant representing higher effectiveness and lower costs.

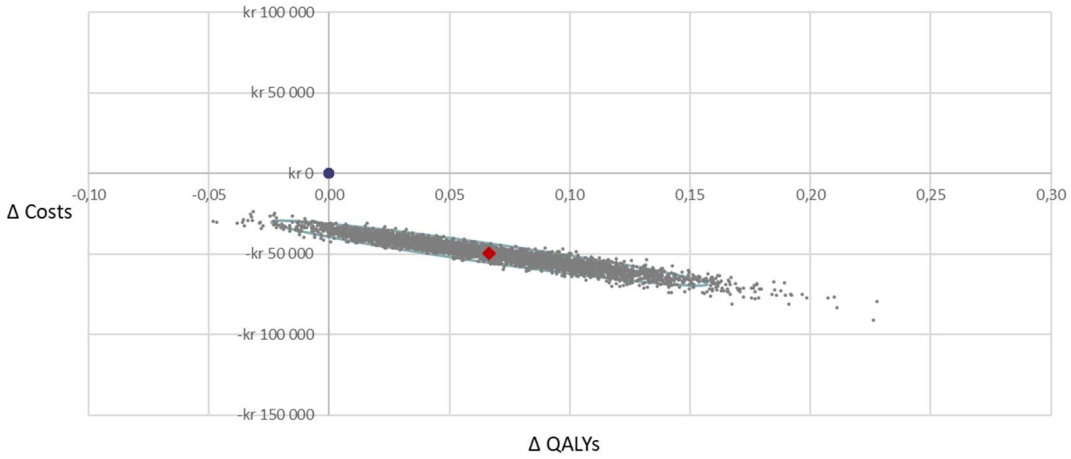

Figure 18. *The submitted incremental cost–effectiveness plot for postmenopausal node positive patients*

The submitted cost-effectiveness acceptability curve for node positive, postmenopausal patients depicted in Figure 19 demonstrates that the likelihood of the Oncotype DX test being cost-effective is 100% even at very low willingness-to-pay thresholds.

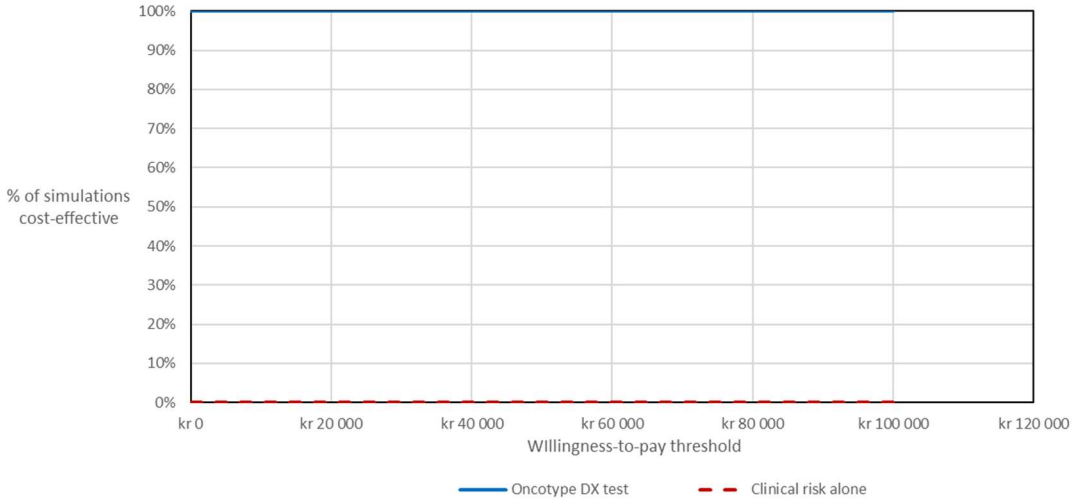

Figure 19. *The submitted cost-effectiveness acceptability curve for postmenopausal node positive patients*

Severity calculation – absolute shortfall

The submitter used 63 as average age for start of treatment stating that the median age of onset of breast cancer according to Cancer in Norway is 62 years (68). Further, they were not able to identify sources that report mean age of onset in Norway, but used data from Cancer Research UK (69). Based on this, they calculated a median age at onset of disease on 62 years as in Norway, and a mean age of onset of disease of 63. The submitted calculation is presented in Table 24.

Table 24. *Submitted calculation of absolute shortfall*

Explanation	Expressed as	Years / QALYs
Average age at the start of treatment	A	63 years
Expected remaining QALYs (undiscounted) for the general population without the disease	QALYs_A	17.7 QALY
Expected remaining QALYs (undiscounted) for those with the disease and without the new treatment (that is, prognosis of patients treated with current standard treatment)	P_A	16.6 QALY
Number of QALYs lost due to disease (absolute shortfall)	AS	1.1 QALY

NIPH's comments and revised severity calculation – absolute shortfall

In the submitted economic model, patients were assumed to enter the model at the age of 57. Using that age in the calculation of absolute shortfall, the expected quality adjusted life remaining in the general population is 22 years (36). Furthermore, the model estimated the expected QALYs for no gene-profiling test strategy to be 20.17. The absolute shortfall under these assumptions is presented in Table 25. Calculation of absolute shortfallTable 25.

Table 25. *Calculation of absolute shortfall*

Explanation	Expressed as	Years / QALYs
Average age at the start of treatment	A	57 years
Expected remaining QALYs (undiscounted) for the general population without the disease	QALYs_A	22 QALY
Expected remaining QALYs (undiscounted) for those with the disease and without the new test (that is, prognosis of patients treated with current standard treatment)	P_A	20.17 QALY
Number of QALYs lost due to disease (absolute shortfall)	AS	1.83 QALY

As outlined in the Report to the Storting (white paper) on priority-setting (35), the cost-effectiveness threshold should be adjusted based on the severity categories proposed by the Norheim and Magnussen commissions. These categories suggest that diseases with an expected QALY value below 4 belong to the least severe group, while those exceeding 20 QALYs are considered among the most severe. Given an expected absolute shortfall of 1.83 QALYs, the argument for granting special priority to Oncotype DX based on severity seems to be of low significance.

Budget impacts

The submitter estimated that approximately 2,000 new patients would be eligible for Oncotype DX test in Norway per year. Among these, they expected that 1,771 women with node negative disease and micro-metastases, 211 postmenopausal women with node positive disease, and around 18 men would be eligible for testing.

Based on experiences in other European healthcare systems, the submitter anticipated that up to 90% of eligible patients would be selected for the Oncotype DX test once it becomes a routine part of clinical practice (in the third year after implementation). This would be approximately 1,800 patients per year in Norway.

The budget impact analysis incorporates various costs related to early-stage breast cancer management, including endocrine therapy, chemotherapy (including adverse events), local recurrence, distant recurrence, acute myloid leukemia, and terminal care costs. The model assumes a 50% uptake of new cases in Year 1 (1,000 patients), which increases to 70% in Year 2 (1,400 patients), and finally reaches a 90% uptake from Year 3 to 5 (1,800 patients). The submitter assumed that 89% of patients are LN0 and 11% are LN+.

The submitted budget impact calculation compares a scenario of no gene-profiling test with a scenario where the Oncotype DX test is used. Table 26, 27 and 28 present the annual budget impact for node negative patients only, postmentopausal node positive patients only, and for both patient groups combined. All costs are in Norwegian kroner.

Table 26. *Submitted budget impact analysis for node negative patients*

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
No gene-profiling test	96,944,000	144,550,000	197,822,000	218,392,000	241,822,000
Oncotype DX	108,952,000	160,553,000	216,830,000	234,497,000	254,156,000
Budget impact	12,009,000	16,003,000	19,008,000	16,104,000	12,333,000

Table 27. *Submitted budget impact analysis for postmenopausal node positive patients*

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
No gene-profiling test	24,018,000	34,753,000	46,203,000	48,814,000	51,785,000
Oncotype DX	17,999,000	26,301,000	35,289,000	37,816,000	40,679,000
Budget impact	-6,019,000	-8,452,000	-10,914,000	-10,999,000	-11,106,000

Table 28. *Submitted budget impact analysis for both node negative and postmenopausal node positive patients*

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
No gene-profiling test	120,961,000	179,303,000	244,025,000	267,207,000	293,607,000
Oncotype DX	126,951,000	186,853,000	252,119,000	272,312,000	294,835,000
Budget impact	5,989,000	7,550,000	8,094,000	5,106,000	1,228,000

The cost-effectiveness results indicated that implementing the Oncotype DX test is a cost-saving strategy in a 45 year time horizon compared to no gene-profiling test. The submitter emphasises that the positive budget impact (Table 26-28) in the five years is due to the test costs being incurred early in the period, while the savings from factors such as reduced local and distant recurrences occur at time points beyond the 5-year time horizon of the calculation.

NIPH's comments on the budget impact analysis

The submitter has compared Oncotype DX with assessment of conventional clinical parameters, i.e. no gene-profiling test. However, in Norway lymph node negative patients are offered the gene-profiling test Prosigna. Thus, the submitted budget impact analysis for node negative patients seems of limited relevance.

Patient perspective

A patient representative was recruited from the Norwegian breast cancer association (Brystkreftforeningen). The patient representative was given information about Oncotype DX including the intended use and implications for breast cancer patients. The patient representative was then asked to complete a questionnaire consisting of three questions:

1. By using Oncotype DX, the number of patients treated with chemotherapy in addition to endocrine therapy can be reduced. What do treatment with or without chemotherapy involve for breast cancer patients?
2. Whether breast cancer patients are recommended chemotherapy, is based on clnical parameters and possibly Oncotype DX. Information about these parameters can be shared with patients. What are the advantages and disadvantages in receiving information about the parmeters that lead to the treatment recommandation?
3. If you have other perspectives/opinions on Oncotype DX than those covered by the questions above, please share them here.

The patient representative described that treatment regimens without chemotherapy probably involve less side effects and improve quality of life for breast cancer patients. However, the patient representative emphasised that also endocrine therapy involves side effects and reduces quality of life. Furthermore, some patients that are not recommended chemotherapy may feel insecure. This insecurity is also a factor.

The patient representative argued that transparency and more rather than less information is the best choice for patients. Patients differ in how they respond to information, but not knowing may lead to insecurity and brooding.

The patient representative did not add other perspectives or opinions.

Discussion

Discussion – clinical effectiveness

Key findings

The Oncotype DX test categorizes patients into groups based on their recurrence score (low RS, intermediate RS, and high RS). The submitter identified four RCTs that investigated whether Oncotype DX can predict chemotherapy benefit in patients with ER+ HER- early-stage breast cancer. Two of the RCTs investigated patients with node negative disease and two investigated patents with node positive disease (1-3 positive lymph nodes).

For patients with node negative disease there is convincing evidence that:

- Patients with low or intermediate RS (0-25) have similar risk of recurrence regardless of whether they are treated with endocrine therapy plus chemotherapy or endocrine therapy alone (no chemotherapy benefit). However, a small chemotherapy benefit was observed for women below 50 years and a RS of 16-25.
- Patents with high RS (>25) treated with endocrine therapy plus chemotherapy have lower risk of recurrence than those treated with endocrine therapy alone (chemotherapy benefit).

For patients with node positive disease there is convincing evidence that:

- Postmenopausal patients with low or intermediate RS (0-25) have similar risk of recurrence regardless of whether they are treated with endocrine therapy plus chemotherapy or endocrine therapy alone (no chemotherapy benefit).
- Postmenopausal patients with high RS treated with endocrine therapy plus chemotherapy probably have lower risk of recurrence than those treated with endocrine therapy alone (chemotherapy benefit).
- Premenopausal patients with low and intermediate RS (0-25) treated with endocrine therapy plus chemotherapy have lower risk of recurrence than those treated with endocrine therapy alone (chemotherapy benefit).

The included RCTs also demonstrated that Oncotype DX provides prognostic information. Thus, the risk of recurrence increased with increasing RS, both when patients were treated with endocrine therapy alone and when patients were treated with endocrine therapy plus chemotherapy (for both node negative and node positive patients).

Distributions of RS in populations of breast cancer patients were provided in RCTs and non-randomized studies. 76-86% of the patients with node negative disease and 84-90% of the patients with node positive disease had low or intermediate RS (0-25) and could omit chemotherapy.

Decision-impact studies demonstrated that Oncotype DX reduced chemotherapy assignment by 16-27% for node negative patients and by 50-73% for node positive patients. The studies illustrated that treatment decisions were not based entirely on the RS because some patients with low and intermediate RS were assigned to chemotherapy.

Evidence quality and limitations

The Oncotype DX test is intended to aid decisions on whether to add chemotherapy for patients with ER+ HER- early-stage breast cancer. Four RCTs demonstrated that Oncotype DX predicted chemotherapy benefit for this population. The RCTs were well designed, and risks of bias were deemed low (only minor concerns were identified). Together the four RCTs provided convincing evidence and represent a major strength. One of the RCTs investigating node positive patients (RxPONDER (10)) is still ongoing and has only reported 5 years survival data. The other RCT investigating node positive patiens (SWOG-8814 (9)) demonstrated that effects observed after 10 years also were apparent after 5 years. It is therefore expected that the 5-years results reported in RxPONDER will be confirmed when the 10 years survival data are available.

Oncotype DX is intended for patients with node negative disease (regardless of menopausal status) and for postmenopausal patients with node positive disease (1-3 positive lymph nodes). The gene profiling test Prosigna was approved for node negative patients by the Norwegian Decision Forum in 2019, and is now implemented in clinical practice (2). Oncotype DX thus represents an alternative to Prosigna for node negative patients, but Oncotype DX was not compared with Prosigna in the submitted documentation or in this STA. The submitter claims that RCTs investigating the ability of Prosigna to predict chemotherapy benefit have not been reported. Hence it is hard to compare the ability to predict chemotherapy benefit between the two tests. However, the prognostic value of the tests could have been compared. Actually, Sestak and colleagues compared the prognostic performance of six gene-profiling tests (including Oncotype DX and Prosigna) in a secondary analysis of a RCT of breast cancer patients with node negative disease (45). In this analysis, all gene-profiling tests were found to provide prognostic value, and Prosigna was found to be more prognostic than Oncotype. This study was identified in the submitter's literature search but was not described in the submission file. The reason for not describing the study was (according to the submitter's list): "No data reported on data relevant to dossier". NIPH find it hard to agree with this claim.

No gene-profiling test is currently recommended for node positive patients in Norway (2). Oncotype DX may thus fulfill an unmet need for postmenopausal patients with node positive disease. A comparison between Oncotype DX and Prosigna is thus not required for the node positive population.

NIPH conducted a STA of the Prosigna test in 2019 (4). The main conclusions of the Prosigna-STA is compared with the conclusions of Oncotype DX in the table below. The Prosigna test provided prognostic information for early stage breast cancer patients with node negative disease, but evidence that the test predicted chemotherapy benefit was not identified. In contrast, Oncotype DX predicted chemotherapy benefit and provided prognostic information for both node negative and postmenopausal node positive patients.

Table 29. *Main conclusions of the Prosigna-STA conducted in 2019 and the current STA evaluating Oncotype DX*

Important considerations	Oncotype DX	Prosigna (as assessed in 2019)
Can the test predict chemotherapy benefit?	Oncotype DX can predict chemotherapy benefit for early stage breast cancer patients that are node negeative or postmenopausal and node positive.	Studies investigating chemotherapy benefit was not available.
Does the test provide prognostic information?	Oncotype DX can provide prognostic information for early stage breast cancer patients that are node negeative or postmenopausal and node positive.	Prosigna can provide prognostic information for early stage breast cancer patients that are node negeative.
Is the test likely to be cost-effective?	Oncotype DX seems to be more effective and less costly compared to no gene-profiling test.	Conclusions about the cost-effectiveness of Prosigna could not be made as reliable data on chemotherapy use and clinical outcomes for patients who have or have not undergone Prosigna testing were not available.

Consistency

NICE published an HTA investigating the performance of Oncotype DX and four additional gene profiling tests in 2019 (3). The HTA was based on a literature search conducted in 2017 and found that Oncotype DX could predict chemotherapy benefit. Patients with high RS showed chemotherapy benefit and patients with low RS did not. The HTA also indicated that patients with intermediate RS did not show chemotherapy benefit, but this result was uncertain, because the result mainly relied on two RCTs with a relative low number of included patients (NSABP B-20 for node negative patients (7), and SWOG-8814 for node positive patients (9)). Use of Oncotype DX in clinical practice resulted in low chemotherapy use among node negative patients with a low RS. However, the authors of the HTA emphasised that the number of patients that will be assigned to chemotherapy based on their test result, will depend on how patients with intermediate RS are handled and whether node positive patients are handled similar to node negative patients in future clinical practice.

After the NICE HTA was conducted, results from the two RCTs TailorX and RxPONDER were reported (10;12). TailorX and RxPONDER were designed to investigate whether

patients with intermediate (and low) RS show any chemotherapy benefit, and included a sufficient number of patients to address this question (sufficient statistical power). Consequently, our STA (which included TailorX and RxPONDER) provided more convincing evidence than the NICE HTA. Our STA concluded that also patients with intermediate RS can omit chemotherapy, and this applied to both node negative patients and postmenopausal node positive patients.

Furthermore, TailorX (12) introduced a new set of RS thresholds (low RS: 0-10, intermediate RS: 11-25, high RS: 26-100) and these thresholds are now widely applied. Most studies included in the NICE HTA used the old RS thresholds (low RS: 0-17, intermediate RS: 18-30, high RS: 31-100). The distribution of RS in populations of breast cancer patients reported in our STA are therefore not directly comparable to the distributions reported in the NICE HTA. However, it is worth to mention that also the NICE HTA found that Oncotype DX had prognostic power. Thus, the risk of distant recurrence increased with increasing RS, in line with the findings in our STA. This observation implies that the prognostic power of Oncotype DX is robust and valid for different sets of RS thresholds.

Discussion – health economic evaluation

Key findings

The base case cost-effectiveness analysis demonstrated that Oncotype DX was dominant compared to assessment of conventional clinical parameters, i.e. no gene-profiling test, for both node negative and postmenopausal node positive patients, i.e. providing greater QALY gains at a lower cost. The probabilistic sensitivity analyses showed that, with a willingness-to-pay threshold of 250,000 Norwegian kroner per QALY, the Oncotype DX test compared to no gene-profiling test had a 99% probability of being cost-effective for node negative patients. Correspondingly, for postmenopausal node positive patients the likelihood of Oncotype DX test being cost-effective was 100%.

The submitted budget impact analysis for LN0 and postmenopausal LN+ patients showed that Oncotype DX incurred costs the first five years after implementation when compared to no gene-profiling test. The net costs are due to the test costs being incurred early in the period, while the savings from factors such as reduced local and distant recurrences occur at time points beyond the 5-year time horizon.

Limitations and uncertainties

The cost-effectiveness analysis was conducted by integrating various sources of evidence and assumptions, which may have contributed to overall uncertainty in the model.

Regarding the distribution of recurrence scores for postmenopausal LN+ these specific data are not reported in the original article of RxPONDER (10). The RxPONDER study focuses only on low and intermediate RS (0-25), and excludes patients with high RS. However, the distribution provided by the submitter (percentage of patients with high

RS) aligns reasonably well with the results from a large registry study (see Table 9 in the chapter of evaluation of clinical effectiveness).

Another challenge is that different studies have used different RS thresholds. For example, the probability of receiving adjuvant chemotherapy are sourced from two registry studies, Stemmer et al. 2017 (44) and Stemmer et al. 2019 (23). Stemmer et al. 2017 employed the old RS thresholds (low 0-17, intermediate 18-30, high >30), whereas Stemmer et al. 2019 employed the new RS thresholds (low 0-10, intermediate 11-25, high >25). However, we ran the model with alternative probabilities for receiving adjuvant chemotherapy based on other references (23;44) and the outcomes showed minimal changes. We for example did a scenario analysis with probabilities used in the STA of Prosigna by NIPH for lymph node negative patients in the no gene-profiling test strategy, which was informed by a clinical expert (4). The result remained in favour of Oncotype DX (dominant strategy).

Notable uncertainty was observed in the sensitivity analyses regarding the clinical input values. For LN0 patients, the hazard ratio of the high RS group appears as the primary source of uncertainty in the model. The upper bound for the hazard ratio of 0.62 corresponds to an ICER of NOK 85,934 per QALY, which is considerably lower than a willingness-to-pay threshold of NOK 275,000, which is usually considered as a low threshold.

For postmenopausal LN+ patients, the hazard ratio for the low and intermediate RS group appears as the primary source of uncertainty in the model. The upper bound for the hazard ratio, of 1.52, corresponds to a dominant ICER.

In Norway, LN0 patients are offered the gene-profiling test Prosigna. The submitter has not performed a cost-effectiveness analysis of Oncotype vs. Prosigna. It therefore remains unclear whether Oncotype DX is more cost-effective than Prosigna for lymph node negative patients.

The budget impact analysis for no gene-profiling test vs. Oncotype for lymph node negative patients seem of limited relevance since Prosigna is already offered to this patient population in Norway. There are uncertainties associated with the budget impact analyses.

Implications of the findings for practice

The submission file investigated the performance of Oncotype DX in ER+ HER- early-stage breast cancer. The findings imply that Oncotype DX may be used to identify node negative patients that can omit chemotherapy (patients with low or intermediate RS). These patients can avoid chemotherapy-induced side-effects without increasing the risk of recurrence. Oncotype DX may also be used to identify node negative patients that should be recommended chemotherapy (patients with high RS). These patients showed lower recurrence rates when treated with endocrine therapy plus chemotherapy compared to endocrine therapy alone.

Similar results were found for postmenopausal patients with node positive disease (1-3 positive lymph nodes). Oncotype DX may thus be used to identify node positive patients that can omit chemotherapy (postmenopausal patients with low or intermediate RS), and to identify node positive patients that should be recommended chemotherapy (postmenopausal patients with high RS).

For premenopausal patients with node positive disease (1-3 positive lymph nodes), some chemotherapy benefit was found for the low and intermediate RS populations. This finding implies that Oncotype DX did not identify premenopausal patients that can omit chemotherapy. In line with this, the submitter did not recommend Oncotype DX for premenopausal women with node positive disease.

The distributions of RS in populations of breast cancer patients suggested that 76-86% of the patients with node negative disease and 84-90% of the patients with node positive disease had low or intermediate RS and could omit chemotherapy. The current use of chemotherapy is particularly high in patients with node positive disease, suggesting that chemotherapy use can be substantially reduced in this group. In line with this, decision-impact studies conducted in Italy and Canada demonstrated that chemotherapy use was reduced by 16-27% for node negative patients and by 50-73% for node positive patients when Oncotype DX was applied. However, the decision-impact studies also illustrated that treatment decisions were not based entirely on the RS. It is likely that physicians will combine RS with clinical parameters also in Norway, but it is not clear how different parameters should be weighted in such combinations.

The Oncotype DX test is performed on paraffin-embedded, formalin-fixed tumor tissue. The manufacturer requires that the tissue is shipped to a commercial laboratory located in the US for analysis. This shipment may delay test results compared to profiling test that can be performed in Norwegian hospital laboratories (such as Prosigna). Remaining tissue blocks, but not individual slides, are returned. Specific information about the patients is also required, including name, date of birth, sex, diagnosis, and pathological information (lymph-node status, estrogen receptor status, and other information from the post-surgery pathology report). According to the submission file, strict measures are followed to secure privacy, including the GDPR compliance program and regulations for transfers of patient data outside the EU. NIPH has not evaluated these measures or considered possible legal and ethical issues related to the transfer of patient data and patient tissue outside Norway.

Need for further research

The submission file documented that Oncotype DX alone can predict chemotherapy benefit, and this documentation is convincing. Results from Oncotype DX (i.e. the recurrence score, RS) may also be combined with traditional clinical parameters such as tumor grade, tumor size, proliferation status, and lymph node status. Indeed, Tang and colleagues demonstrated that a combination of clinical parameters and RS were more prognostic than RS alone for early stage breast cancer patients (13). The submission

file did not discuss or present strategies for combining RS with clinical parameters. It is therefore not clear how different parameters should be weighted in such combinations. Detailed guidelines for combining results from Prosigna with clinical parameters have been applied in Norway (2), but it is not obvious that the same guidelines can be applied for Oncotype DX. If one wish to combine Oncotype DX with clinical parameters, guidelines on how the different parameters should be weighted are needed.

Conclusion

Oncotype DX predicted 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). In these groups, patients with low or intermediate RS (0-25) did not show chemotherapy benefit and could omit chemotherapy, whereas patients with high RS (>25) showed chemotherapy benefit and should be offered chemotherapy to reduce the risk of recurrence.

The distribution of RS in breast cancer populations suggested that chemotherapy use can be substantially reduced. Decision-impact studies demonstrated that Oncotype DX can reduce chemotherapy assignment in clinical practice, but also illustrated that treatment decisions were not based entirely on the RS. RS can predict chemotherapy when used alone, but RS may also be combined with traditional clinical parameters such as tumor grade, tumor size, proliferation status, and lymph node status. If one wish to combine RS with clinical parameters, guidelines on how the different parameters should be weighted are probably needed.

Oncotype DX seems to be more effective and less costly compared to no gene-profiling test. Sensitivity analyses confirmed that Oncotype DX is probably cost-effective, also at low thresholds of willingness-to-pay. As the two tests were not compared, it remains unclear whether Oncotype DX is more cost-effective than Prosigna for node negative patients in Norway.

The budget impact analysis for node negative patients indicate incurred net costs in the five years after implementation, but this analysis is of limited relevance since Oncotype is compared to no gene-profiling test, rather than Prosigna. Implementation of Oncotype DX for postmenopausal lymph node positive patients seems to be cost saving the first five years.

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Appendix 1: Literature search strategy

The literature search strategy for the Medline database is shown below. The search strategy is taken from the submission file. Similar search strategies were also provided for the databases Embase (OvidSP), Cochrane Database of Systematic Reviews, Episte-monikos Database, Cochrane CENTRAL Register of Controlled Trials, NIH Clinicaltrials, and WHO International Clinical Trials Registry Platform.

2020 search:
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to February 11, 2020>
Search Strategy:
1 exp Breast Neoplasms/ (288778)
2 exp mammary neoplasms/ (22212)
3 exp "Neoplasms, Ductal, Lobular, and Medullary"/ (39108)
4 ((breast$ or mammar$) adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or ad-enocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraductal$ or lobular or medullar$)).ti,ab. (350490)
5 or/1-4 (427803)
6 (oncotype or "oncotype dx" or "Breast Recurrence Score" or 21-gene or gene21 or gene?twentyone or twentyone?gene or "ghi recurrence score" or ghi-rs or 92-gene or gene92 or gene?ninetytwo or ninetytwo?gene or (rct-pcr adj5 "21")).ti,ab. (1389)
7 (EndoPredict or "myriad genetics" or "sividon diagnostics" or Epclin or "ep score" or "epclin score").ti,ab. (185)
8 (mammaprint or 70-gene or gene70 or gene?seventy or seventy?gene or "amsterdam profile").ti,ab. (735)
9 (prosigna or pam50 or 50-gene or gene50 or gene?fifty or fifty?gene or "breast bio-classifier" or ihc4).ti,ab. (558)
10 or/6-9 (2603)
11 5 and 10 (1380)
12 (2017$ or 2018$ or 2019$ or 2020$).ed. (3271592)
13 11 and 12 (439)

2022 search:
Searched 12/07/22 via OvidSP interface.
Date limited to 2020 onwards.
Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to July 11, 2022>
Search Strategy:
1 exp Breast Neoplasms/ (328722)
2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ (44642)
3 ((breast$ or mammar$) adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or ad-enocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraductal$ or lobular or medullar$)).ti,ab. (402609)

4 or/1-3 (483161)
5 (oncotype or "oncotype dx" or "Recurrence Score Pathology Clinical" or "Recurrence Score Pathology-Clinical" or "Recurrence Score-Pathology-Clinical" or Recurrence-Score-Pathology-Clinical or RSPC or "Breast Recurrence Score" or 21-gene or gene21 or gene?twentyone or twentyone?gene or "ghi recurrence score" or ghi-rs or 92-gene or gene92 or gene?ninetytwo or ninetytwo?gene or (rct-pcr adj5 "21")).ti,ab. (1745)
6 (EndoPredict or "myriad genetics" or "sividon diagnostics" or Epclin or "ep score" or "epclin score").ti,ab. (222)
7 (mammaprint or 70-gene or gene70 or gene?seventy or seventy?gene or "amsterdam profile").ti,ab. (833)
8 (prosigna or pam50 or 50-gene or gene50 or gene?fifty or fifty?gene or "breast bio-classifier" or ihc4).ti,ab. (753)
9 or/5-8 (3222)
10 4 and 9 (1809)
11 (2020$ or 2021$ or 2022$).ed. (3188822)
12 10 and 11 (462)

Appendix 2: Costs used in the health economic model

Table 1. *Drug and administration costs*

Drug acquisition costs	*Cost per tablet/vial (NOK) ex. VAT*	*Cost per mg*	*Concentratio n*	*Tablet Capsule. or Vial Size (mg)*	*Reference*
Fluorouracil	263.68	0.02	50mg/20ml	vial	NoMA database (Accord)
Epirubicin	678.4	17.51	2mg/75ml	vial	Felleskatalogen.no (Medac)
Cyclophospha mide	72.10	0.28	200g	vial	NoMA database (Actavis)
Cyclophospha mide	215.4	0.16	1000mg	vial	NoMA database (Baxter Medical AB)
Docetaxel	8 330.88	52.07	160mg/8ml (20mg/ml)	vial	NoMA database (Baxter Medical AB)
Docetaxel	1 177.12	58.86	20mg/1ml (20mg/ml)	vial	NoMA database (Accord)
Paclitaxel	5 115.68	34.10	150mg/25m l	vial	NoMA database (Accord)
Carboplatin	2 978.00	49.63	600mg/60m l	vial	Felleskatalogen.no (Accord)
Doxorubicin	354.10	NA	200mg/100 ml	vial	Felleskatalogen.no (Accord)
Doxorubicin	464.40	18.58	50mg/25ml	vial	Felleskatalogen.no (Accord)
Capecitabine	4.83	0.02	300mg/60 tablets	tablets	Felleskatalogen.no (Accord)
Capecitabine	14.62	0.03	500mg/120 tablets	tablets	NoMA (Accord)
(Caelyx) Pegylated liposomal doxorubicin	3 524.00	176.20	2mg/25ml	vial	Felleskatalogen.no (Pfizer)
Eribulin	3 251.84	3 695.27	0.88mg/2ml	vial	NoMA (Eisai)
Tamoxifen	7.94	1.32	20mg	tablets	Felleskatalogen.no (Mylan)
Anastrozole	16.15	56.51	1mg	tablet	Felleskatalogen.no (Medical Valley)
Letrozole	13.36	19.09	2.5mg	tablet	NoMA (Mylan)
Exemestane	29.39	16.29	25mg	tablet	NoMA (Accord)
Fulvestrant	2 571.36	4.07	250mg/5ml		NoMA (Astra Zeneca AB)
Everolimus with examestane	632.61	126.52	5mg	tablets	Felleskatalogen.no (Novartis)
Everolimus with examestane	860.60	86.06	10mg	tablet	Felleskatalogen.no (Novartis)
Abemaciclib	607.13	8.10	150mg	capsule	Felleskatalogen.no (Lilly)
Palbociclib	1 046.66	8.37	125mg	capsule	Felleskatalogen.no (Pfizer)

Ribociclib	672.85	10.09	200mg	tablet	Felleskatalogen.no (Novartis)
Aprepitant pre- made pack	507.52	1.78	NA		Felleskatalogen.no (MSD)
Filgrastim	397.10	1323.68	300mcg/0.5 ml	pre-filled sy-ringes	Felleskatalogen.no (Amgen)
Filgrastim	501.25	1 044.27	480mcg/0.5 ml	pre-filled sy-ringes	NoMA (Amgen)
Drug administration costs					
IV administration cost per infusion visit (same fee for first and subsequent visits)	2378.75				NoMA 2020. Unit costs V. 1
Intramuscular administra-tion	219.00				NoMA 2020. Unit costs V. 1
Outpatient visit	1868.76				DRG 930A
Blood tests (leucocytes. CRP. electrolytes)	46.00				Fürst Medical Laboratory. Price list.

Table 2. *Costs of Docetaxel and Cyclophosphamide*

TC	No. of doses	Vial sharing	Full wastage
Cyclophosphamide 600mg/m^2	4	kr 235	kr 878
Docetaxel 75mg/m^2	4	kr 27 336	kr 33 324
Supportive: aprepitant	4	kr 2 030	kr 2 030
Supportive: filgrastim	4	kr 9 329	kr 9 639
Total		**kr 37 306**	**kr 44 247**

Table 3. *Costs of EC90/TC75 – Epirubicin and Cyclophosphamide + Docetaxel*

EC90/T75	No. of doses	Vial sharing	Full wastage
Epirubicin 90 mg/m^2	4	kr 8 550	kr 10 857
Cyclophosphamide 600mg/m^2	4	kr 235	kr 878
Docetaxel 75mg/m^2	12	kr 82 007	kr 99 971
Supportive: aprepitant	8	kr 4 060	kr 4 060
Supportive: filgrastim	8	kr 18 658	kr 19 279
Total		**kr 102 799**	**kr 124 085**

Table 4. *Costs of EC90/TC75 – Epirubicin and Cyclophosphamide*

EC90	No. of doses	Vial sharing	Full wastage
Epirubicin 90 mg/m^2	4	kr 8 550	kr 10 857
Cyclophosphamide 600mg/m^2	4	kr 235	kr 878
Supportive: aprepitant	4	kr 2 030	kr 2 030
Supportive: filgrastim	4	kr 9329x20%§	kr 9 639
Total		**kr 11 057**	**kr 14 069**

Table 5. *Early BC – model cycle costs*

Regimens	%	Acquisition cost
Tamoxifen	10 %	kr 2 890
Anastrozole	20 %	kr 2 938
Letrozole	50 %	kr 2 432
Everolimus & exemestane	20 %	kr 5 349
Weighted average	**-**	**kr 3 152,25**

Table 6. *Subsequent BC – model cycle costs*

	Metastatic BC 1st line		Metastatic BC 2nd line		Metastatic BC 3rd line	
Regimens	**%**	**Acquisition**	**%**	**Acquisition**	**%**	**Acquisition**
Tamoxifen	18 %	kr 1 445	15 %	kr 1 445	29 %	kr 1 445
Anastrozole	31 %	kr 2 938	9 %	kr 2 938	14 %	kr 2 938
Letrozole	39 %	kr 2 432	18 %	kr 2 432	14 %	kr 2 432
Exemestan e	7 %	kr 2 224	18 %	kr 2 224	14 %	kr 2 224
Everolimus &	0 %	kr 158 853	16 %	kr 158 853	29 %	kr 158 853

Table 7. *Adverse event costs*

Adverse event	Cost	Comment	Source
Alopecia	NOK 10 000	Wig*	NAV/Communication with wig maker
Anemia	NOK 10 582	FHI 2012a, inflated to 2020 price level by CPI	Report from Kunnskapssenteret No 4–2012 (71)
Diarrhea	NOK 1 869	Assumed to be one extra outpatient visit DRG930A	ISF Norge 2021 (62)
Edema	NOK 1 869	Assumed to be one extra outpatient visit DRG930A	
Febrile neutropenia	NOK 40 178	DRG 399 Retikuloendoteliale og immunologiske sykd ITAD u/bk	
Infection	NOK 71 433	DRG 423. Sykdommer i HDG 18. From ICD 10 B99.9	
Lethargy	NOK 1 869	Assumed to be one extra outpatient visit DRG930A	
Musculoskeletal	NOK 26 163	DRG 247 Uspesifikke tilstander fra muskel og skjellet	
Myalgia/arthralgia	NOK 26 163	DRG 247	
Nail/skin disorder	NOK 1 869	Assumed to be one extra outpatient visit DRG930A	
Nausea/vomiting	NOK 1 869	Assumed to be one extra outpatient visit DRG930A	
Neuropathy	NOK 40 412	ICD10 G62.8 in NiceF grouper gives DRG 19. “Sykdommer i hjernenerver og perifere nerver u/bk2“	
Stomatitis	NOK 1 869	Assumed to be one extra outpatient visit/RG930A	
Thrombocytopenia	NOK 46 205	DRG 397 Koagulasjonsforstyrrelser	
Treatment-related death	NOK 60 174	2020: Kostnader livets sluttfase	NoMA, unit costs V1, 2020 (64)

Constipation	NOK 1 869	Assumed to be one extra outpatient visit DRG930A	ISF Norge 2021 (62)
Fatigue	NOK 1 869	Assumed to be one extra outpatient visit DRG930A	ISF Norge 2021 (62)

*According to the submitter, the maximum reimbursement for a wig is NOK 5 725. The submitter also contacted a wigmaker that total cost very seldom would be less than NOK 10 000. In addition, for patients with deviating head shape, the maximum reimbursement is NOK 14 825. The unit cost used can therefore be considered a conservative estimate according to the submitter.

***Table 8**. Adverse event weighing for cost calculation*

Grade 3 or 4 AE	PACS-01 (%)	TACT (%)	
		FEC60	FEC-D
Alopecia	82,6%	9,0%	10,2%
Anemia	0,7%	0,5%	0,6%
Diarrhoea	0,0%	2,0%	3,7%
Edema	4,8%	1,0%	0,8%
Febrile neutropenia	11,2%	2,0%	7,1%
Infection	1,6%	7,0%	14,2%
Lethargy	0,0%	13,0%	22,1%
Leukopenia	0,0%	18,0%	24,6%
Musculoskeletal	0,0%	1,0%	7,0%
Myalgia/arthralgia	0,0%	0,1%	5,0%
Nail/skin disorder	10,3%	1,0%	3,3%
Nausea/vomiting	11,2%	10,0%	9,7%
Neuropathy	0,0%	0,3%	4,8%
Neutropenia	28,1%	40,0%	45,5%
Pain	0,0%	0,1%	2,8%
Stomatitis	5,9%	2,0%	7,6%
Thrombocytopenia	0,4%	0,9%	0,6%
Treatment-related mortality	0,0%	0,0%	0,3%

LN0	FEC75	FEC-D	Weighted
Weighted average	kr 8 123,62	kr 20 481,39	kr 22 729,54

LN+	FEC75	FEC-D	Weighted
Weighted average	kr 8 123,62	kr 20 481,39	kr 25 960,52

Selected source	**RxPONDER**		
	CET		
Active values		kr	1 645,91

Appendix 3: The submitted parameter overview in the sensitivity analyses

Table 1. *The submitted parameter overview and distributions*

Parameter	Base case	DSA range	PSA SE and distribution	Reference
RS 0-10 Distribution	17%	Not varied	Dirichlet (1619,6711,1389)	TAILORx (8)
RS 11-25 Distribution	69%			
RS 26-100 Distribution	14%			
Prob of chemo, no test, LN0	27%	26%,28%	Beta (α=4229;β=8905)	NICE 2018 (47)
Prob of chemo, no test, LN+	75%	74%, 76%	Beta (α=4557;β=1526)	NICE 2018 (47)
RS 0-10 Prob of chemo, ODX	0%	Not varied	Not varied	Stemmer et al., 2017 (44)
RS 11-25 Prob of chemo, ODX	9%	7%,11%	Beta (α=80;β=773)	
RS 26-100 Prob of chemo, ODX	70%	64%,76%	Beta (α=188;β=81)	
RS 0-10 9-year DRFS with ET, ODX, LNO	96.8%	95%,98%	Beta (α=611; β=20)	TAILORx (8)
RS 11-25 9-year DRFS with ET, ODX, LNO	94.5%	94%, 96%	Beta (α=1964; β=114)	
RS 26-100 9-year DRFS with ET, ODX, LNO	62.0%	48%, 81%	Beta (α=20; β=12)	Geyer et al. 2018 (6)
RS 0-14 10-year DRFS with ET, ODX LN+	81.8%	73%, 88%	Beta (α=79; β=18)	TransATAC. (45), NICE DG34 (72)
RS 15-25 10-year DRFS with ET, ODX LN+	75.4%	63%, 84%	Beta (α=47; β=15)	
RS 26-100 10-year DRFS with ET, ODX LN+	68.6%	45%, 84%	Beta (α=14; β=6)	
RS 0-10 HR of DR with chemo, ODX, LN0	1.19	0.41,3.51	Gamma (k=2; θ=0.53)	Geyer et al., 2018 (6)
RS 11-25 HR of DR with chemo, ODX, LN0	0.91	0.71,1.18	Gamma (k=58; θ=0.02)	TAILORx (8)
RS 26-100 HR of DR with chemo, ODX. LN0	0.27	0.12,0.62	Gamma (k=4; θ=0.06)	Geyer et al., 2018 (6)
RS 0-14 HR of DR with chemo, ODX, LN+	1.02	Not re-ported	Gamma (k=8.3; θ=0.12)	Albain et al., 2010 (9)

RS 15-25 HR of DR with chemo, ODX, LN0	0.72	Not reported	Gamma (k=58; θ=0.02)	
RS 26-100 HR of DR with chemo, ODX, LN0	0.59	Not reported	Gamma (k=4; θ=0.06)	
Probability of local recurrence prior to distant recurrence	10.5%	8.8%,12.3%	Beta (α=129; β=1095)	De Bock et al., 2009 (73)
Reduction in DR rate in years 11-15	50%	Nor varied	Not varied	NICE 2018 (72)
Reduction in DR rate in years >15	50%	Not varied	Not varied	UK Clinical expert opinion
6-month probability of AML	0.006	0.000, 0.012	Beta (α=4; β=639)	Petrelli et al. 2012 (50)
Probability of death, recurrence-free	Norwegian life tables	Not varied	Not varied	Statistics Norway (42)
Survival in DR after 40.1 months	50%	38.7%,61.3 %	Beta (α=39; β=39)	Thomas et al., 2009 (74)
6-month, Probability of death, AML	0.53	0.42,0.64	Beta (α=45; β=40)	NICE 2011 (source not specified further in the submission file)

RS: Recurrence Score; Chemo: Chemotherapy; ODX: Oncotype DX; AML: Acute myloid leukemia; LN0: Lymph Node Negative; LN+: Lymph Node Positive; PSA: Probabilistic Sensitivity Analysis; DSA: deteministic sensitivity analysis; ET: Endocrine therapy; SE: standard error; Prob: Probability; DR: distant recurrence; DRFS: distant recurrence-free survival; HR: Hazard ratio

Appendix 4: Progress log

Date	Milestone
27.09.21	STA commissioned
01.10.21	Contact with agent (Oecona) established
28.11.21	First meeting between NIPH and Exact Scienses and Oecona, and they confirmed to submit
11.21-02.22	Clinical experts and a patient representative (Brystkreftforeningen via FFO) recruited
02.08.22	NIPH received first submission file
25.08.22	NIPH and Oecona had a meeting. Oecona explained the submitted health economic model
12.09.22	NIPH ask manufacturer/Oecona for a list of all included studies, a list of the studies that were used in the documentation, and an explanation of why they chose to use some of the included studies and not others, literature search strategy, and RoB assessment.
11.10.22	NIPH received an e-mail from Oecona and company with some information about the excluded studies
24.10.22	NIPH gave the submitter two options: 1. Provide revised documentation that addressed a list of requirements, or 2. Not provide revised documentation. NIPH explained that if the submitter chose option 2, NIPH would inform the commissioner about the decision. Based on that information, the commissioner might have canceled the assignment and instead ordered a full HTA (not based on documentation from the manufacturer). If that had happened, NIPH explained that the health economic model provided by the submitter could still be used (if allowed by the submitter).
01.11.22	The submitter notified NIPH that they were willing to provide revised documentation
09.02.23	NIPH received a revised submission file from submitter (project start)

10.03.23	NIPH accepted revised submission file
13.03.23	NIPH updated clinical experts and Brystkreftforeningen
05.07.23	Report draft sent for review to clinical experts, patient representative, internal experts and Sykehusinnkjøp
22.08.23	Reviews received
07.09.23	Revised report sent to submitter for review (Oecona)
15.09.23	Received feedback from Oecona/Exact Sciences
04.10.23	Submitted report