Alberta Health Evidence Review Report

Clinical effectiveness and cost-effectiveness of Oncotype DX and Prosigna genetic testing in early-stage breast cancer

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The views expressed in this report are of the Institute of Health Economics.

Inquiries

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Declared Competing Interest of Authors

Competing interest is considered to be financial interest or non-financial interest, either direct or indirect, that would affect the research contained in this report or create a situation in which a person's judgement could be unduly influenced by a secondary interest, such as personal advancement.

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Executive Summary

Background

Breast cancer is one of the most common cancers in Alberta, affecting approximately one in eight women in their lifetime, with an estimated 2,600 women newly diagnosed in 2017. First-line treatment for early-stage, estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2−) breast cancer typically involves surgery (total or partial mastectomy), followed by adjuvant therapies such as endocrine therapy and chemotherapy to reduce the risk of cancer recurrence. While daily endocrine therapy for five years is the current standard of care for ER+ breast cancer, about 20% of patients who receive endocrine therapy will still experience long-term distant recurrence. Additional chemotherapy may help further reduce the risk of long-term distant recurrence in this patient population. However, uncertainties remain regarding the optimal use of adjuvant chemotherapy in these patients. Oncotype DX and Prosigna, two gene expression profiling tests that can help determine the risk of distant recurrence and the potential benefit of adjuvant chemotherapy, have been used in Alberta when further information is needed to inform treatment decisions.

In 2016, a research team at the University of Alberta was commissioned to examine the clinical effectiveness and cost-effectiveness of Oncotype DX and Prosigna. The team found that Prosigna was likely to lead to better population health outcomes at a lower cost. In 2017, based on the results in the University of Alberta report, Prosigna testing replaced Oncotype DX testing as the standard of care for breast cancer patients requiring genetic testing. In 2018, the results of a clinical trial, TAILORx, were published, showing that Oncotype DX was predictive of no additional benefit of chemotherapy in most patients at intermediate risk of distant recurrence. Since the publication of the TAILORx results, Alberta medical oncologists have substantially increased their ordering of Oncotype DX, which must be approved on a case-by-case basis.

In light of the publication of the TAILORx results, Alberta Health Services (AHS) wished to receive an update of the 2016 University of Alberta report. The Laboratory Formulary Committee (Alberta Public Laboratories, AHS) made a request to Alberta Health via the Alberta Health Evidence Reviews Process for a clinical review and economic evaluation of the most recent research evidence. The Institute of Health Economics (IHE) was commissioned to conduct this work.

The clinical review and economic evaluation aimed to determine how Oncotype DX and Prosigna can be optimally used to determine which patients with early-stage breast cancer will benefit from adjuvant chemotherapy. This report addresses the following research question: *For patients with early-stage (I–III), ER+, HER2−, node-negative or node-positive (one to three nodes) breast cancer, what are the clinical and economic benefits of Oncotype DX and Prosigna genetic testing, and how do these differ by node status, risk status, age, and menopausal status?*

Clinical Review

Methods

The clinical review consisted of three rapid reviews examining, respectively:

1. the clinical validity (prognostic ability) and utility (predictive ability) of the Oncotype DX and Prosigna genetic tests in predicting risk of cancer recurrence, survival, and response to adjuvant chemotherapy, in patients with early-stage breast cancer;

2. clinician and patient treatment decisions about adjuvant chemotherapy in patients with early-stage breast cancer, with and without the results of the Oncotype DX or Prosigna genetic tests; and
3. the health-related quality of life of patients with early-stage breast cancer who receive and do not receive adjuvant chemotherapy.

For each rapid review, a single reviewer searched for, selected, extracted data from, and analyzed the results of relevant systematic reviews and primary studies, with assistance from a second reviewer as needed.

Rapid review 1 searched for primary studies published from 2002 onward (the year when the first genetic test was introduced); rapid review 2 included a systematic review that was published in 2016 and searched for all relevant primary studies published subsequent to this systematic review; and rapid review 3 searched for systematic reviews (none were found) and primary studies published from 2007 onward (the publication date of the primary study that provided quality of life information for the economic analysis included in the 2016 University of Alberta report).

Results

Clinical validity and utility

Rapid review 1 included 12 primary studies and used an established tumour marker utility grading system to assess the level of evidence as level 1A (highest level), 1B, 2, or 3 (lowest level), based on the number of category A (strongest design; that is, a randomized controlled trial), B, or C (weak design; that is, an observational study) studies contributing data.

Prognostic ability

Level 1B to level 3 evidence from nine category B and C studies supported the prognostic ability of both Oncotype DX and Prosigna, with lower-risk patients generally, but not always, experiencing better 5- to 15-year outcomes than higher-risk patients ($p<0.05$). The prognostic ability of both genetic tests was observed in various patient groups, including node-negative and node-positive (one to three nodes) patients, pre- and postmenopausal patients, and patients receiving endocrine or chemoendocrine therapy, and results were consistent regardless of the risk cut-off used in the study. However, there are important limitations and gaps in the evidence base for both genetic tests, particularly for intermediate-risk patients, premenopausal patients, and patients with micrometastatic disease. No ongoing clinical trials were identified to address these gaps.

Level 2 evidence from one category B study indicated that Prosigna was more prognostic than Oncotype DX in node-negative, postmenopausal patients receiving endocrine therapy only ($p<0.05$). There were no other comparative data available for any other patient groups, and no ongoing clinical trials were identified to address these gaps.

Predictive ability

Level 1A evidence from one category A study (TAILORx) indicated that Oncotype DX is predictive of a lack of adjuvant chemotherapy benefit at nine years in most node-negative patients at intermediate risk (a risk score [RS] between 11 and 25, which differs from the standard intermediate-risk range of 18 to 30) of distant recurrence ($p>0.05$). This finding was supported by three additional category B and C studies that used variable risk cut-offs and assessed outcomes at time points ranging from 5 to 10 years. Exploratory, post-hoc subgroup analyses from TAILORx showed a

benefit of chemotherapy in node-negative patients aged 50 years or younger with intermediate-risk scores between 21 and 25 ($p<0.05$).

No conclusions can be drawn regarding the predictive ability of Oncotype DX in node-positive (one to three nodes) patients due to conflicting level 3 evidence from two category C studies, or Prosigna in node-negative or node-positive (one to three nodes) patients due to a lack of evidence. Two ongoing clinical trials (RxPONDER and OPTIMA) are expected to contribute level 1A evidence (in 2022 and 2023) for the above-described patient groups, respectively.

Clinician and patient treatment decisions

Data from one systematic review (with five relevant primary studies) and eight additional prospective observational studies examining the impact of genetic testing on clinician and patient treatment choices were generally consistent for both node-negative and node-positive (one to three nodes) patients. After receiving test results, clinician treatment recommendations changed for a median of 32% of patients tested with Oncotype DX and 16% of patients tested with Prosigna. Following Oncotype DX testing, there was a median 11% and 22% net decrease in the use of adjuvant chemotherapy in node-negative and node-positive (one to three nodes) patients, respectively, largely driven by more low- and intermediate-risk patients foregoing chemotherapy. Following Prosigna testing, there was a median 9% net increase in the use of adjuvant chemotherapy in node-negative patients, largely driven by more intermediate- and high-risk patients choosing to receive chemotherapy. Quality improvement data from Alberta showed similar trends for both tests. Limited evidence suggests that both genetic tests help support clinician and patient decision-making.

Risk category cut-offs and stratifications

Most studies examining clinical validity/utility and clinician/patient treatment decisions used standard risk cut-offs to define intermediate-risk patients, for both genetic tests (that is, an RS between 18 and 30 or 31 for Oncotype DX, and a risk of recurrence [ROR] between 41 and 60 for Prosigna). However, two studies (including TAILORx) used a lower RS cut-off (between 11 or 12 and 25) for Oncotype DX, and three studies used ROR cut-offs that varied based on node status. Overall, the risk stratifications differed across the tests for both node-negative and node-positive (one to three nodes) patients, with more patients classified as low risk by Oncotype DX and as high risk by Prosigna.

Health-related quality of life

Fifteen primary studies with variable study designs found that chemotherapy treatment, as well as different chemotherapy regimens (for example, different types and dosing of chemotherapy), had variable effects on quality of life, as measured using two generic instruments (EQ-5D [EuroQol 5 dimensions] and SF-36 [36-Item Short Form Health Survey]).

Economic Evaluation

Methods

A model-based cost-utility analysis was undertaken from the perspective of AHS to evaluate the expected patient outcomes, costs, and cost-effectiveness of Prosigna-guided adjuvant chemotherapy compared with either Oncotype DX-guided adjuvant chemotherapy or the provision of adjuvant chemotherapy without guidance from either test ("No testing"), where a decision on chemotherapy is made on clinical grounds by the clinician and patient. The patient population was a hypothetical cohort of patients aged 55 years who were diagnosed with early-stage, ER+ (and/or progesterone

receptor positive [PR+]), HER2−, node-negative breast cancer, who are candidates for adjuvant chemotherapy. The impact of testing node-positive patients was also considered. The outcome measure was the quality-adjusted life year (QALY), which is a composite measure of length and quality of life.

The model parameters were obtained from a range of secondary sources. The key parameters that describe the characteristics of each test include: the proportion of patients in each risk category, the proportion of patients receiving chemotherapy by risk category, and the risk of future distant recurrence by risk category. The selection of sources to inform these parameters was based on extensive discussions with the Expert Advisory Group.

Uncertainty in the model parameters was accounted for by using probabilistic sensitivity analysis. Fifteen thousand Monte Carlo simulations were used to promulgate this uncertainty through the model, to capture the resulting uncertainty in the model outputs (for example, the estimated cost and outcomes for each of the treatment strategies being compared). Four sensitivity analyses were conducted to examine the impact of varying the menopausal status of the patients, the price of Oncotype DX, the risk category stratification by test result, and the discount rate.

Results

The results indicate that Prosigna is more cost-effective than Oncotype DX for patients with either node-negative or node-positive early-stage breast cancer. While the implementation of Prosigna testing did lead to increased average lifetime costs per patient, the improved patient outcomes in terms of cases of distant recurrence averted and QALYs gained mean that it would be acceptable on cost-effectiveness grounds. For example, for node-negative patients, the expected cost of the Prosigna strategy compared with the Oncotype DX strategy would be approximately $200,000 greater with a gain of 171 QALYs, per 1,000 patients. When considering parameter uncertainty, Prosigna is more than 76% likely to be cost-effective for willingness-to-pay values for the QALY of $20,000 and above. The conclusion that Prosigna is more cost-effective than Oncotype DX was robust to the variability in the parameter values explored in the sensitivity analyses.

Discussion

The clinical review found that, despite remaining uncertainties, evidence generally supports the additional prognostic ability of both Oncotype DX and Prosigna and the predictive ability of Oncotype DX. Importantly, both tests tend to support different treatment decisions for a small proportion of patients. Oncotype DX testing tends to classify more patients into low-risk groups who are likely to avoid chemotherapy, while Prosigna testing tends to classify more patients into high-risk groups who are likely to receive chemotherapy. This may lead to potentially undertreating some patients based on Oncotype DX test results or overtreating some patients based on Prosigna test results.

The economic evaluation found that Prosigna was likely to be more cost-effective than Oncotype DX across a range of scenarios. In Alberta, using Oncotype DX to avoid potentially unnecessary adjuvant chemotherapy would result in greater costs of testing, reduced costs of chemotherapy, and higher short-term quality of life, but may also be associated with increased risk of future distant recurrence with its associated morbidity, mortality, and increased treatment costs. The budget impact of using Prosigna would be approximately $1,000 extra per patient in the first year after testing due to the extra costs associated with testing and chemotherapy. Given that approximately 300 patients require testing in Alberta each year, Prosigna testing of this population

would require an initial extra $300,000, though long-term future cost savings may occur in future years as a result of cases of distant recurrence being averted.

Overall, the quality of the clinical evidence base varied due to differences in study designs and the amount of evidence available. The clinical review also revealed a major limitation in the evidence base for the economic model, in that the key parameters driving the model results were not well informed. For the risk category stratifications, no studies were identified that applied both tests to the same patient population using the RS and ROR cut-offs used in Alberta. The clinical trial TAILORx was used to inform these parameter values for Oncotype DX. However, TAILORx did not consider Prosigna, and it is not known how Prosigna would have categorized the patient group in the trial. Therefore, it was necessary to identify another source to inform the risk categories for Prosigna. For the future risk of distant recurrence in patients without chemotherapy by risk category stratifications, the ideal study would examine the use of both tests in the same patient group for risk of distant recurrence and risk stratification categorization. No such study was found, and thus it was necessary to inform these parameter values using studies that examined different patient populations. While such shortcomings in the parameterization may have impacted the results obtained from the model, the conclusions from the model were found to be robust to reasonable changes in model parameters.

Overall, the results of this report are likely applicable to the Alberta context, as many studies were conducted in countries with large developed economies that have similar patient populations and health systems, and expert opinion from Alberta medical oncologists and pathologists helped inform key clinical and cost parameters of the economic model.

Due to an absence of clinical data comparing both genetic tests, Alberta may benefit from collecting prospective and comparative administrative data for both tests in patients with node-negative disease. Because the clinical evidence suggests a potential, but uncertain, benefit of testing patients with node-positive (one to three nodes) disease, Alberta may consider collecting prospective data in this population on a conditional basis and for a predetermined period of time. Though few studies explicitly reported on patients with micrometastatic disease, it seems reasonable to offer genetic testing to this subset of patients as they are often formally classified as node-positive but treated as node-negative when making clinical treatment decisions.

Conclusions

Overall, results from our clinical review and economic evaluation generally support the additional prognostic ability of both Oncotype DX and Prosigna, the predictive ability of Oncotype DX, and the likely cost-effectiveness of Prosigna compared with Oncotype DX across a range of scenarios. While the publication of the TAILORx results significantly increased clinician and patient confidence in using Oncotype DX test results to guide treatment decisions, there are important evidence gaps regarding the predictive ability of the individual tests in certain patient populations and the comparative predictive ability of both tests. Decision-makers must weigh the evidence for the predictive ability of Oncotype DX in certain populations with the increased cost-effectiveness of Prosigna when determining how the tests can be optimally used in Alberta. This will require careful consideration of the remaining uncertainties in the clinical evidence base, the consequences of potentially undertreating some patients based on Oncotype DX test results or overtreating some patients based on Prosigna test results, and the potential agreements that may be reached between test manufacturers and laboratory services.

Abbreviations

All abbreviations that have been used in this report are listed here unless the abbreviation is well known, has been used only once, or has been used only in figures or tables, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

CCO	Cancer Care Ontario
CEAC	cost-effectiveness acceptability curve
CMF chemotherapy	cyclophosphamide, methotrexate, and fluorouracil
EQ-5D	EuroQol 5 dimensions
EQ-VAS	EuroQol visual analogue scale
ER+	estrogen receptor positive
FFPE	formalin-fixed paraffin-embedded
HER2−	human epidermal growth factor receptor 2 negative
HR	hormone receptor
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
mRNA	messenger ribonucleic acid
N1	node-positive disease with 1–3 positive nodes
p	*p*-value statistic
PICO	population, intervention, comparator, outcome
PR+	progesterone receptor positive
QALY	quality-adjusted life year
RCT	randomized controlled trial
ROR	risk of recurrence (calculated using Prosigna)
RS	recurrence score (calculated using Oncotype DX)
RT-PCR	reverse transcription-polymerase chain reaction
SF-6D, SF-12, SF-36	6-Dimension, 12-Item, 36-Item Short Form Health Survey
TAILORx	Trial Assigning Individualized Options for Treatment
TC chemotherapy	docetaxel and cyclophosphamide
WTP	willingness-to-pay

Glossary

The glossary terms listed below were obtained and adapted from the sources found at the end of the list.

Adjusted hazard ratio – The ratio of the probability of an event (recurrence or death) occurring in the intervention group versus the probability of an event occurring in the comparator group at a specific point in time, adjusted for prognostic factors in order to account for baseline imbalances between groups (also see *hazard ratio* and *unadjusted hazard ratio*).[i]

Adjuvant chemotherapy – Chemotherapy administered after primary treatments, such as surgery to remove visible cancer, to prevent disease recurrence.[ii]

Analytical validity – The accuracy with which a genetic characteristic is identified in a given laboratory test.[iii]

Cancer stage – A rating of the size and spread of cancer, ranging from stage 0 (no cancer) to stage IV (cancer spread to other parts of body) based on the TNM system (tumour size [T], regional lymph node involvement [N], and distant metastasis [M]).[iv]

Chemotherapy – The use of a drug or combinations of drugs to kill cancer cells throughout the body.[v]

Clinical utility – The risks and benefits associated with using a test, which is related to a test's predictive ability (also see *predictive ability*).[vi]

Clinical validity – The ability of a test to correctly identify patients who do and do not have a disease, which is related to a test's prognostic ability (also see *prognostic ability*).[vi]

Cohort study – A longitudinal observational study design where exposures are assessed in a group of individuals, who are then followed over time to observe whether they develop the outcome of interest. Cohort studies may be prospective or retrospective.[vii]

Cost-effectiveness acceptability curve – A figure describing the likelihood of an intervention being cost-effective with variation in the willingness-to-pay for one unit of the outcome being measured.[viii]

Cost-effectiveness plane – A figure showing the cost and effectiveness of an intervention.[viii]

Cross-sectional study – An observational study design in which participants' exposure and outcome status are assessed at a single point in time (for example, questionnaires or interviews).[vii]

Discounting – Time preference for costs and outcomes where their value is assumed to decrease into the future.[viii]

Disease-free survival – Freedom from breast cancer recurrence, second primary cancer, or death without evidence of recurrence.[ix]

Distant recurrence – Recurrence of cancer at any distant site following initial treatment. Outcome data are often reported as *freedom from distant recurrence*.[x]

Distant or locoregional recurrence – Recurrence of cancer at any distant site or in the same area and/or nearby lymph nodes of the original cancer. Outcome data are often reported as *freedom from distant or locoregional recurrence*.[x]

Dominated – An intervention is less effective and more costly than a comparator.[viii]

Early-stage breast cancer – Cancer confined to the breast, either with or without involvement of regional lymph nodes, and no distant metastases.[xi]

Endocrine therapy – For cancers sensitive to hormones, certain treatments can stop hormone production in a patient's body or block the effect of hormones. Also called *hormone therapy*.[xii]

Estrogen receptor positive (ER+) – Breast cancer cells that have estrogen receptors and depend on the hormone estrogen to fuel their growth.[xiii]

Extendedly dominated – A strategy is extendedly dominated if it is dominated (more costly, less effective) by some combination of two other strategies.[viii]

Gene expression profiling test – Tests that examine the patterns of certain genes from breast tissue samples, which are used to predict whether early stage breast cancer is likely to reoccur following initial treatment. Also called *genetic test*. Examples of gene expression profiling tests include Oncotype DX and Prosigna (also see *Oncotype DX* and *Prosigna*).[xiv]

Hazard ratio – The ratio of the probability of an event (recurrence or death) occurring in the intervention group versus the probability of an event occurring in the comparator group at a specific point in time (also see *adjusted hazard ratio* and *unadjusted hazard ratio*).[i]

High-risk patients – Patients who have a higher risk of disease recurrence based on their gene expression profiling test score and are more likely to benefit from chemotherapy.[xiv]

Hormone receptor positive (HR+) – Breast cancer cells that have estrogen receptors and/or progesterone receptors (also see *estrogen receptor positive* and *progesterone receptor positive*).[xiii]

Human epidermal growth factor 2 (HER2) – A growth-promoting protein on the outside of all breast cells. Breast cancer cells with higher than normal levels of human epidermal growth factor 2 are called *HER2-positive* (HER2+); these tend to spread and grow faster than HER2-negative (HER2−) breast cancer cells.[xv]

Immunotherapy – Works with a patient's immune system to fight off any remaining cancer cells by stimulating the body's own defenses or supplementing them.[xvi]

Incremental cost-effectiveness ratio – The difference in costs divided by the difference in outcomes for two alternative strategies.[viii]

Intermediate-risk patients – Patients who have an intermediate risk of recurrence based on their gene expression profiling test score.[xiv]

Ki67 protein – A protein that is a marker of cell proliferation and helps indicate how fast cancer calls will grow.[xvii]

Level of evidence – A hierarchy system of rating studies based on their methodological quality and applicability to a patient population.[xviii]

Low-risk patients – Patients who have a lower risk of disease recurrence based on their gene expression profiling test score and are less likely to benefit from chemotherapy.[xiv]

Luminal breast cancer – Defined by molecular profiling as tumours with gene expression similar to the luminal epithelium of the breast. Luminal A tumours are marked by high expression of the estrogen and progesterone receptors and low expression of the human epidermal growth factor 2 and Ki67 receptors. Luminal B tumours have lower expression of estrogen and progesterone receptors (compared with luminal A tumours), variable expression of human epidermal growth factor 2 receptors, and high expression of Ki67 receptors.[xix]

Micrometastases – Lymph node metastases greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm, that can be detected by sentinel lymph node biopsy but that cannot be clinically detected.[iv]

Node-negative (N0) – Breast cancer tumours that have no regional lymph node involvement. Also called *node-negative disease*.[iv]

Node-positive (N1, N2, or N3) – Breast cancer tumours that have regional lymph node involvement. Lymph node involvement can be further classified according to the number of positive nodes as N1 (one to three positive nodes, with or without micrometastases), N2 (four to nine positive nodes), or N3 (more than nine positive nodes). Also called *node-positive disease*.[iv]

Oncotype DX – A gene expression signature that uses reverse transcription-polymerase chain reaction on formalin-fixed paraffin-embedded tissue to evaluate messenger ribonucleic acid expression levels (of 21 genes, 16 cancer-related and 5 reference), to calculate a recurrence score that predicts the risk of 10-year distant recurrence.[xx]

Overall survival – Freedom from death due to any cause.[xxi]

Partial mastectomy – A surgical procedure in which the cancerous part of the breast tissue and some surrounding normal breast tissue are removed. Also called *breast-conserving surgery* or *lumpectomy*.[xxii]

Predictive ability – Refers to a test's ability to accurately discriminate between patients who will have more or less benefit from chemotherapy, according to the test score and corresponding risk categories.[iii]

Primary study – An article that reports on the results of original, empirical research conducted by the study authors.[xxiii]

Probabilistic sensitivity analysis – Probability distributions applied to the specified ranges for the model parameters and samples drawn at random from these distributions to generate empirical distributions of the costs and consequences.[viii]

Progesterone receptor positive (PR+) – Breast cancer cells that have progesterone receptors and depend on the hormone progesterone to fuel their growth.[xiii]

Prognostic ability – Refers to a test's ability to accurately predict the risk of an event and to accurately discriminate between patients with different event rates.[iii]

Prosigna – A gene expression signature that uses reverse transcription-polymerase chain reaction on formalin-fixed paraffin-embedded tissue to evaluate messenger ribonucleic acid expression levels (of 72 genes, 50 cancer-related and 22 reference), to calculate the risk of recurrence at a distant site over a 10-year period in postmenopausal patients.[xxiv]

Prospective study – A study design in which participants' exposure is documented prior to the occurrence of the outcome of interest.[xxv]

Quality-adjusted life year (QALY) – A composite measure of length and quality of life, where one QALY is equal to one year lived in perfect health.[viii]

Radiation therapy – Uses high-powered energy beams, such as x-rays or protons, to kill cancer cells. It can be given internally or externally. Also called *radiotherapy*.[xxvi]

Randomized controlled trial (RCT) – An experimental study design in which participants are randomly assigned to intervention and control groups in order to prevent systematic differences in participant baseline characteristics between groups.[xxvii]

Recurrence score (RS) – A score that is calculated using Oncotype DX, which predicts the risk of 10-year distant recurrence of breast cancer. Also called *breast recurrence score*.[xx]

Retrospective analysis or **study** – A study design in which the outcome of interest has occurred before the study is initiated.[xxviii]

Risk of recurrence (ROR) – A score that is calculated using Prosigna, which indicates risk of breast cancer recurrence at a distant site over a 10-year period in postmenopausal patients.[xxiv]

Systematic review – A type of literature review that uses explicit, reproducible, systematic methods in attempt to summarize all relevant empirical evidence to answer a given research question.[xxvii]

Targeted therapy – Drugs that target specific abnormalities present within cancer cells, which are designed to prevent the growth and spread of cancer cells, while limiting harm to normal cells. For example, a targeted therapy is available to block the action of human epidermal growth factor receptor 2 in patients with breast cancer.[xxix]

TNM staging system – Cancer staging system that assigns patients to a stage (0, I, II, III, or IV) based on tumour size (T), regional lymph node involvement (N), and distant metastasis (M).[iv]

Total mastectomy – A surgical procedure in which the entire breast is removed.[xxii]

Tumour grade – A rating of the appearance of cancer cells, which is assessed by a pathologist using a tissue sample of the tumour. Tumours are graded from 1 (low grade) to 3 (high grade), with a higher grade indicating more abnormality compared with normal cells, a tendency to grow more quickly, and greater likelihood of spreading.[xxx]

Unadjusted hazard ratio – The ratio of the probability of an event (recurrence or death) occurring in the intervention group versus the probability of an event occurring in the comparator group at a specific point in time, without adjusting for covariates. When there are no large imbalances in the baseline prognostic factors between groups, then adjusted and unadjusted ratios should be similar. (also see *hazard ratio* and *adjusted hazard ratio*).[i]

Willingness-to-pay (WTP) – The value of health benefit in monetary terms.[viii]

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Table of Contents

SECTION 1: Background

Michelle Pollock, PhD; Jennifer Seida, MPH; Bing Guo, MD, MSc

1.1. Breast Cancer

Breast cancer is one of the most common cancers in Alberta, affecting approximately one in eight women in their lifetime. In 2017, an estimated 2,600 women were diagnosed with breast cancer in Alberta, with more than 80% diagnosed at an early stage (stage I or II).[1] In the same year, an estimated 410 women in the province died of breast cancer.[1]

The long-term survival of patients with breast cancer has been steadily improving, with 5-year survival being achieved in more than 90% of Canadian patients. This increased survival is largely attributed to early screening and awareness, as well as the use of adjuvant therapies following initial surgical treatment.[2] Patients diagnosed at an early stage are more likely to benefit from surgery and adjuvant therapies and have a better prognosis than those diagnosed at a later stage.

1.2. Staging and Prognosis

A number of factors influence breast cancer prognosis, including tumour size, tumour grade (1, 2, or 3), histologic subtype, lympho-vascular invasion of tumour cells and axillary lymph node status, as well as the presence or absence of hormonal receptors (HRs), including the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2).

The most common classification system for breast cancer is the TNM staging system, which assigns patients to a stage (0, I, II, III, or IV) based on tumour size (T), regional lymph node involvement (N), and distant metastasis (M).[3,4] Breast cancer is further classified by the presence (positive, +) or absence (negative, −) of three hormone receptors, ER, PR, and HER2. Tumours that are ER+ will almost always be PR+ and may be referred to as *hormone receptor positive* (HR+), meaning that they express estrogen and/or progesterone. Based on the presence or absence of the three main receptors as well as an additional receptor for the Ki67 protein (a marker of cell proliferation that helps indicate how fast cancer cells will grow), breast cancer can be further classified into one of four molecular subtypes: luminal A, luminal B, HER2 enriched, or triple negative/basal-like (see Table 1).[5]

Approximately 80% of patients with breast cancer have early-stage, ER+, HER2− tumours (luminal A or B).[6] These patients have a good prognosis and often have tumours that progress slowly.[5] *Early-stage cancer* is variably defined but may be considered to be stage I–II or I–III (cancer is present, with or without regional lymph node involvement, and without distant metastases). Lymph node involvement may be classified by the absence (node-negative) or presence (node-positive) of regional nodes, with node-positive disease further classified by the number of positive nodes: one to three positive nodes with or without micrometastases (N1), four to nine positive nodes (N2), or more than nine positive nodes (N3).[3]

TABLE 1: Breast cancer molecular subtypes

Subtype	ER	PR	HER2	Ki67	Prevalence (%)	Cancer growth	Prognosis
Luminal A	+	+	−	Low	30–70%	Slow	Best
Luminal B	+	+	+ or −	High	10–20%	Slightly faster than luminal A	Worse than luminal A
HER2 enriched	−	−	+	Any	5–15%	Faster than luminal A and B	Worse than luminal A and B
Triple negative/ basal-like	−	−	−	Any	15–20%	Aggressive	Poor

ER: estrogen receptor; HER2: human epidermal growth factor 2 receptor; Ki67: Ki67 protein; PR: progesterone receptor

1.3. Treatment Decisions

First-line treatment for early-stage, ER+, HER2− breast cancer typically involves surgery (total or partial mastectomy), followed by adjuvant therapies such as endocrine therapy (also called *hormone therapy*), chemotherapy, radiation therapy, immunotherapy, and targeted therapy (for details, see the Glossary).

ER+ (and/or PR+) patients often benefit from endocrine therapy that disrupts the tumour's HRs and impedes the ability of cancer cells to grow and spread. While daily endocrine therapy for five years is the current standard of care for ER+ breast cancer, about 20% of patients who receive endocrine therapy will still experience long-term cancer recurrence.[7] Additional chemotherapy may help reduce the risk of long-term distant recurrence in this patient population. However, uncertainties remain regarding the optimal use of adjuvant chemotherapy in these patients, due to the associated toxicities, potential reduction in health-related quality of life (HRQoL), and uncertainty in determination of a patient's risk of distant recurrence.

Clinical tools such as Adjuvant![i] and Predict[ii] have been developed to help clinicians and patients better understand the potential prognostic benefit of adjuvant therapy after surgery and choose the treatment option that best fits their preferences.[8] Both Adjuvant! and Predict are online clinical prognostic tools that provide personalized 10-year all-cause or breast cancer-specific mortality estimates based on patient (for example, age) and tumour (for example, size, node status, ER status and grade) characteristics. Predict also takes into account the method of presentation (screen-detected or symptomatic) and HER2 status.[8] Clinical features may be integrated with immunohistochemical measures that use antibodies to identify ER, PR, and HER2 receptors as well as Ki67 molecules in breast tissue.[9]

Even with these clinical and immunohistochemical measures, deciding whether to administer adjuvant chemotherapy to a patient often remains an uncertain process. As such, there is demand for tests that can accurately: (1) determine the risk of a future event, such as long-term distant recurrence or mortality; and (2) identify patients at different risk categories of recurrence who would be likely to benefit from adjuvant chemotherapy (for example, high-risk patients) or who would be

[i] For more information on Adjuvant!, see: *www.openclinical.org/app_adjuvant.html*.

[ii] For more information on Predict, see: *breast.predict.nhs.uk/*.

unlikely to benefit from adjuvant chemotherapy and can thus avoid unnecessary chemotherapy (for example, low-risk patients).

1.4. Gene Expression Profiling Tests

Gene expression profiling tests (also called *genetic tests*) are intended to supplement clinical judgement in cases where clinical, pathological, and/or patient-related factors lead to uncertainty in the decision-making process. Two commercially available gene expression profiling tests (also called *genetic tests*), Oncotype DX and Prosigna, are commonly used to determine the risk of distant recurrence and the potential benefit of adjuvant chemotherapy in patients with early-stage, ER+, HER2− breast cancer who have node-negative or node-positive (N1) disease. Both tests have demonstrated analytical validity, meaning that they can accurately and reliably measure the expression of messenger ribonucleic acid (mRNA) by breast cancer tumour cells.[10-12] However, because the tests were validated in different patient groups, it is unclear which test has the greatest analytical validity.

Descriptions of the tests are provided below, and are summarized in Table 2.

TABLE 2: Summary of Oncotype DX and Prosigna genetic tests

	Oncotype DX	Prosigna
Manufacturer	Genomic Health (Redwood City, California)	NanoString Technologies (Seattle, Washington)
Number of genes tested	21[a] (16 cancer-related, 5 reference)	72[a] (50 cancer-related, 22 reference)
Testing location	Central laboratory (all tissue samples shipped to one laboratory in California for testing)	Local laboratory (contingent on initial purchase of NanoString Technologies' nCounter Analysis System)[b]
Target population	• Stage I–IIIA invasive breast cancer • Node-negative or node-positive (N1) • ER+ (and/or PR+), HER2− • Pre- and postmenopausal patients	• Stage I–II, node-negative invasive breast cancer, or stage II node-positive (N1) invasive breast cancer • ER+ (and/or PR+), HER2− • Postmenopausal patients only
Risk of recurrence (corresponding standard chemotherapy recommendation)	RS ranges from 0 to 100 • Low RS: 0–17[c] (no chemotherapy) • Intermediate RS: 18–31[c] (uncertain) • High RS: 31–100[c] (chemotherapy)	ROR ranges from 0 to 100 Node-negative patients: • Low ROR: 0–40 (no chemotherapy) • Intermediate ROR: 41–60 (uncertain) • High ROR: 61–100 (chemotherapy) Node-positive (N1) patients: • Low ROR: 0–40 (uncertain) • High ROR: 41–100 (chemotherapy)
Regulatory status	No FDA or Health Canada approval, as it is marketed as a laboratory-developed test (see section 1.4.3)	FDA and Health Canada approval, for postmenopausal patients only

[a] Most of the genes are not common across the tests.

[b] In Alberta, testing is done at the University of Alberta Hospital.

[c] These standard cut-offs differ from those used in TAILORx (see section 1.5).[13]

ER+: estrogen receptor positive; FDA: US Food and Drug Administration; HER2−: human epidermal growth factor 2 receptor negative; N1: 1–3 nodes; PR+: progesterone receptor positive; ROR: risk of recurrence; RS: recurrence score

1.4.1. Oncotype DX

Oncotype DX was developed in 2004 by Genomic Health for use in pre- and postmenopausal patients. It is a gene expression signature that uses reverse transcription-polymerase chain reaction (RT-PCR) to evaluate mRNA expression levels (of 21 genes, 16 cancer-related and 5 reference), to calculate a recurrence score (RS) that predicts the risk of 10-year distant recurrence. To use the test, local pathology laboratories prepare and send formalin-fixed paraffin-embedded (FFPE) tissue to a central laboratory in California, where the test is conducted. Results are sent back to medical oncologists after a two- to three-week processing period. The RS ranges from 0 to 100 and divides patients into three risk categories. Various risk cut-offs have been proposed, though the standard cut-offs as specified by Genomic Health are as follows: *low risk* is an RS between 0 and 17, *intermediate risk* is an RS between 18 and 30, and *high risk* is an RS between 31 and 100. In Alberta, the risk categories for Oncotype DX are defined as follows: *low risk* is an RS of 25 or less; *high risk* is an RS of 26 or more; and *intermediate risk* is an RS between 20 and 25, for premenopausal patients only (personal communication, Expert Advisory Group, March 2019).

1.4.2. Prosigna

Prosigna was developed in 2013 by NanoString Technologies for use in postmenopausal patients. It is a gene expression signature that uses RT-PCR on FFPE tissue to evaluate mRNA expression levels (of 72 genes, 50 cancer-related and 22 reference). The test is conducted locally using NanoString Technologies' nCounter Analysis System, which can also be used to conduct other gene expression profiling tests.[14] An algorithm uses the results of the gene signature, combined with information about the molecular subtype, node status, and tumour size, to calculate a risk of recurrence (ROR) that predicts the risk of 10-year distant recurrence. The ROR ranges from 0 to 100 and divides patients into three risk categories with cut-offs that vary by node status. The standard risk cut-offs for node-negative patients are as follows: *low risk* is an ROR between 0 and 40, *intermediate risk* is an ROR between 41 and 60, and *high risk* is an ROR between 61 and 100. The standard risk cut-offs for node-positive (N1) patients are as follows: *low risk* is an ROR between 0 and 40, and *high risk* is an ROR between 41 and 100. In Alberta, the risk categories for Prosigna are defined as follows: *low risk* is an ROR between 0 and 40; *intermediate risk* is an ROR between 41 and 60; and *high risk* is an ROR of 61 to 100 (personal communication, Expert Advisory Group, March 2019).

1.4.3. Regulatory status

Currently, Oncotype DX has not undergone regulatory approval from Health Canada or from the United States Food and Drug Administration (FDA). Oncotype DX is marketed in the United States as a laboratory-developed test, meaning that it cannot specify a diagnosis but is only permitted to state the correlation between the test score and a likely outcome. The test can only be conducted at a Clinical Laboratory Improvement Amendments certified, state-licensed central laboratory in California. Historically, laboratory-developed tests were not required to have FDA premarket clearance, yet the increasing complexity of tests and their impact on clinical decision-making have raised concerns regarding the risk of misdiagnosis and inappropriate treatment.[15] The FDA released guidance in 2014 proposing greater oversight of laboratory-developed tests and premarket approval of higher-risk tests, but, as of yet, no changes have been made to legislation.[16] The continued marketing of Oncotype DX without regulatory approval has resulted in reimbursement hurdles from some insurance companies and has become a source of controversy.[17, 18]

In September 2013, NanoString Technologies received clearance from the FDA to market and distribute Prosigna as a prognostic indicator of distant recurrence in postmenopausal patients.[19] Health Canada approved Prosigna for use in postmenopausal patients in April 2014.[20] To date, NanoString Technologies has not received regulatory approval or made any submission to regulatory bodies for use of Prosigna in premenopausal patients (personal communication, NanoString Technologies, March 2019).[iii]

1.5. TAILORx

In July 2018, results were published from TAILORx (Trial Assigning Individualized Options for Treatment), a prospective randomized controlled trial (RCT) that studied Oncotype DX in patients with early-stage, ER+, HER2−, node-negative breast cancer.[13] This study assigned patients with an RS of less than 11 (low risk) to endocrine therapy only and of more than 25 (high risk) to chemoendocrine therapy (that is, endocrine therapy plus chemotherapy), and randomized patients with an RS between 11 and 25 (intermediate risk) to either endocrine therapy only or chemoendocrine therapy. When the predictive benefit of the test was assessed after a follow-up period of nine years, no additional benefit of chemotherapy was found in patients with an RS of between 11 and 25, though subgroup analyses suggested a benefit of chemotherapy in patients aged 50 years or younger with an RS between 16 and 25. TAILORx is considered the first study to provide level 1A evidence (that is, an RCT designed with the tumour biomarker/assay as the intervention; see section 2.1, Table 4) regarding the ability of a genetic test to predict the benefit of adjuvant chemotherapy in patients at intermediate risk of long-term distant recurrence.

The results of TAILORx will be discussed in further detail in section 2.3.3.

1.6. The Alberta Situation

In March 2014, Oncotype DX testing became publicly funded in Alberta for use in pre- and postmenopausal patients, and became the standard of care. In 2015, the University of Alberta Hospital obtained NanoString Technologies' nCounter Analysis System and also began conducting Prosigna testing locally.

In October 2016, a research team at the University of Alberta was commissioned to examine the clinical effectiveness and cost-effectiveness of Oncotype DX and Prosigna.[21] The team found that Prosigna was likely to lead to better population health outcomes at a lower cost. Based on the results in their internal report, in October 2017, Prosigna testing replaced Oncotype DX testing as the standard of care for breast cancer patients requiring genetic testing. However, following the publication of the TAILORx results in July 2018, Alberta medical oncologists have substantially increased their ordering of Oncotype DX instead of Prosigna (personal communication, Expert Advisory Group, March 2019).

As of October 2017, Oncotype DX can be requested by clinicians on a case-by-case basis with justification, and all requests need pre-approval by the Alberta Health Services (AHS) Oncotype Approval Committee, while no approval is required for ordering Prosigna.[22] This policy continues to be in effect to date, pending further review from the Alberta Public Laboratories Laboratory Formulary Committee (personal communication, Expert Advisory Group, March 2019).

[iii] The search strategy used to locate regulatory status information for Oncotype DX and Prosigna is provided in Appendix D, Table D.5.

In addition to Oncotype DX and Prosigna, two other genetic tests, MammaPrint (developed by Agendia) and EndoPredict (developed by Myriad Genetics), also analyze gene activity to help inform decisions about adjuvant chemotherapy treatment. Because these two genetic tests are not currently used in Alberta, they are excluded from this report.

1.7. Clinical Practice Guidelines

Current clinical practice guidelines in Alberta recommend both Oncotype DX and Prosigna to support adjuvant chemotherapy decision-making in patients with early-stage, node-negative and micrometastatic, grade 2 or 3 breast cancer.[23] As previously stated, use of Oncotype DX but not Prosigna requires pre-approval on a case-by-case basis.

In Canada, guidelines from both British Columbia and Ontario recommend the use of both tests to support decisions regarding adjuvant chemotherapy, while guidelines from Quebec recommend the limited use of Oncotype DX and do not recommend the use of Prosigna. In British Columbia, Prosigna became available as of July 2017, but approval is required on a case-by-case basis from the Compassionate Access Program for Prosigna Testing.[24] In Ontario, the Cancer Care Ontario (CCO) guidelines[25] state that, in node-negative patients, clinicians may withhold chemotherapy based on low-risk Oncotype DX or Prosigna scores, and offer chemotherapy based on high-risk Oncotype DX scores. Clinicians may withhold chemotherapy in some patients with one to three positive nodes and a low-risk Oncotype DX or Prosigna score when additional clinical and pathological factors support this decision. These tests are not approved or funded for patients with node-positive disease, except for micrometastatic disease. No recommendations were made for patients with intermediate-risk scores, due to pending analysis of TAILORx. In Quebec, the Institut national d'excellence en santé et en services sociaux (INESSS) recommends that Oncotype DX be used only in certain subgroups of node-negative patients when clinical decision-making is difficult, and suggests that Oncotype DX be ordered only after consulting with the patient and only by the clinician who will make the decision to recommend or not recommend chemotherapy.[26] They do not recommend the use of Prosigna. INESSS states that data are lacking to assess the superiority of either test.[27, 28]

In the United States, the American Society of Clinical Oncology recommends use of Oncotype DX or Prosigna to guide adjuvant chemotherapy decisions in node-negative but not node-positive patients.[29] On the other hand, the 2019 National Comprehensive Cancer Network guidelines, which incorporate evidence from TAILORx, refers to Oncotype DX as the preferred genetic test for node-negative patients and strongly recommends that Oncotype DX be considered to inform adjuvant therapy decisions in this patient population.[30] The guidelines note that Prosigna may be considered in prognosticating the risk of distant recurrence for node-negative and node-positive (N1) patients.

The United Kingdom's National Institute for Health and Care Excellence (NICE) guidelines, published in December 2018 and informed by the findings of TAILORx, recommend Oncotype DX or Prosigna for guiding adjuvant chemotherapy decisions in patients with node-negative or micrometastatic disease (though the latter term was not defined).[31] The tests are recommended for use in patients who are assessed as being at intermediate risk of distant recurrence based on Predict or Nottingham Prognostic Index scores, when the additional testing information is deemed to help make a treatment choice. These recommendations are contingent on no changes in test pricing, and on making testing data available to the National Cancer Registration and Analysis Service.

Appendix B summarizes the characteristics (Table B.1) and recommendations (Table B.2) of the North American and NICE clinical practice guidelines related to the use of Oncotype DX and Prosigna.[iv]

1.8. Objective

In light of the publication of the TAILORx results, AHS wished to receive an update of the 2016 University of Alberta report.[21] The Laboratory Formulary Committee (Alberta Public Laboratories, AHS) made a request to Alberta Health via the Alberta Health Evidence Reviews Process for a clinical review and economic evaluation of the most recent research evidence. The Institute of Health Economics (IHE) was commissioned to conduct this work. An Expert Advisory Group was also established to provide guidance throughout all stages of the project (see Appendix A).

The clinical review and economic evaluation aimed to determine how Oncotype DX and Prosigna can be optimally used to determine which patients with early-stage breast cancer will benefit from adjuvant chemotherapy. This report addresses the following research question: *For patients with early-stage (I–III), ER+, HER2−, node-negative or node-positive (one to three nodes) breast cancer, what are the clinical and economic benefits of Oncotype DX and Prosigna genetic testing, and how do these differ by node status, risk status, age, and menopausal status?*

The clinical review and economic evaluation are presented in sections 2 and 3, and the overall discussion and conclusions in section 4.

[iv] The search strategy used to locate clinical practice guidelines for Oncotype DX and Prosigna is provided in Appendix D, Table D.5.

SECTION 2: Clinical Review

Michelle Pollock, PhD; Ann Scott, PhD; Jennifer Seida, MPH; Paula Corabian, MPH; Lisa Tjosvold, MLIS; Bing Guo, MD, MSc

2.1. Methods

The clinical review consisted of three rapid reviews examining, respectively:

1. the clinical validity (prognostic ability) and utility (predictive ability) of the Oncotype DX and Prosigna genetic tests in predicting risk of cancer recurrence, survival, and response to adjuvant chemotherapy, in patients with early-stage breast cancer;
2. clinician and patient treatment decisions about adjuvant chemotherapy in patients with early-stage breast cancer, with and without the results of the Oncotype DX or Prosigna genetic tests; and
3. the health-related quality of life (HRQoL) of patients with early-stage breast cancer who receive and do not receive adjuvant chemotherapy.

The three rapid reviews searched for relevant systematic reviews and primary studies addressing the questions of interest, and included those that met our predefined inclusion criteria (see Table 3). For rapid reviews 1 and 2, we were aware of a relevant systematic review by CCO that was published in 2016[25] and updated in 2018 (internal document).[32] The CCO review included relevant primary studies published from 2002 (the year when the first genetic test was introduced) to week 7 of 2016. In accordance with existing best practices on incorporating existing systematic reviews into new reviews,[33, 34] we used the following approaches:

- For rapid review 1, we used the lists of included primary studies from the 2016 CCO systematic review and 2018 update as a starting point, to identify all primary studies that met our inclusion criteria. The full texts of all relevant primary studies were then retrieved and assessed for inclusion.
- For rapid review 2, we included the 2016 CCO systematic review and summarized its results as they appeared in the systematic review (that is, the full texts of the primary studies were not retrieved).

For both rapid reviews 1 and 2, we then updated CCO's search strategies and identified and included additional relevant primary studies that had been published since CCO's last search date. As such, rapid review 1 searched for primary studies published from 2002 onward. Rapid review 2 included the 2016 CCO systematic review (and its relevant primary studies published from 2002 onward) and searched for additional primary studies published from 2016 onward.

For rapid review 3, no relevant systematic reviews were located, so we identified and summarized the results of all relevant primary studies. Searches were conducted for studies published from 2007 onward, as this was the publication date of the primary study that provided quality of life information for the economic analysis included in the 2016 University of Alberta report.[21] As such, rapid review 3 covers the time period spanning from 2007 onward.

For all rapid reviews, we also scanned the reference lists of included studies and other relevant reports (including the 2018 CCO update) and consulted experts to help identify additional relevant studies that might have been missed by our own searches.

All three rapid reviews searched for, selected, extracted data from, and analyzed the results of the relevant systematic reviews and primary studies that were identified. A single reviewer conducted each rapid review, with assistance from a second reviewer as needed (for example, help with screening, inclusion, or data extraction, or help resolving uncertainties). The inclusion criteria for each rapid review are presented in Table 3. Only English-language studies were included, study authors were not contacted to request additional data, and formal quality assessments were not conducted. For rapid review 1, the tumour marker utility grading system was used to describe the study category and overall level of evidence supporting the prognostic and predictive ability of the genetic tests (see Table 4).[35]

The full methods used to conduct each rapid review are described in Appendix C, and the search strategies are provided in Appendix D.

TABLE 3: General inclusion criteria

PICO criterion	Rapid review		
	1: Clinical validity and utility (prognostic and predictive ability)	**2: Clinician and patient treatment choices**	**3: Health-related quality of life**
Population	Patients of any age with early-stage (I–III), ER+ (and/or PR+), HER2−, N0 or N1[a] breast cancer	Same as rapid review 1	Patients of any age with early-stage (I–III) breast cancer[b]
Intervention/ index test	• Oncotype DX • Prosigna	Same as rapid review 1	Adjuvant CT
Comparator/ alternate test	• Oncotype DX • Prosigna • No genetic test[c]	Same as rapid review 1	• Adjuvant CT • No adjuvant CT • No comparator group

Outcomes	• Long-term freedom from distant recurrence
	• Long-term freedom from distant or locoregional recurrence
	• Long-term overall survival
	• Long-term disease-free survival
		• Treatment decisions:
		  ○ Proportion of patients recommended CT before and after assay results were obtained
		  ○ Proportion of patients for whom a treatment recommendation changed after assay results were obtained (treatment change)
		  ○ Proportion of patients following treatment recommendations after assay results were obtained (treatment received)
		• Decisional outcomes:
		  ○ Patient and clinician confidence, preferences, and satisfaction
		  ○ Patient decisional conflict and psychological effects
			Health-related quality of life, measured using:
			  ○ EQ-5D (index score and visual analogue score)
			  ○ SF-36 (domain and summary scores)
			  ○ SF-12 (domain and summary scores)
			  ○ SF-6D (index score)

[a] *N0* was defined as no regional lymph node involvement identified histologically; *N1* was defined as 1–3 positive nodes with or without micrometastases.[3]

[b] Studies that focused only on patients who were ER−, HER2+, or had ≥4 positive nodes were excluded.

[c] Though the original workplan (25 Feb 2019) also included clinical status with or without immunohistochemistry as comparators of interest, we opted to summarize the main findings in section 4.1.

CT: chemotherapy; EQ-5D: EuroQol 5 dimensions; ER+: estrogen receptor positive; HER2−: human epidermal growth factor 2 negative; N0: node-negative; N1: node-positive (1–3 nodes); PR+: progesterone receptor positive; SF-6D, -12, -36: 6-Dimension, 12-Item, 36-Item Short Form Health Survey

TABLE 4: Rapid review 1 – description of study categories and levels of evidence

Rating	Description
Study category	
A	Randomized controlled trial designed with tumour marker as the intervention.
B	Randomized controlled trial designed to address a treatment intervention that is not the tumour marker. Study prospectively enrols and follows patients and collects tumour samples, and then uses archived tumour tissue retrospectively to evaluate the tumour marker.
C	Prospective observational registry study. Study prospectively enrols patients in a registry and collects, processes, and archives tumour specimens, but treatment and follow up are standard of care. Archived tumour tissue is used retrospectively to evaluate the tumour marker.
Level of evidence	
1A	One category A study.
1B	At least two category B studies with consistent results.
2	One category B study OR at least two category B studies with inconsistent results OR at least two category C studies with consistent results.
3	One category C study OR at least two category C studies with inconsistent results.

Adapted from Simon et al. (2009),[35] with permission from Oxford University Press.

2.2. Results

The primary studies included in the three rapid reviews are listed in Table 5. Results of the rapid reviews are described below (sections 2.3 to 2.5).

TABLE 5: Summary of included primary studies

Rapid review	Records identified through literature search	Records screened after duplicates removed	Full-text articles assessed for eligibility	Primary studies included
1: Clinical validity and utility (prognostic and predictive ability)	292	242	63	13 (representing 12 unique primary studies)[13, 36-47]
2: Clinician and patient treatment decisions	2,967	2,469	27	8[a 48-55]
3: Health-related quality of life	8,941	5,721	205	16 (representing 15 unique primary studies)[56-71]

[a] The 2016 CCO systematic review[25] was also included, which contained five relevant primary studies.[72-76]

2.3. Rapid Review 1: Clinical Validity and Utility

Rapid review 1 examined the clinical validity and utility of Oncotype DX and Prosigna in early-stage (I–III), ER+ (and/or PR+), HER2−, node-negative and node-positive (N1) breast cancer. It searched for primary studies published from 2002 onward, using the lists of included primary studies

from the 2016 CCO systematic review[25] and 2018 CCO update[32] as a starting point to help locate relevant primary studies.

2.3.1. Description of included studies

The literature searches identified 13 articles,[13, 36-47] representing 12 unique primary studies. The included studies were found by: checking the reference list of the 2016 CCO systematic review (two studies[43, 47]), checking the reference list of the 2018 CCO update (six studies[13, 37, 40-42, 44, 46]), screening search results from our update search (two studies[36, 38]), searching reference lists of other relevant reports (one study[39]), and consulting experts to help identify additional relevant studies (one study[45]). Details of the search strategies are presented in Appendix D, Table D.1; the flow of primary studies through the different phases of the selection process are presented in Appendix E, Figure E.1; and a list of excluded studies can be found in Appendix F, Box F.1.

The primary studies included one RCT (category A), four retrospective analyses of RCTs (category B), one prospective study (category C), and six retrospective analyses of prospective studies (category C). These studies were published between 2013 and 2018 (median: 2017) and were conducted in the United States (five studies), the United Kingdom (three studies), and Denmark, Germany, Israel, and Norway (one study each). The follow-up periods ranged from 5 to 15 years (median: 10 years). Nine studies examined Oncotype DX and five examined Prosigna, with one study comparing both tests. One or more authors in 78% of Oncotype DX studies and 80% of Prosigna studies were affiliated with Genomic Health and NanoString Technologies, respectively.

The total number of patients enrolled in the studies ranged from 569 to 73,185 (median: 2,534). Across the studies, the mean or median age of the patients ranged from 51 to 64 years. A median of 100% of patients were ER+ or HR+ (range: 73 to 100%) and HER2− (range: 88 to 100%). When reported, median tumour size ranged from 1.5 cm to 1.9 cm (median: 1.8 cm), with 9 to 55% (median: 17%) of tumours measuring less than 1 cm in size (see Appendix G, Table G.2).

Eleven studies contained data for node-negative patients, and nine contained data for node-positive (N1) patients. All studies examining Oncotype DX included both pre- and postmenopausal patients that received endocrine or chemoendocrine therapy. In contrast, most studies examining Prosigna included only postmenopausal patients receiving endocrine therapy. Overall, tumour grades were similar across studies examining both Oncotype DX and Prosigna. A median of 17% of patients had grade 1 tumours (range: 5 to 28% for Oncotype DX; 21 to 25% for Prosigna) and a median of 17% (Oncotype DX) and 18% (Prosigna) of patients had grade 3 tumours (range: 14 to 31% for Oncotype DX; 0 to 27% for Prosigna).

Overall, nine studies provided data on prognostic ability, and four provided data on predictive ability. Eight of the included studies provided data for the primary outcome of interest (long-term distant recurrence).

For a summary of the included studies, see Table 6; for complete study and patient characteristics, see Appendix G, Tables G.1 and G.2. Outcome data are presented below (for a description of how the outcomes were defined, calculated, and interpreted, see Appendix C, section C.1.4).

TABLE 6: Summary of included studies and outcome data

Study	Study category	# of patients[a]	Node status		Menopausal status		Treatment		Prognostic ability				Predictive ability			
			N0	N1	Pre	Post	ET	CT	DR	DLRR	OS	DFS	DR	DLRR	OS	DFS
Oncotype DX																
Sparano et al. (2018)[13]	A	9,719	●		●	●	●	●					●	●	●	●
Geyer et al. (2018)[36]	B	569	●		●	●	●	●					●			
Nitz et al. (2017)[37]	C	2,642	●	●	●	●	●	●			●					
Ibraheem et al. (2018)[38]	C	73,185	●	●	●	●	●	●							●	
Roberts et al. (2017)[39]	C	6,483		●	●	●	●	●			●	●				
Stemmer et al. (2017)[40, 41]	C	2,510	●	●	●[b]	●	●	●	●		●		●		●	
Petkov et al. (2016)[42]	C	44,825	●	●	●	●	●	●				●				
Prosigna																
Gnant et al. (2015)[43]	B	2,197	●	●		●	●		●							
Lænkholm et al. (2018)[44]	C	2,558	●	●		●	●		●							
Ohnstad et al. (2017)[45]	C	653	●		●	●	●				●	●				
Both tests																
Sestak et al. (2018)[46]	B	774	●	●		●	●		●							
Dowsett et al. (2013)[47]	B	739	●			●	●		●							

[a] Only N0 or N1 patients were counted.

[b] Median age of 61 years (interquartile range: 52–67).

CT: chemotherapy; DFS: disease-free survival; DLRR: distant or locoregional recurrence; DR: distant recurrence; ET: endocrine therapy; LRR: locoregional recurrence; N0: node-negative; N1: node-positive (1–3 nodes); OS: overall survival; Post: postmenopausal; Pre: premenopausal

2.3.2. Prognostic ability

Node-negative patients

Oncotype DX

Two category B studies examined the prognostic ability of Oncotype DX in node-negative patients. Both studies were retrospective analyses of the same RCT (TransATAC), were conducted by similar author teams, and included patients with similar characteristics.

- Sestak et al. found that low-risk patients (RS of 17 or less) were 41% more likely to be free from 10-year distant recurrence compared with intermediate-risk (RS between 18 and 31) or high-risk patients (RS of 32 or more) (94.1% versus 72.8% or 83.3%; $p<0.05$).[46]
- Dowsett et al. found that low-risk patients (RS of 17 or less) were 85% more likely to be free from 10-year distant recurrence compared with high-risk patients (RS of 32 or more) (94.5% versus 69.1%; p-value not reported).[47]

There were also three category C studies.

- Stemmer et al. found significantly lower 5-year distant recurrence rates in low-risk patients (RS of 17 or less) compared with high-risk patients (RS of 31 or more) ($p<0.05$).[40]
- Nitz et al. found significantly higher 5-year overall survival rates in low-risk patients (RS of 11 or less) compared with high-risk patients (RS of 26 or more) ($p<0.05$), and in intermediate-risk patients (RS between 12 and 25) compared with high-risk patients (RS of 26 or more) ($p<0.05$).[37]
- Nitz et al. and Petkov et al. found significantly higher 5-year disease-free survival rates in low-risk patients (RS of 11 or less and of 17 or less, respectively) compared with high-risk patients (RS of 26 or more and of 31 or more, respectively) ($p<0.05$), in low-risk patients (RS of 17 or less) compared with intermediate-risk patients (RS between 18 and 30) ($p<0.05$), and in intermediate-risk patients (RS between 12 and 25) compared with high-risk patients (RS of 26 or more) ($p<0.05$).[37, 42] These survival rates remained significantly higher in lower-risk compared with higher-risk patients across all age subgroups examined (40 years or younger, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, 80 years and older) ($p\leq0.001$).[42]

For complete outcome data, see Appendix G, Tables G.3 and G.4.

Prosigna

Three category B studies examined the prognostic ability of Prosigna in node-negative patients.

- Sestak et al. found that low-risk patients (ROR of 26 or less) were 61% more likely to be free from 10-year distant recurrence compared with intermediate-risk (ROR between 27 and 68) or high-risk patients (ROR of 69 or more) (97.0% versus 85.9% or 67.6%; $p<0.05$).[46]
- Dowsett et al. found that low-risk patients (ROR not reported) were 86% more likely to be free from 10-year distant recurrence compared with high-risk patients (ROR not reported) (95.0% versus 69.6%; p-value not reported).[47]
- Gnant et al. found significantly lower 10-year distant recurrence in low-risk patients (ROR of 48 or less) compared with high-risk patients (ROR of 68 or more) (95.1% versus 79.9%; $p<0.001$).[43]

There were also two category C studies.

- Lænkholm et al. found significantly lower 5-year distant recurrence rates in low-risk patients (ROR of 40 or less) compared with high-risk patients (ROR of 61 or more) ($p<0.001$).[44]
- Ohnstad et al. found significantly lower 15-year disease-free survival rates in low-risk patients (ROR of 40 or less) compared with high-risk patients (ROR of 61 or more) ($p<0.05$), and in low-risk patients compared with intermediate-risk patients (ROR between 41 and 60) ($p<0.05$).[45]

For complete outcome data, see Appendix G, Table G.5.

Oncotype DX compared with Prosigna

One category B study compared the prognostic ability of Oncotype DX and Prosigna in node-negative patients. More patients were categorized as high risk with Prosigna (27%) compared with Oncotype DX (11%).

- Sestak et al. found that Prosigna compared with Oncotype DX was associated with significantly higher freedom from 10-year distant recurrence ($p<0.05$).[46]

For complete outcome data, see Appendix G, Table G.6.

Node-positive (N1) patients

Oncotype DX

One category B study examined the prognostic ability of Oncotype DX in node-positive (N1) patients.

- Sestak et al. found that low-risk patients (RS of 17 or less) were 28% more likely to be free from 10-year distant recurrence compared with intermediate-risk (RS between 18 and 31) or high-risk patients (RS of 32 or more) (80.6% versus 70.9% or 62.0%; $p<0.05$).[46]

There were also three category C studies.

- Stemmer et al. found significantly lower 5-year distant recurrence rates observed in low-risk patients (RS of 17 or less) compared with high-risk patients (RS of 31 or more) ($p<0.05$), and in low-risk patients compared with intermediate-risk patients (RS between 18 and 30) ($p<0.05$). Subgroup analyses remained significant when looking at patients with risk cut-offs of an RS of 25 or less versus 26 or more ($p<0.001$).[41]
- Stemmer et al. found significant differences in 5-year overall survival across risk categories (RS of 17 or less, between 18 and 30, and 31 or more), with lower levels of risk corresponding to increased survival ($p\leq0.002$).[39, 41] Survival remained significantly higher in patients with risk cut-offs of an RS of 25 or less compared with 26 or more ($p<0.001$).[41]
- Roberts et al. and Petkov et al. found significant differences in 5-year disease-free survival across risk categories (RS of 17 or less, between 18 and 30, and 31 or more), with lower levels of risk corresponding to increased disease-free survival ($p<0.001$).[39, 42] Survival remained significantly higher in lower-risk patients compared with higher-risk patients across almost all age subgroups examined (40 years or younger, 40 to 49 years, 60 to 69 years, 70 to 79 years, and 80 years or older; $p\leq0.035$).[42]

For complete outcome data, see Appendix G, Tables G.7 and G.8.

Prosigna

One category B study examined the prognostic ability of Prosigna in node-positive (N1) patients.

- Sestak et al. found that low-risk patients (ROR of 26 or less) were 31% more likely to be free from distant recurrence compared with intermediate-risk (ROR between 27 and 68) or high-risk patients (ROR of 69 or more) (100.0% versus 79.3% or 69.3%; $p<0.05$).[46]

There was also one category C study.

- Lænkholm et al. found significantly lower 5-year distant recurrence in low-risk patients compared with high-risk patients, in low-risk patients versus intermediate-risk patients, and in intermediate-risk patients versus high-risk patients (ROR cut-offs differed by node status; $p<0.05$).[44]

For complete outcome data, see Appendix G, Table G.9.

Oncotype DX compared with Prosigna

No studies compared the prognostic ability of Oncotype DX and Prosigna in node-positive (N1) patients.

2.3.3. Predictive ability

Node-negative patients

Oncotype DX

One category A study examined the predictive ability of Oncotype DX in node-negative patients.

- TAILORx (Sparano et al.)[13] prospectively assigned 9,719 patients to three treatment groups based on their risk status: low-risk patients (RS of 10 or less) received endocrine therapy only, high-risk patients (RS of 26 or more) received chemoendocrine therapy, and intermediate-risk patients (RS between 11 and 25) were randomized to one of the above two treatments. After nine years of follow up, there was no additional benefit of chemotherapy over endocrine therapy alone for intermediate-risk patients when looking at distant recurrence, distant or locoregional recurrence, overall survival, or disease-free survival. Post hoc exploratory subgroup analyses showed a benefit of chemotherapy in patients aged 50 years or younger with an RS between 21 and 25 (see Table 7).

There was one additional category B study.

- Geyer et al. found no additional benefit of chemotherapy over endocrine therapy alone when looking at 10-year distant recurrence in intermediate-risk patients (RS between 11 and 25, or between 18 and 30).[36]

There were also two category C studies.

- Stemmer et al. found no additional benefit of chemotherapy on 5-year distant recurrence when looking at intermediate-risk (RS between 18 and 25) and high-risk patients (RS between 26 and 30).[40]
- Ibraheem et al. found a trend toward additional benefit of chemotherapy on 5-year overall survival in intermediate-risk patients (RS between 18 and 25; $p=0.052$), and a significant additional benefit of chemotherapy in high-risk patients (RS between 26 and 30; $p=0.029$).[38]

For complete outcome data, see Appendix G, Tables G.10 and G.11.

TABLE 7: Additional benefit of chemotherapy over endocrine therapy only, by age and menopausal status, for intermediate-risk patient subgroups in Sparano et al. (2018)

Subgroup	Intermediate-risk subcategory	Freedom from distant recurrence	Freedom from distant or locoregional recurrence	Overall survival	Disease-free survival
Age ≤50	RS 11–15	X	X	--	X
	RS 16–20	X	X	--	✓ p=0.0016
	RS 21–25	✓ p<0.05	✓ p<0.05	--	✓ p=0.035
Age 51–64	RS 11–15	X	X	--	X
	RS 16–20	X	X	--	X
	RS 21–25	X	X	--	X
Age ≥65	RS 11–15	X	X	--	X
	RS 16–20	X	X	--	X
	RS 21–25	X	X	--	X
Pre-menopausal	RS 11–15	X	X	--	X
	RS 16–20	X	X	--	✓ p=0.003
	RS 21–25	X	✓ p<0.05	--	X
Post-menopausal	RS 11–15	X	X	--	X
	RS 16–20	X	X	--	X
	RS 21–25	X	X	--	X

Sparano et al. (2018)[13]

X: no additional benefit of chemotherapy over endocrine therapy only; ✓: significant additional benefit of chemotherapy over endocrine therapy only; NR: not reported; RS: recurrence score

Prosigna

No studies examined the predictive ability of Prosigna in node-negative patients.

Node-positive (N1) patients

Oncotype DX

Two category C studies examined the predictive ability of Oncotype DX in node-positive (N1) patients.

- Ibraheem et al. found a significant additional benefit of chemotherapy on 5-year overall survival for intermediate-risk patients with an RS between 11 and 17 (p=0.044), between 18 and 25 (p=0.001), and between 26 and 30 (p=0.018).[38]
- Stemmer et al. found no additional benefit of chemotherapy on 5-year overall survival for intermediate-risk patients with an RS between 18 and 25, between 18 and 30, between 26 and 30, or of 25 or less.[40]

For complete outcome data, see Appendix G, Table G.12.

Prosigna

No studies examined the predictive ability of Prosigna in node-positive (N1) patients.

2.3.4. Ongoing clinical trials

Two ongoing RCTs relevant to rapid review 1 were identified through searches of trial registers. The RxPONDER trial examines the predictive ability of Oncotype DX in pre- and postmenopausal patients with node-positive (N1) disease. Patients with an RS of 25 or less are randomized to endocrine or chemoendocrine therapy, and the primary outcome of interest is disease-free survival at time points up to 15 years. The RxPONDER trial is scheduled for completion in 2022. The OPTIMA trial examines the predictive ability of Prosigna in pre- and postmenopausal patients with either node-negative or node-positive (one to nine nodes) disease. Patients are randomized to chemoendocrine therapy or Prosigna-directed treatment consisting of chemoendocrine therapy for patients with an ROR of more than 60, and endocrine therapy alone for patients with an ROR of 60 or less. The primary outcome of interest is 10-year disease-free survival. The OPTIMA trial is scheduled for completion in 2023.

One additional RCT, the OPTIGEN trial, was identified. This trial was designed to compare the predictive ability (disease-free survival) of four genetic tests, including Oncotype DX and Prosigna. However, this trial was withdrawn prior to patient enrolment due to lack of funding.

For further details on these ongoing clinical trials, see Appendix G, Table G.13.

2.3.5. Summary of main findings

Twelve unique studies contributed outcome data supporting the prognostic ability of Oncotype DX and Prosigna, and the predictive ability of Oncotype DX. The quality of the evidence base varied due to differences in study designs and the amount of evidence available. Though no studies were conducted in Canada, results are likely applicable to the Canadian context as many studies were conducted in countries with large developed economies, similar levels of resources to devote to health care, and comparable target populations.[77]

Prognostic ability

For node-negative patients, three category B studies[43, 46, 47] and five category C studies[37, 40, 42, 44, 45] supported the prognostic ability of both Oncotype DX and Prosigna, with lower-risk patients generally, but not always, experiencing better 5- to 15-year outcomes than higher-risk patients ($p<0.05$). This difference was most pronounced when comparing the low- and high-risk patients; differences were not always reported or observed when comparing the low- and intermediate-risk patients, or the intermediate- and high-risk patients. The prognostic ability of both tests was observed despite the use of variable risk cut-offs across the studies. There was level 1B evidence supporting the prognostic ability of Oncotype DX and Prosigna for postmenopausal patients receiving endocrine therapy. In contrast, there was level 2 evidence (Oncotype DX) and level 3 evidence (Prosigna) for premenopausal patients receiving endocrine and/or chemoendocrine therapy. Level 2 evidence from one category B study suggested an increased prognostic ability of Prosigna over Oncotype DX in postmenopausal patients receiving endocrine therapy only (see Table 8).

For node-positive (N1) patients, one category B study[46] and four category C studies[39, 41, 42, 44] contributed level 2 evidence supporting the prognostic ability of both Oncotype DX (pre- and postmenopausal patients receiving endocrine or chemoendocrine therapy) and Prosigna

(postmenopausal patients receiving endocrine therapy). Lower-risk patients experienced better 5- to 10-year outcomes than higher-risk patients. This difference was most pronounced when comparing the low- and high-risk patients; differences were not always reported or observed when comparing the low- and intermediate-risk patients, or the intermediate- and high-risk patients. The prognostic ability of both tests was observed despite the use of variable risk cut-offs across the studies. No studies compared the prognostic ability of both tests in node-positive (N1) patients (see Table 9).

TABLE 8: Evidence supporting the prognostic ability of Oncotype DX and Prosigna testing in node-negative patients

Genetic test	Menopausal status	Treatment received	Level of evidence	Time point	Outcome(s) examined	Studies contributing data	Key findings from category B studies
Oncotype DX	Pre	ET	2	5 years	DR (primary), OS (secondary), DFS (secondary)	Consistent results from 3 category C studies[37, 40, 42]	NA
		ET+CT	2	5 years	DR (primary), OS (secondary), DFS (secondary)	Consistent results from 3 category C studies[37, 40, 42]	NA
	Post	ET	1B	10 years	DR (primary), OS (secondary), DFS (secondary)	Consistent results from 2 category B studies,[46, 47] 3 category C studies[37, 40, 42]	Low- vs. intermediate-/high-risk patients were 41–85% more likely to be free from 10-year DR (p<0.05)[46, 47]
		ET+CT	--	--	--	--	--
Prosigna	Pre	ET	3	8–15 years	DR (primary), DFS (secondary)	Results from 1 category C study[45]	NA
		ET+CT	--	--	--	--	--
	Post	ET	1B	8–15 years	DR (primary), DFS (secondary)	Consistent results from 3 category B studies,[43, 46, 47] 2 category C studies[44, 45]	Low- vs. intermediate-/high-risk patients were 61–85% more likely to be free from 10-year DR (p<0.05)[46, 47]
		ET+CT	--	--	--	--	--
Oncotype DX vs. Prosigna	Pre	ET	--	--	--	--	--
		ET+CT	--	--	--	--	--
	Post	ET	2	10 years	DR (primary)	Results from 1 category B study[46]	Prosigna was significantly more prognostic than Oncotype DX (p<0.05)
		ET+CT	--	--	--	--	--

CT: chemotherapy; DFS: disease-free survival; DR: distant recurrence; ET: endocrine therapy; NA: not applicable; OS: overall survival; Post: postmenopausal; Pre: premenopausal; primary: primary outcome; secondary: secondary outcome

TABLE 9: Evidence supporting the prognostic ability of Oncotype DX and Prosigna testing in node-positive (N1) patients

Genetic test	Menopausal status	Treatment received	Level of evidence	Time point	Outcome(s) examined	Studies contributing data	Key findings from category B studies
Oncotype DX	Pre	ET or ET+CT[a]	2	5 years	DR (primary), OS (secondary), DFS (secondary)	Consistent results from 3 category C studies[39, 41, 42]	NA
	Post	ET or ET+CT[a]	2	5–10 years	DR (primary), OS (secondary), DFS (secondary)	Consistent results from 1 category B study,[46] 3 category C studies[39, 41, 42]	Low- vs. intermediate-/high-risk patients receiving ET only were 28% more likely to be free from 10-year DR (p<0.05)[46]
Prosigna	Pre	ET	--	--	--	--	--
		ET+CT	--	--	--	--	--
	Post	ET	2	10 years	DR (primary)	Consistent results from 1 category B study,[46] 1 category C studies[44]	Low- vs. intermediate-/high-risk patients receiving ET were 37% more likely to be free from 10-year DR (p<0.05)[46]
		ET+CT	--	--	--	--	--
Oncotype DX vs. Prosigna	Pre	ET	--	--	--	--	--
		ET+CT	--	--	--	--	--
	Post	ET	--	--	--	--	--
		ET+CT	--	--	--	--	--

[a] The treatments have been combined because the 3 category C studies did not clearly report the treatments received.

CT: chemotherapy; DFS: disease-free survival; DR: distant recurrence; ET: endocrine therapy; N1: 1–3 nodes; NA: not applicable; OS: overall survival; Post: postmenopausal; Pre: premenopausal; primary: primary outcome; secondary: secondary outcome

Predictive ability

For node-negative patients, one category A study (TAILORx),[13] one category B study,[36] and two category C studies[38, 40] contributed level 1A evidence indicating that Oncotype DX is predictive of a lack of adjuvant chemotherapy benefit in most intermediate-risk pre- and postmenopausal patients, at time-points up to 10 years. These results remained consistent despite the use of variable risk cut-offs across studies. Post hoc subgroup analyses from TAILORx indicated a potential benefit of chemotherapy in patients aged 50 years or younger with an RS between 21 and 25. No studies were found that examined the predictive ability of Prosigna in node-negative patients, but the results of an ongoing clinical trial (OPTIMA) are expected to contribute level 1A evidence, in 2023 (see Table 10).

For node-positive (N1) patients, two conflicting category C studies[38, 40] contributed level 3 evidence suggesting that Oncotype DX may be predictive of chemotherapy benefit, or no chemotherapy benefit, in combined pre- and postmenopausal intermediate-risk (RS between 11 and 30) patients at a time-point of five years. The results of an ongoing clinical trial (RxPONDER) can help reconcile these differences, as this trial is expected to contribute level 1A evidence, in 2022. No studies examined the predictive ability of Prosigna in node-positive (N1) patients, but, as with the node-negative population, the results of the ongoing OPTIMA trial are expected to contribute level 1A evidence, in 2023 (see Table 11).

No studies compared the predictive ability of both Oncotype DX and Prosigna, though a planned clinical trial on this topic (OPTIGEN) was withdrawn prior to patient enrolment due to lack of funding.

TABLE 10: Evidence supporting the predictive ability of Oncotype DX and Prosigna testing in node-negative intermediate-risk patients (RS 11–25)

Genetic test	Menopausal status	Level of evidence	Time point	Outcome(s) examined	Studies contributing data	Key findings from category A studies
Oncotype DX	Pre	1A	5–10 years	DR (primary), DLRR (secondary), OS (secondary), DFS (secondary)	Consistent results from, 1 category A study,[13] 1 category B study,[36] 2 category C studies[38, 40]	Lack of CT benefit in most intermediate-risk patients at 5–10 years[13, 36, 38, 40] Some benefit of CT in patients aged ≤50 years with RS 21–25[13]
	Post	1A	5–10 years	DR (primary), DLRR (secondary), OS (secondary), DFS (secondary)	Consistent results from 1 category A study,[13] 1 category B study,[36] 2 category C studies[38, 40]	Lack of CT benefit in intermediate-risk patients at 5–10 years[13, 36, 38, 40]
Prosigna[a]	Pre[a]	--[a]	--	--	--	--
	Post[a]	--[a]	--	--	--	--

[a] Level 1A evidence will be available from 1 category A study (OPTIMA) in 2023 (see section 2.3.4).

CT: chemotherapy; DFS: disease-free survival; DLRR: distant or locoregional recurrence; DR: distant recurrence; OS: overall survival; Post: postmenopausal; Pre: premenopausal; primary: primary outcome; RS: recurrence score; secondary: secondary outcome

TABLE 11: Evidence supporting the predictive ability of Oncotype DX and Prosigna testing in node-positive (N1) intermediate-risk patients (RS 18–25 or 18–30)

Genetic test	Menopausal status	Level of evidence	Time point	Outcome(s) examined	Studies contributing data	Key supporting data
Oncotype DX[a]	Pre[a]	3	5 years	OS (secondary)	Inconsistent results from 2 category C studies[38, 40]	1 study[38] (n=13,163) found a benefit of CT in intermediate-risk patients 1 study[40] (n=624) found no benefit of CT in intermediate-risk patients
	Post[a]					
Prosigna[b]	Pre[b]	--[b]	--	--	--	--
	Post[b]	--[b]	--	--	--	--

[a] Level 1A evidence will be available from 1 category A study (RxPONDER) in 2022 (see section 2.3.4).

[b] Level 1A evidence will be available from 1 category A study (OPTIMA) in 2023 (see section 2.3.4).

CT: chemotherapy; N1: 1–3 nodes; OS: overall survival; Post: postmenopausal; Pre: premenopausal; RS: recurrence score; secondary: secondary outcome

2.4. Rapid Review 2: Clinician and Patient Treatment Choices

Rapid review 2 examined the impact of Oncotype DX and Prosigna testing on clinician and patient treatment decisions for adjuvant chemotherapy in early-stage (I–III), ER+ (and/or PR+), HER2−, node-negative and node-positive (N1) breast cancer. It included the 2016 CCO systematic review[25] and searched for all primary studies published subsequent to the 2016 CCO search.

2.4.1. Description of included studies

The 2016 CCO systematic review[25] contained five relevant primary studies.[72-76] The subsequent literature searches identified eight additional primary studies.[48-55] Additional quality improvement data from patients in Alberta who received Oncotype DX and Prosigna testing were also included due to their contextual relevance. Details of the search strategies are presented in Appendix D, Table D.2; the flow of primary studies through the different phases of the selection process are presented in Appendix E, Figure E.2; and a list of excluded studies can be found in Appendix F, Box F.2.

All five prospective primary studies[72-76] included in the CCO systematic review[25] examined Oncotype DX. They were published between 2010 and 2016 (median: 2013). Five studies provided data for node-negative patients, and two provided data for node-positive (N1) patients.

The eight primary studies published after the CCO systematic review included six prospective cohort studies and two retrospective analyses of prospectively collected data. These studies were published between 2016 and 2018 (median: 2017). They were conducted in Canada, France, Germany, Greece, Italy, Turkey, and the United Kingdom (one study each), with one multicentre study spanning three of the above-listed countries and Spain. Five studies provided data for node-negative patients, and three provided data for node-positive (N1) patients. Six studies examined Oncotype DX and included both pre- and postmenopausal patients, and two studies examined Prosigna in postmenopausal patients only. No studies were comparative. Four of the studies examining Oncotype DX included only patients with an intermediate risk of distant recurrence based on clinicopathologic factors,[49, 51-53] and one included only patients slated to receive chemotherapy based on clinicopathological risk factors and a Predict calculation.[52] One or more authors in 67% of Oncotype DX studies and 100% of Prosigna studies were affiliated with Genomic Health and NanoString Technologies, respectively. The total number of patients enrolled in the studies ranged from 67 to 565 (median: 199). Across the studies, the mean or median age of the patients ranged from 49 to 64 years. All patients were ER+ and HER2−. When reported, mean or median tumour size ranged from 1.3 cm to 2.6 cm (median: 1.8 cm), with 46 to 79% (median: 77%) of tumours measuring less than or equal to 2 cm in size. The majority of the patients in the studies had grade 2 tumours (52 to 71%), with the remaining patients evenly distributed among the grade 1 and 3 tumour categories; however, two studies had between 25 and 46% of patients with grade 3 tumours.[49, 52]

Overall, all studies reported data on total treatment change, and 10 studies reported data on net change in chemotherapy use, though only 1 study noted the treatment regimen actually received by the patients following the final decision. Six studies also presented data on the psychological aspects of the treatment decision process among clinicians and their patients.

For a summary of the included studies, see Table 12; for complete study and patient characteristics, see Appendix H, Tables H.1 to H.3. Outcome data are presented below (for a description of how the outcomes were defined, calculated, and interpreted, see Appendix C, section C.2.4).

TABLE 12: Summary of included studies and key outcome measures reported

Study	Study design	# of patients	Node status		Total treatment change	Net change in CT	Treatment received	Decisional outcomes[a]
			N0	N1				
Oncotype DX (primary studies from 2016 CCO systematic review[25])								
Albanell et al. (2012)[72]	Systematic review's inclusion criteria: Study designs must involve prospectively enrolled patients and prospectively collected tumour samples	107	●		●	●		●
Bargallo et al. (2015)[73]		96	●	●	●			●
de Boer et al. (2013)[74]		151	●	●	●	●		
Levine et al. (2016)[75]		972	●		●			
Lo et al. (2010)[76]		89	●		●			●
Oncotype DX (primary studies)								
Albanell et al. (2016)[48]	Prospective cohort study	527	●		●	●		●
Dieci et al. (2018)[49]	Prospective cohort study	250	●	●	●	●		
Ozmen et al. (2016)[50]	Prospective cohort study	165	●		●	●		●
Torres et al. (2018)[51]	Prospective cohort study	67		●	●	●	●	●
Loncaster et al. (2017)[52]	Retrospective analysis of prospectively collected data	201	●	●	●	●		
Panousis et al. (2017)[53]	Retrospective analysis of prospectively collected data	144	●		●	●		
Prosigna (primary studies)								
Hequet et al. (2017)[54]	Prospective cohort study	210	●		●	●		●
Wuerstlein et al. (2016)[55]	Prospective cohort study	201	●		●	●		●
Quality improvement data from Alberta								
Urgoiti et al. (n.d.)[78] (Oncotype DX)	Retrospective analysis of prospectively collected data	150	●		●			●
Provincial Quality Assurance Working Group (personal communication, Jan 2019) (Prosigna)	Retrospective analysis of prospectively collected data	95	●		●	●		

[a] Decisional outcomes may include but are not limited to: patient and clinician confidence, preferences, and satisfaction; patient decisional conflict and psychological effects.

CCO: Cancer Care Ontario; CT: chemotherapy; N0: node-negative; N1: node-positive (1–3 nodes); n.d.: no date

2.4.2. Total treatment change and net change in chemotherapy use

Node-negative patients

Oncotype DX

Across nine studies (five from the 2016 CCO systematic review[72-76] and four additional studies[48, 49, 50, 53]), treatment decisions changed in a median of 32% of cases following Oncotype DX testing (range: 12 to 52%). In six studies with data on pre- and post-test chemotherapy recommendations,[48-50, 53, 72, 74] the median proportion of patients recommended chemotherapy before Oncotype DX testing was 39% (range: 30 to 56%), while the median post-test proportion was 32% (range: 23 to 37%). This corresponded to a median net reduction in chemotherapy use of 11% (range: 0 to 19%). These changes were statistically significant in three of the six studies.[48, 50, 53] In the two studies that stratified these changes by test risk categories,[48, 50] low- and intermediate-risk patients contributed the majority of the treatment changes (20% and 10% decreases in chemotherapy uses, respectively). The net reduction in chemotherapy use mainly occurred in low-risk patients, with the intermediate- and high-risk patients registering a net increase in chemotherapy use of up to 5%.

In a tenth study where all patients were initially recommended adjuvant chemotherapy based on clinicopathological risk factors and a Predict calculation, there was a net decrease of 60% in chemotherapy use following Oncotype DX testing, with 33% of low-risk, 25% of intermediate-risk, and 2% of high-risk patients foregoing chemotherapy.

For complete outcome data, see Appendix H, Table H.4.

Prosigna

In two primary studies,[54, 55] treatment decisions changed in 14 to 18% of cases following Prosigna testing. The proportion of patients recommended chemotherapy before Prosigna testing ranged from 23 to 30%, while the post-test proportion ranged from 31 to 39%. This corresponded to a statistically significant 9% net increase in chemotherapy use in both studies. In the single study that stratified these changes by test risk categories,[55] high-risk patients contributed the majority of the treatment changes (8% increase in chemotherapy use). The net change was minimal in the intermediate- and low-risk patients. One study[55] also noted that the chemotherapy regimen changed in nine patients (four were high risk), but further details were not provided.

For complete outcome data, see Appendix H, Table H.5.

Node-positive (N1) patients

Oncotype DX

Across four studies (two from the 2016 CCO systematic review[73, 74] and two additional studies[49, 51]), treatment decisions changed in a median of 31% of cases following Oncotype DX testing (range: 20 to 41%). In three studies with data on pre- and post-test chemotherapy recommendations,[49, 51, 74] the median proportion of patients recommended chemotherapy before Oncotype DX testing was 74% (range: 57 to 79%), while the median post-test proportion was 52% (range: 45 to 52%). This corresponded to a median net reduction in chemotherapy use of 22% (range: 12 to 27%). These changes were statistically significant in all three studies. In the single study that stratified changes by test risk category,[51] low-risk patients contributed the majority of the treatment changes (27% decrease in chemotherapy use), and the 3% net decrease in chemotherapy use in intermediate-risk

patients was offset by an equivalent increase in high-risk patients. One study[51] also noted that the intensity of chemotherapy was often reduced, with more taxane-only treatments and fewer regimens with anthracyclines being prescribed after Oncotype DX testing.

In a fifth study where all patients were initially recommended chemotherapy,[52] there was a net decrease of 69% in chemotherapy use following Oncotype DX testing, with 57% of low-risk, 11% of intermediate-risk, and 1% of high-risk patients foregoing chemotherapy.

One study also asked patients about their treatment choices before and after Oncotype DX testing.[51] Treatment decisions changed in 53% of patients, resulting in a statistically significant 12% net reduction in chemotherapy use. Most decision changes occurred in the low-risk patients (32%), where patients who were initially unsure or had been recommended chemotherapy chose not to have chemotherapy after receiving Oncotype DX results. Overall, the proportion of patients who were unsure about their treatment choices decreased from 41% to 23% after Oncotype DX testing. However, because the surveys used in this study included an "unsure" option, this study may overestimate the treatment change.

One study examined the final proportion of patients receiving chemotherapy.[51] Though 52% of patients were recommended chemotherapy after Oncotype DX testing, 42% actually received chemotherapy. This difference may be due to the referring oncologists disagreeing with the final treatment decision from the testing centre (as many patients were referred to the study from other centres). Patient preferences may have also played a role, given that many patients had multiple comorbidities and most of the patients who decided to forego chemotherapy were intermediate risk.

For complete outcome data, see Appendix H, Table H.6.

Prosigna

No studies examined the impact of Prosigna testing on total treatment change or net change in chemotherapy use in node-positive (N1) patients.

2.4.3. Clinician decisional outcomes

For complete clinician decisional outcome data for node-negative and node-positive (N1) patients, see Appendix H, Table H.7.

Node-negative patients

Oncotype DX

Five studies (three from the 2016 CCO systematic review[72, 73, 76] and two additional studies[48, 50]) reported increased clinician confidence in treatment recommendations following Oncotype DX testing. In one study,[48] 33% of surveyed clinicians stated that their confidence in treatment decisions was significantly increased ($p<0.01$); in another study,[50] 88% of clinicians stated that the genetic testing contributed to the final treatment decision.

Prosigna

Two studies[54, 55] reported increased clinician confidence in treatment recommendations following Prosigna testing. In one study,[54] 75% of clinicians felt that Prosigna testing provided additional useful information and also contributed to the final treatment decision. Clinicians' confidence in the final treatment decision increased after utilizing the test result in nearly 40% of cases. When surveyed six months after they used the test, 98% of clinicians said they would use Prosigna again. A

second study[55] reported that clinicians' confidence in the final recommendation was increased in 89% of cases after receiving the test results.

Node-positive (N1) patients

Oncotype DX

One study[51] found that clinicians' confidence in their treatment recommendations for node-positive (N1) patients increased by 49% ($p<0.001$), but, when analyzed by risk category, only the 56% increase in the low-risk patients was statistically significant.

Prosigna

No studies examined the impact of Prosigna testing on clinician decisional outcomes in node-positive (N1) patients.

2.4.4. Patient decisional outcomes

For complete patient decisional outcome data for node-negative and node-positive (N1) patients, see Appendix H, Table H.8.

Node-negative patients

Oncotype

No studies examined the impact of Oncotype DX testing on patient decisional outcomes in node-negative patients.

Prosigna

Two studies reported a statistically significant decrease in mean decisional conflict score (25% to 37%) following receipt of Prosigna results.[54, 55] Overall patient anxiety also decreased after Prosigna testing (45%), mostly due to changes among patients in the low-risk category.[54, 55] In one study,[54] the test results also improved emotional well-being and personal perceptions of uncertainty in choosing treatment options, resulting in an overall positive psychosocial impact on patients. In a second study,[55] patients also reported having better knowledge about their breast cancer status and treatment options after the test and feeling more involved in the decision-making process ($p<0.01$). This meant that they also felt less uncertain about their choice and more capable of making an effective decision ($p<0.05$). Prosigna testing also had a generally positive effect on emotional well-being among patients in the high-risk category.

Node-positive (N1) patients

Oncotype DX

In one study,[51] 74% of node-positive (N1) patients were clear about what choice of treatment was best for them following Oncotype DX testing. Patients' overall confidence in their treatment choices increased in 54% of cases ($p<0.001$), particularly for the low- and intermediate-risk patients ($p\leq0.02$). There was no difference in the high-risk category, with 60% reporting no change in their level of confidence.

Prosigna

None of the included studies on Prosigna evaluated node-positive (N1) patients.

2.4.5. Quality improvement data from Alberta

Oncotype DX

For study and patient characteristics, see Appendix H, Tables H.9 and H.10.

A retrospective quality improvement study (Urgoiti et al.)[78] of 150 node-negative patients found that use of Oncotype DX changed treatment recommendations in 25% of cases, with 95% of these patients opting for no chemotherapy. The highest rate of change occurred in the pre-test clinician-designated high-risk category. In nearly 60% of cases, the clinicians were initially unsure about recommending chemotherapy, and the test results assisted in making the final decision.

Prosigna

In a retrospective quality improvement study of 95 node-negative patients, 26% were recommended chemotherapy before Prosigna testing and 40% after (29% were initially unsure), resulting in a total treatment change of 28% and a net 14% increase in chemotherapy use. The majority of treatment changes occurred among intermediate- and high-risk patients who had been either undecided about their treatment (15%) or not originally recommended chemotherapy (10%). While 40% of patients were recommended chemotherapy after Prosigna testing, only 32% of the patients received it; four patients in each of the intermediate- and high-risk categories opted to avoid chemotherapy (personal communication, Provincial Quality Assurance Working Group, January 2019).

For complete outcome data, see Appendix H, Table H.11.

2.4.6. Ongoing clinical trials

Two prospective cohort studies relevant to rapid review 2 were identified through a search of trial registers. One Canadian study examined the impact of Oncotype DX testing on clinician treatment recommendations in patients with node-positive (N1) disease. One American study examined the impact of Prosigna testing on clinician treatment recommendations, actual treatment received, and patient decisional conflict and anxiety in patients with node-negative disease. The studies were scheduled for completion in December 2017 and October 2017, respectively, but, to our knowledge, no results have been published to date.

One RCT, the OPTIGEN trial, was designed to compare the impact of Oncotype DX, Prosigna, and two more genetic tests on treatment decision-making. However, this trial was withdrawn due to lack of funding.

For further details on these studies, see Appendix H, Table H.12.

2.4.7. Supplemental outcome data

Six studies (including one study from the 2016 CCO systematic review) included combined outcome data for node-negative and node-positive (N1) patients that could not be disaggregated by node status. These data were excluded from the rapid review, but are summarized in Appendix I for the purpose of comparing and contrasting the outcome data with those for the node-negative and node-positive (N1) patient groups. All six studies examined Oncotype DX, and their results were generally consistent with the above-mentioned findings for Oncotype DX, with minor differences. As expected, the median pre-test rate of chemotherapy recommendations (52%) was midway between that of the separate node-negative patient group (39%) and node-positive (N1) patient group (74%). The rate of change in treatment decisions was slightly higher for the combined group (37% versus 31 to 32%). The median net decrease in chemotherapy use (14%), which mostly occurred among the

low-risk patients, was similar to that of the node-negative patients (11%), and reflected the fact that this patient group comprised 62 to 81% of the combined data sample. Overall, the combined data from node-negative and node-positive (N1) patients tested with Oncotype DX slightly overestimated the total treatment changes.

2.4.8. Summary of main findings

One systematic review (with five relevant primary studies) and eight additional primary studies published after the search date of the 2016 CCO systematic review examined the effects of Oncotype DX and Prosigna testing on clinician and patient decisions regarding adjuvant chemotherapy. The quality of the evidence base was limited by study designs that may have introduced bias, combined with heterogeneity in study populations that limited opportunities for cross-study comparisons. There were no comparative studies of Oncotype DX and Prosigna. Though only two studies were conducted in Canada,[51, 75] results are likely applicable to the Canadian context as many studies were conducted in countries with large developed economies, similar levels of resources to devote to health care, and comparable target populations.[77] However, it is important to note that clinicians and patients who choose to order a genetic test are more likely to be influenced by its result, especially when chemotherapy was initially recommended, which may overestimate the effect that genetic testing has on treatment decisions.[52, 79]

Total treatment change and net change in chemotherapy use

For node-negative patients, treatment decisions changed in a median of 32% and 16% of patients after Oncoytpe DX and Prosigna testing, respectively. Oncotype DX testing led to a median 11% net decrease in chemotherapy use, and Prosigna testing led to a median 9% net increase. The treatment changes after Oncotype DX testing largely occurred in low- and intermediate-risk patients choosing to avoid chemotherapy, whereas changes after Prosigna testing were largely due to increased chemotherapy use in intermediate- and high-risk patients. Results from quality improvement data from Alberta on 150 node-negative patients receiving Oncotype DX testing showed similar trends, with treatment changes occurring in 25% of patients, most of whom avoided chemotherapy. Quality improvement data from Alberta on 95 node-negative patients receiving Prosigna testing showed a higher rate of treatment change and subsequent chemotherapy use than the published studies, likely due to the inclusion of patients who were unsure about their treatment choice prior to testing.

For node-positive (N1) patients receiving Oncotype DX testing, the median total treatment change was comparable to that of node-negative patients (median: 31% versus 32%), but the median proportion of patients with a pre-test chemotherapy recommendation was almost double (74% versus 39%). Consequently, the net reduction in chemotherapy use was more dramatic in the node-positive (N1) patients (22% versus 11%), with changes largely due to low-risk patients avoiding chemotherapy. One study[51] noted that fewer regimens with anthracyclines were prescribed after Oncotype DX testing, indicating that genetic testing may alter other aspects of treatment such as chemotherapy intensity. No studies examined the effect of Prosigna testing in node-positive (N1) patients.

In node-negative patients receiving Oncotype DX testing, the range of chemotherapy recommendations narrowed considerably after genetic testing (23 to 37%) compared with before genetic testing (30 to 56%). This trend was particularly dramatic in the node-positive (N1) patients. This suggests that Oncotype DX testing may reduce heterogeneity in treatment decisions.

Clinician decisional outcomes

Oncotype DX testing resulted in increased clinician confidence in treatment decisions for both node-negative and node-positive (N1) patients. Further, test results directly contributed to final treatment decisions in at least one-third of cases. One study of node-positive (N1) patients found that the most significant increase in confidence occurred when deciding to avoid chemotherapy in the low-risk category.[51] There were no data on the effect of Prosigna testing on clinician decisional outcomes.

Patient decisional outcomes

For node-positive (N1) patients, especially those at low risk, one study found that Oncotype DX testing increased patients' confidence about their treatment choice.[51] Prosigna testing also reduced decisional conflict in node-positive (N1) patients, with patients reporting less uncertainty and more engagement in the decision-making process.

2.5. Combined Data from Rapid Reviews 1 and 2: Risk Category Cut-offs and Stratifications

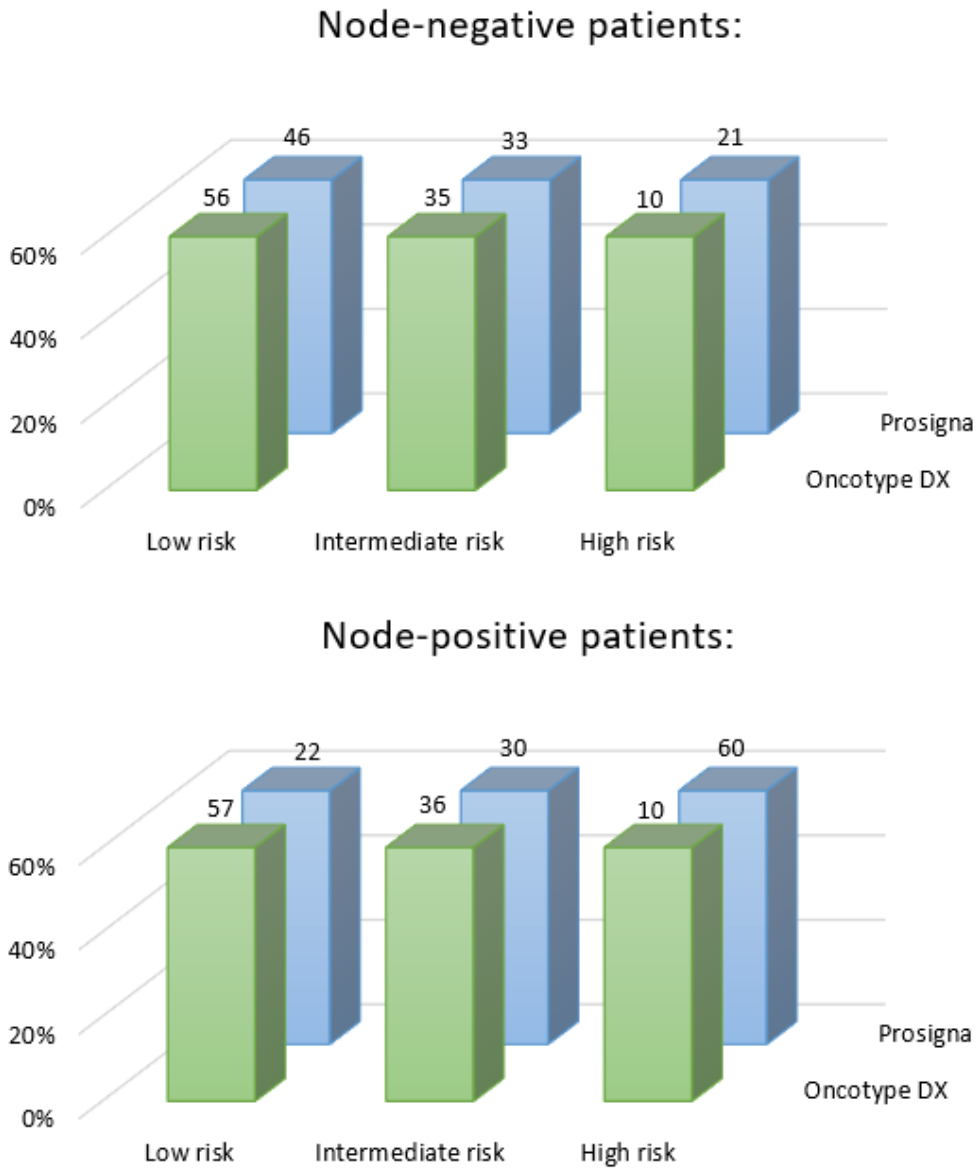
Because the studies in rapid reviews 1 and 2 used risk cut-offs to stratify patients as low, intermediate, or high risk following genetic testing, we opted to combine these data across both rapid reviews (see Figure 1).

To define intermediate-risk patients, most studies across both rapid reviews used the standard risk cut-offs for both genetic tests (that is, an RS between 18 and 30 or 31 for Oncotype DX, and an ROR between 41 and 60 for Prosigna). However, two studies in rapid review 1 (including TAILORx) used a lower RS cut-off for Oncotype DX, of between 11 or 12 and 25.[13, 37] For Prosigna, one study in rapid review 1 used an ROR cut-off of between 27 and 68,[46] and two studies in rapid review 1 used cut-offs that varied based on node status.[43, 44]

Across both rapid reviews, more node-negative patients were classified as low risk by Oncotype DX (median: 56%) compared with Prosigna (median: 46%), and as high risk by Prosigna (median: 21%) compared with Oncotype DX (median: 10%). A similar pattern of results was observed for node-positive (N1) patients, though the differences between tests were more pronounced: more node-positive (N1) patients were classified as low risk (median: 57%) by Oncotype DX compared with Prosigna (median: 22%), and as high risk by Prosigna (median: 60%) compared with Oncotype DX (median: 10%). These risk stratifications were generally consistent across rapid reviews, though rapid review 2 contained no studies examining node-positive (N1) patients tested with Prosigna.

The use of different risk cut-offs affected the above results. As expected, when using standard low-risk cut-offs (an RS of 17 or less) compared to TAILORx cut-offs (an RS of 10 or less) for Oncotype DX, more patients were classified as low risk for the node-negative (median: 58% versus 19%) and node-positive (N1) (median: 57% versus 21%) patient groups. Breakdowns by cut-off scores were not possible for Prosigna due to the small number of studies and the variable risk cut-offs used.

FIGURE 1: Median percentage of node-negative and node-positive (N1) patients at low, intermediate, and high risk, for Oncotype DX and Prosigna



RS: recurrence score

2.6. Rapid Review 3: Health-Related Quality of Life

Rapid review 3 examined the HRQoL of patients with early-stage (I–III) breast cancer in the presence or absence of chemotherapy treatment. It searched for systematic reviews and primary studies published from 2007 onward (though no systematic reviews were identified).

2.6.1. Description of included studies

The literature searches identified 16 relevant articles,[56-71] representing 15 unique primary studies. Details of the search strategies are presented in Appendix D, Table D.3; the flow of primary studies

through the different phases of the selection process are presented in Appendix E, Figure E.3; and a list of excluded studies can be found in Appendix F, Box F.3.

The primary studies examined patients with early-stage (I–III) breast cancer and included eight cross-sectional studies, four prospective cohort studies, and three RCTs. These studies were published between 2007 and 2018 (median: 2014) and were conducted in Japan, Korea, and the United States (two studies each), as well as Brazil, China, India, Iran, Palestine, Spain, Sweden, Tunisia, and Turkey (one study each). The total number of patients enrolled in the studies ranged from 26 to 2,626 (median: 230). Across the studies, the mean age of the patients ranged from 38 to 62 years. A control group of breast cancer-free patients was used in three studies,[67, 68, 70] and a control group of patients with precancerous lesions was used in one study.[71]

The included studies reported HRQoL using the EQ-5D (EuroQol 5 dimensions) (seven studies) and the SF-36 (36-Item Short Form Health Survey) (ten studies); none of the studies used the SF-12 (12-Item Short Form Health Survey) or the SF-6D (6-Dimension Short Form Health Survey). Four observational studies[56-58, 60] compared the HRQoL of patients who had received chemotherapy versus patients who did not receive chemotherapy. Three RCTs compared the HRQoL among patients randomized to different chemotherapy regimens.[61-63] The remaining eight observational studies provided non-comparative HRQoL data for patients receiving chemotherapy. Reporting on chemotherapy drugs and dosages was not present in the majority of studies (nine), and varied across the studies that did include drug or dosing regimens. The majority of studies used other adjuvant therapy(s) in addition to chemotherapy, including endocrine therapy, radiation therapy, and/or targeted therapy (12 studies).

For a summary of the included studies, see Table 13; for complete study and patient characteristics, see Appendix J, Tables J.1 and J.2. Outcome data are presented below (for a description of how the outcomes were defined, calculated, and interpreted, see Appendix C, section C.3.4).

TABLE 13: Summary of included studies and outcome data

Study	Study design	# of patients	EQ-5D		SF-36			
			Index score	EQ-VAS	PCS	MCS	Domain scores	Total score
Chemotherapy vs. no chemotherapy								
Kim et al. (2015)[56]	Cross-sectional study	827	●	●				
Lidgren et al. (2007)[57]	Cross-sectional study	345	●					
Moro-Valdezate et al. (2014)[58, 59]	Prospective cohort study	364	●	●				
Tiezzi et al. (2017)[60]	Cross-sectional study	112					●	
Different chemotherapy regimens								
Berger et al. (2009)[61]	RCT	158			●	●		
Paskett et al. (2009)[62]	RCT	245					●	
Shiroiwa et al. (2011)[63]	RCT	299	●					
Chemotherapy without comparator								
Abu Farha et al. (2017)[64]	Cross-sectional study	170	●					
Daldoul et al. (2018)[65]	Cross-sectional study	70						●
Kaur et al. (2018)[66]	Cross-sectional study	230			●	●	●	
Lee et al. (2012)[67]	Cross-sectional study	96					●	
Safarinejad et al. (2013)[68]	Prospective cohort study	186					●	
Tonosaki et al. (2014)[69]	Prospective cohort study	28					●	
Turan et al. (2009)[70]	Prospective cohort study	26					●	
Wang et al. (2018)[71]	Cross-sectional study	2,626	●					

EQ-5D: EuroQol 5 dimensions; EQ-VAS: EuroQol visual analogue scale; MCS: Mental Component Summary; PCS: Physical Component Summary; RCT: randomized controlled trial; SF-36: 36-Item Short Form Health Survey

2.6.2. Impact of chemotherapy versus no chemotherapy on HRQoL

Four observational studies examined the impact of chemotherapy compared with no chemotherapy on the HRQoL of patients with breast cancer using either the EQ-5D[56-58] or the SF-36.[60]

EQ-5D

Of the three relevant observational studies,[56-58] none described the chemotherapy drugs or dosages used. One prospective cohort study conducted in Spain reported a significant difference between the EQ-5D index score of patients receiving adjuvant chemotherapy versus those receiving no chemotherapy, with better HRQoL scores for the chemotherapy group ($p<0.001$).[58] One Korean study found no significant difference between chemotherapy and no chemotherapy groups for the index or EQ-VAS (EuroQol visual analogue scale) scores.[56] In one Swedish study, it was unclear whether there was a significant difference between groups (p-value not reported).[57]

For complete outcome data, see Appendix J, Table J.3.

SF-36

One cross-sectional study[60] conducted in Brazil compared patients with stages I–IIA breast cancer who received no adjuvant chemotherapy with patients with stages IIA/B–III breast cancer who received adjuvant chemotherapy (fluorouracil, epirubicin and cyclophosphamide, or epirubicin and cyclophosphamide with or without a taxane) using the SF-36. Patients who did not receive chemotherapy had significantly better scores for the physical functioning ($p=0.01$) and physical role functioning ($p=0.01$) domains. There was no significant difference between patients who did and did not receive chemotherapy in the other domains.

For complete outcome data, see Appendix J, Table J.4.

2.6.3. Impact of different chemotherapy regimens on HRQoL

Three RCTs assessed the impact of different adjuvant chemotherapy drug or dosing regimens on the HRQoL of patients with breast cancer using either the EQ-5D[63] or the SF-36.[61, 62]

EQ-5D

One RCT compared the HRQoL of patients receiving four different chemotherapy drug regimens (an anthracycline with paclitaxel, an anthracycline with docetaxel, paclitaxel alone, and docetaxel alone) using the EQ-5D.[63] Compared with patients treated with docetaxel alone, patients treated with an anthracycline with paclitaxel or an anthracycline with docetaxel had significantly better HRQoL as measured by the EQ-5D index score ($p=0.005$ and $p<0.0001$, respectively). There was no significant difference in the type of taxane (paclitaxel versus docetaxel) used.

For complete outcome data, see Appendix J, Table J.5.

SF-36

Two RCTs compared the HRQoL across patients receiving different dosages or types of chemotherapy using the SF-36.[61, 62] One study[61] randomized patients to three anthracycline-based chemotherapy regimens, namely dose-dense chemotherapy with a taxane, standard-dose chemotherapy with a taxane, or standard-dose chemotherapy without a taxane. Patients receiving standard-dose chemotherapy without a taxane had significantly higher Physical Component Summary scores than patients receiving taxane-based treatment, but no difference was found between groups for Mental Component Summary scores. A second study[62] found a significant

difference in physical role functioning among patients who had been randomized to the low-dose, standard-dose, and high-dose cyclophosphamide, doxorubicin, and fluorouracil regimens, with better functioning in patients who received the high-dose treatment ($p<0.0001$). There were no significant differences between dosing groups for the other scales.

For complete outcome data, see Appendix J, Table J.6.

2.6.4. Impact of chemotherapy without comparator on HRQoL

Eight observational studies reported the HRQoL of patients who received adjuvant chemotherapy without providing an eligible chemotherapy or no chemotherapy comparator group. Two studies used the EQ-5D,[29,46] and six used the SF-36.[65-70]

EQ-5D

Two studies provided non-comparative data for the HRQoL of patients receiving chemotherapy.[64, 71] One study treated patients with doxorubicin and cyclophosphamide and/or paclitaxel.[64] Patients also received endocrine therapy, radiation therapy, and/or symptomatic treatment alongside chemotherapy.

For complete outcome data, see Appendix J, Table J.7.

SF-36

Six observational studies[65-70] provided single-arm HRQoL estimates for patients receiving adjuvant chemotherapy. One study used a variety of different chemotherapy drugs for patients (doxorubicin and cyclophosphamide, docetaxel and cyclophosphamide, and doxorubicin and cyclophosphamide plus paclitaxel),[69] while the remaining studies did not report the type of chemotherapy used. All the studies reported scores for each of the eight SF-36 scales, with the exception of one study that calculated a total score.[65]

For complete outcome data, see Appendix J, Table J.8.

2.6.5. Summary of main findings

Rapid review 3 examined the HRQoL of patients with early-stage breast cancer in the presence or absence of chemotherapy treatment. Fifteen unique studies contributed limited outcome data. The evidence base varied across comparisons in terms of both quality and applicability to the Canadian context (described below). Because this rapid review was conducted primarily to help inform the economic evaluation, eligible HRQoL outcomes were limited to generic measures that allowed for comparison across diseases in describing and valuing health states. This meant that a large body of literature reporting on the impact of chemotherapy on HRQoL using cancer- or breast cancer-specific measures (for example, *European Organisation for Research and Treatment of Cancer quality of life questionnaires* and *Functional Assessment of Cancer Therapy*) was excluded.

Chemotherapy versus no chemotherapy

The four observational studies comparing HRQoL for patients with chemotherapy versus no chemotherapy[56-58, 60] had study designs that were prone to bias, heterogeneity across the study populations and interventions, small sample sizes that were often imbalanced between treatment arms, and poor reporting (for example, chemotherapy drugs and regimens were only described in one study). The findings across these four studies were discordant, with results including significantly favouring chemotherapy (EQ-5D index score), showing no difference by chemotherapy

status (EQ-5D index score, EQ-VAS), and significantly favouring no chemotherapy (SF-36 physical functioning and physical role functioning). The applicability of the HRQoL results to the Canadian context may be limited, as none of these studies were conducted in Canada or in countries with major developed economies. Due to these limitations, the results should be interpreted with caution.

Different chemotherapy regimens

Three RCTs examined the impact of three different chemotherapy drug or dosing regimens on patient HRQoL.[61-63] The studies all found that the type or dosage of chemotherapy had a significant impact on patient HRQoL, with some drugs and dosing schedules resulting in less reduction in HRQoL than others. Although the quality of these trials was not assessed, all were described as randomized. These results are likely applicable to the Canadian context, as two studies were conducted in North America and all studies were all conducted in countries with large developed economies.

Chemotherapy without comparator

Few conclusions can be drawn from the eight observational studies that provided non-comparative data on the effect of chemotherapy on HRQoL. These studies rarely provided a description of chemotherapy treatment, and patients received additional adjuvant therapies (for example, radiation therapy, endocrine therapy, targeted therapy) that may have impacted HRQoL.

SECTION 3: Economic Evaluation

Andrew Sutton, PhD; Mike Paulden, PhD; Lisa Tjosvold, MLIS; Christopher McCabe, PhD

The choice of whether to use Oncotype DX or Prosigna has the potential to have a large impact on patients in terms of patient outcomes, and on healthcare providers in terms of the resources allocated to the testing and treatment of patients with breast cancer. This economic evaluation examines the cost-effectiveness of Oncotype DX versus Prosigna in the testing of patients with early-stage breast cancer.

3.1. Methods

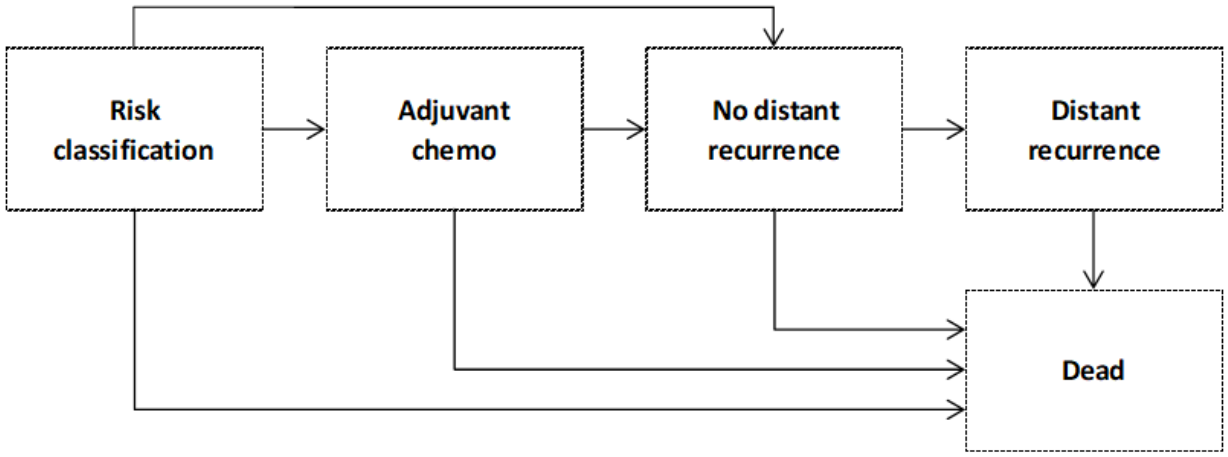
A model-based cost-utility analysis was undertaken from the perspective of AHS to evaluate the expected patient outcomes, costs, and cost-effectiveness of Prosigna-guided adjuvant chemotherapy compared with either Oncotype DX-guided adjuvant chemotherapy or the provision of adjuvant chemotherapy without guidance from either test ("No testing"), where a decision on chemotherapy is made on clinical grounds by the clinician and patient. The patient population was a hypothetical cohort of patients aged 55 years who were diagnosed with early-stage, ER+ (and/or PR+), HER2−, node-negative breast cancer, who are candidates for adjuvant chemotherapy. The impact of testing node-positive patients was also considered.

The outcome measure was the quality-adjusted life year (QALY), a composite measure of length and quality of life where one QALY is one year lived in perfect health. A lifetime time horizon was adopted. Costs were measured in 2018 Canadian dollars, and a discount rate of 1.5% for costs and outcomes was applied as recommended by the latest Canadian Agency for Drugs and Technologies in Health (CADTH) methods and guidelines.[80] The analysis was conducted in March 2019.

3.1.1. Model

A Markov model was implemented using MATLAB (R2018b), with a one-month time step and lifetime time horizon. The model structure along with selected model parameters were informed by a previous cost-effectiveness analysis of Oncotype DX and Prosigna published by Paulden et al. in 2013.[81] In the model structure, patients were initially stratified into low-, intermediate-, or high-risk categories depending on the Oncotype DX or Prosigna test result, or they remained unclassified in the "No testing" arm. Next, depending on the risk classification, a proportion of patients received adjuvant chemotherapy (for all chemotherapy patients, there is a risk of toxicity that requires hospital treatment). Patients were then followed up for the rest of their lives, with the risk of distant recurrence over their lifetime dependent on their risk category and previous chemotherapy treatment. All patients in the model eventually die, due to breast cancer or other reasons (see Figure 2).

FIGURE 2: Overview of model structure



Reprinted from Paulden et al. (2013),[81] with permission from Elsevier.

3.1.2. Transition probabilities

Risk classification

In Alberta, the risk categories for Oncotype DX are defined as follows: *low risk* is an RS of 25 or less; *high risk* is an RS of 26 or more; and *intermediate risk* is an RS between 20 and 25, for premenopausal patients only. For Prosigna, the risk categories used in Alberta are defined as follows: *low risk* is an ROR between 0 and 40; *intermediate risk* is an ROR between 41 and 60; and *high risk* is an ROR of 61 to 100 (personal communication, Expert Advisory Group, March 2019). For node-negative patients, the probabilities of patients being classified into each of the Oncotype DX risk categories were informed using the results from TAILORx as described by Sparano et al.,[13] where the intermediate-risk category was informed by the premenopausal patients in TAILORx that had an RS between 21 and 25. As TAILORx did not incorporate Prosigna, to inform the risk categories for Prosigna for a similar patient population, concordance data from Dowsett et al.[47] was used that links the ROR for Prosigna with the RS for Oncotype DX. These are shown in Table 14, using percentages. By applying these percentages, the TAILORx risk categories for Oncotype DX were utilized to calculate the risk categories for Prosigna (see Table 15). For node-positive patients, risk stratification as used by Sestak et al.[46] for both tests were applied to the same node-positive postmenopausal patients (see Table 16). In this case, the cut-offs were different to those used in Alberta; this must be considered when drawing conclusions from this analysis.

TABLE 14: Comparison of proportion of node-negative patients by risk category, using Oncotype DX risk score versus Prosigna risk of recurrence from Dowsett et al.

Oncotype DX RS	Prosigna ROR			Total
	Low	Intermediate	High	
Low	71%	25%	3%	100%
Intermediate	47%	28%	26%	100%
High	8%	24%	68%	100%

Dowsett et al. (2013)[47]

ROR: risk of recurrence; RS: recurrence score

TABLE 15: Proportion of node-negative patients assigned to each risk category, by test

Risk category	% of patients (n)	Source and notes
Oncotype DX		
Low risk	80.4% (n=7,816)	Sparano et al. (2018), Table S1[13] (RS <20, 21–25, >26) Sparano et al. (2018), Figure S12[13] (intermediate risk; premenopausal)
Intermediate risk	5.3% (n=514)	
High risk	14.3% (n=1,389)	
Prosigna		
Low risk	60.9% (n=5,918)	Oncotype DX proportions above combined with concordance data from Dowsett et al. (2013)[47]
Intermediate risk	25.3% (n=2,549)	
High risk	13.8% (n=1,342)	

n: number of patients; RS: recurrence score

TABLE 16: Proportion of node-positive patients assigned to each risk category, by test

Risk category	% of patients (n)	Source and notes
Oncotype DX		
Low risk	57.4% (n=105)	Sestak et al. (2018)[46] (RS <18, 18–31, >31; postmenopausal)
Intermediate risk	31.7% (n=58)	
High risk	10.9% (n=20)	
Prosigna		
Low risk	8.2% (n=15)	Sestak et al. (2018)[46] (ROR ≤26, 27–68, ≥69; postmenopausal)
Intermediate risk	31.7% (n=58)	
High risk	60.1% (n=110)	

n: number of patients; ROR: risk of recurrence; RS: recurrence score

Adjuvant chemotherapy

Expert opinion from the Expert Advisory Group was sought to inform what proportion of patients would receive adjuvant chemotherapy based on a test result (see Table 17). These opinions were based on the experiences of treating 1,000 to 1,500 patients (assumed to be 100 patients for the purposes of probabilistic sensitivity analysis, see below) in Alberta since 2014. It was assumed that chemotherapy uptake by risk category would be the same for Prosigna and Oncotype DX, and that these would be same for node-negative and node-positive patients. For the strategy in which "No testing" was conducted, the probability of being provided adjuvant chemotherapy was derived from estimates from Paulden et al.[81] To account for parameter uncertainty, a beta distribution was assigned to each probability. Adjuvant chemotherapy patients were assumed to receive docetaxel and cyclophosphamide chemotherapy (commonly referred to as *TC chemotherapy*), specifically docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2, given every three weeks for four cycles. All patients were also assumed to receive granulocyte-colony stimulating factor (G-CSF) prophylaxis with 300 mcg filgrastim per day for 10 days, provided alongside half of the chemotherapy cycles. Furthermore, all patients were assumed to be given the aromatase inhibitor anastrozole (one 1 mg tablet) daily for five years.

TABLE 17: Proportion of patients receiving chemotherapy, by test and risk category

Risk category	% of patients (# receiving chemotherapy/total patients in risk category)	Source and notes
Oncotype DX		
Low risk	5% (4/80.4)	EAG opinion, based on the experience of treating 1,000–1,500 patients Denominators calculated based on percentage in each risk category, assuming 100 patients
Intermediate risk	67% (3.6/5.3)	
High risk	95% (13.6/14.3)	
Prosigna		
Low risk	5% (3/60.9)	EAG opinion based on the experience of treating 1,000–1,500 patients Denominators calculated based on percentage in each risk category for Prosigna, assuming 100 patients
Intermediate risk	67% (17/25.3)	
High risk	95% (13.1/13.8)	
No testing		
No risk category	48.96%	Paulden et al. (2013)[81]

EAG: Expert Advisory Group

Distant recurrence

The probability of distant recurrence was assumed to depend on: (a) the associated risk category (low, intermediate, or high); (b) the test used for classification (Prosigna, Oncotype DX, or no test); and (c) whether or not adjuvant chemotherapy was provided. The probability of distant recurrence for patients in each of the Oncotype DX and Prosigna risk categories for node-negative and node-positive patients who do not receive adjuvant chemotherapy was estimated using the 9-year distant recurrence-free survival curves published by Sestak et al.[46] (see Table 18).[v] These values were based on the results from a preplanned secondary study of data from an RCT comparing 5-year treatment with anastrozole versus tamoxifen with 10-year follow-up data. The patient group included 774 postmenopausal patients with ER+, HER2− breast cancer. For each Oncotype DX risk category, a beta distribution was assigned to the risk of 9-year distant recurrence to account for parameter uncertainty. On each model simulation, the risk of distant recurrence for earlier and later time periods was estimated from the value drawn for the risk of 9-year distant recurrence, on the assumption that patients face a constant risk of distant recurrence over time.

It is important to note that it was necessary to ensure that the probabilities of distant recurrence were coherent between the Prosigna and Oncotype DX risk categories. For example, within any given patient population, the probability of distant recurrence for patients categorized as low risk using Prosigna should "co-vary" with the probability of distant recurrence for patients categorized as low risk using Oncotype DX. Consequently, the risk of distant recurrence for patients in each Prosigna risk category should not be considered independently of the risk of distant recurrence for patients in each Oncotype DX risk category. To model this coherence, we estimated a separate *relative risk* of distant recurrence, in the absence of adjuvant chemotherapy, for each Prosigna risk

[v] In particular, see Figure 1 in Sestak et al.[46]

category (low, intermediate, and high) compared with the corresponding Oncotype DX risk category (low, intermediate, and high, respectively).

Distant recurrence with adjuvant chemotherapy

Paik et al.[82] reported the relative risk of 10-year distant recurrence for patients receiving cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy, compared with patients not receiving chemotherapy, for each Oncotype DX risk category. Uncertainty in these estimates was incorporated into the analysis by assigning log-normal distributions to each relative risk (see Table 18).

The team was unaware of comparable estimates of the relative risk of distant recurrence with chemotherapy versus without chemotherapy for each Prosigna risk category. It was therefore assumed that the relative risks derived from Paik et al.[82] for the Oncotype DX risk categories (low, intermediate, and high) could be applied to the corresponding Prosigna risk categories (low, intermediate, and high, respectively).

Furthermore, all chemotherapy patients in the study considered by Paik et al.[82] received CMF chemotherapy. In the model, a further adjustment to the risk of distant recurrence was required since patients are assumed here to receive TC chemotherapy. We applied the same relative risk of distant recurrence for TC chemotherapy versus CMF chemotherapy as that used by Paulden et al.[81] (see Table 18).

Mortality

Data from relevant life tables were used to model the risk of death from causes other than breast cancer. Patients were subject to a higher risk of mortality during chemotherapy and following a distant recurrence (see Table 18).

TABLE 18: Parameters related to distant recurrence, chemotherapy toxicity, and mortality

Parameter	Value	Source and notes
Distant recurrence		
Risk of 9-year distant recurrence without chemotherapy for node-negative patients, by risk category		
Oncotype DX low risk	5.1% (n=374)	Sestak et al. (2018), Figure 1[46] (postmenopausal)
Oncotype DX intermediate risk	16.1% (n=156)	
Oncotype DX high risk	27.2% (n=61)	
Prosigna low risk	3% (n=318)	
Prosigna intermediate risk	12.1% (n=178)	
Prosigna high risk	31.1% (n=95)	
Risk of 9-year distant recurrence without chemotherapy for node-positive patients, by risk category		
Oncotype DX low risk	14.2% (n=105)	Sestak et al. (2018), Figure 1[46] (postmenopausal)
Oncotype DX intermediate risk	29.0% (n=58)	
Oncotype DX high risk	37.8% (n=20)	
Prosigna low risk	0% (n=15)	
Prosigna intermediate risk	18.6% (n=58)	

Parameter	Value	Source and notes
Prosigna high risk	26.4% (n=110)	
Relative risk of distant recurrence, by risk category and/or chemotherapy status		
All patients, CMF chemotherapy vs. without chemotherapy	0.6154	Paik et al. (2006)[82] (Oncotype DX, CMF chemotherapy) Assumed to be the same for Prosigna risk categories
Low risk (RS <18), CMF chemotherapy vs. without chemotherapy	1.31	
Intermediate risk (RS 18–30), CMF chemotherapy vs. without chemotherapy	0.61	
High risk (RS >30), CMF chemotherapy vs. without chemotherapy	0.26	
TC chemotherapy vs. CMF chemotherapy	0.85	Paulden et al. (2013)[81]
Hospital visits due to toxicity		
Risk of hospital visit due to toxicity	6.8%	Barcenas et al. (2014)[83] (TC chemotherapy, n=1,060)
Cause of hospital visits due to toxicity		
Neutropenia/fever/infection	53.56%	Paulden et al. (2013)[81]
Injuries and trauma	11.48%	
Malignant neoplasm	10.89%	
Pain and pain management	7.51%	
Nausea/vomiting/dehydration	6.02%	
Gastrointestinal tract	5.64%	
Chest pain	4.89%	
Mortality		
Risk of mortality due to chemotherapy-related toxicity	0.35%	Paulden et al. (2013)[81]
Median life expectancy following distant recurrence (months)	21.0	Paulden et al. (2013)[81]
Risk of mortality due from other causes	Life table	Statistics Canada (2018)[84]

CMF: cyclophosphamide, methotrexate, and fluorouracil; RS: recurrence score (calculated using Oncotype DX); TC: docetaxel and cyclophosphamide

Costs

In Alberta, the price of Prosigna testing per patient is $2,870, and the price of Oncotype DX testing per patient is $3,742. The costs associated with chemotherapy and other treatment were obtained from a variety of sources and supported by a previous cost-effectiveness analysis of Oncotype DX in Alberta conducted by Tiwana et al. (2013),[85] and inflated to 2018 Canadian dollars using the Alberta Consumer Price Index for health care. All other costs were obtained from a variety of secondary sources and inflated to 2018 Canadian dollars where appropriate (see Table 19).

TABLE 19: Cost parameters

Parameter	Cost	Source and notes
Cost of Oncotype DX and Prosigna, per patient		
Oncotype DX	$3,742.00	Personal communication, Expert Advisory Group, Mar 2019
Prosigna	$2,870.00	
Chemotherapy costs applicable to all regimens, per cycle		
Laboratory costs	$65.07	Tsoi et al. (2010)[86]
Human resources	$154.45	
TC chemotherapy costs, per cycle		
Docetaxel (Taxotere), 75 mg/m^2	$317.32	ABCDPL, 14 Jan 2019[87] Every 3 weeks for 4 cycles; 28 mg/ml
Cyclophosphamide (Procytox), 600 mg/m^2	$112.29	ABCDPL, 14 Jan 2019[87] Every 3 weeks for 4 cycles; 1,000 mg/vial injection
G-CSF prophylaxis, per day		
Filgrastim (Neupogen), 300 mcg	$173.19	ABCDPL, 14 Jan 2019[87] All patients receive G-CSF prophylaxis; 300 mcg filgrastim per day for 10 days, provided alongside half of the chemotherapy cycles
Aromatase inhibitor		
Anastrozole, 1 mg tablet	$2.55	ABCDPL, 14 Jan 2019[87] Taken daily for 5 years
Ongoing care for distant recurrence-free patients, per month		
First year	$57.04	Paulden et al. (2013)[81]
Second year	$51.51	
Third year	$45.99	
Fourth year	$40.46	
Fifth year and beyond	$34.93	
Cost of treating distant recurrence		
Initial cost of treatment (one time)	$8,876.93	Paulden et al. (2013)[81]
Hospitalization	$586.27	
Medical services in hospital	$42.50	
Medical services out of hospital	$48.36	
Palliative radiation therapy	$63.74	Paulden et al. (2013)[81] Based on 2.2% of patients receiving radiation therapy
Ongoing care (per month)	$740.89	Paulden et al. (2013)[81] Hospitalization + medical services in hospital + medical services out of hospital + palliative radiation therapy

Parameter	Cost	Source and notes
Average cost per day for hospitalization for terminal care	$828.11	Paulden et al. (2013)[81] Average length of stay is 27 days
Medical services in hospital for terminal care	$193.47	
Medical services out of hospital for terminal care	$82.08	
Total cost of palliative radiation therapy for terminal care	$1,229.70	Paulden et al. (2013)[81] Received by 10% of patients
End-of-life care (last three months)	$22,757.39	Paulden et al. (2013)[81]
Cost of treatment of non-fatal chemotherapy toxicity		
Neutropenia/fever/infections	$7,252.03	Paulden et al. (2013)[81]
Injuries and trauma	$7,630.87	
Malignant neoplasm	$6,908.10	
Pain and pain management	$4,533.90	
Nausea/vomiting/dehydration	$4,399.15	
Gastrointestinal tract	$6,899.58	
Chest pain	$3,214.04	
Treatment of fatal toxicity	$35,853.69	

ABCDPL: Alberta Blue Cross Drug Price List; G-CSF: granulocyte-colony stimulating factor; TC: docetaxel and cyclophosphamide

Utility values

Utility values were obtained from Lidgren et al.,[57] who obtained responses to the EQ-5D questionnaire administered to 361 consecutive patients with breast cancer who attended a breast cancer outpatient clinic at Karolinska University Hospital, Solna for outpatient visits between April and May 2005 (see Table 20). This study was used in the 2016 University of Alberta report[21] and Paulden et al.[81] We conducted a comprehensive literature search for HRQoL studies published since 2007, but could not identify any newer studies with similar quality and health states (see Appendix C, section C.3).

TABLE 20: Utility parameters

Parameter	Value (95% CI)	Source
First year following diagnosis while receiving aromatase inhibitor	0.744 [0.573, 0.841]	Lidgren et al. (2007)[57]
First year following diagnosis while on chemotherapy	0.620 [0.509, 0.697]	
Second and subsequent years prior to distance recurrence	0.779 [0.745, 0.811]	
Following distant recurrence	0.685 [0.620, 0.735]	

CI: confidence interval

3.1.3. Sensitivity analyses

Uncertainty in the model parameters was accounted for by using probabilistic sensitivity analysis, where the uncertainty in each parameter is described through the use of a probability distribution

(rather than single point value). Fifteen thousand Monte Carlo simulations were used to promulgate this uncertainty through the model, to capture the resulting uncertainty in the model outputs (for example, the estimated cost and outcomes for each of the treatment strategies being compared). The uncertainty in whether a specific strategy is cost-effective at a specific willingness-to-pay (WTP) for a QALY is shown using cost-effectiveness acceptability curves (CEACs) and scatterplots on the cost-effectiveness plane.

The sensitivity analyses examined the impact of varying one or more parameters in the model, namely the menopausal status of the patients, the price of Oncotype DX, the risk category stratification by test result, and the discount rate. Unless explicitly stated, the remaining parameters remained unchanged from those parameters used in the main analysis above.

Menopausal status

In order to investigate the impact of the risk category stratification on the model results, further analysis was conducted for pre- and postmenopausal patients, using parameter values informed by Sparano et al.[13] for Oncotype DX and the concordance values from Dowsett et al.[47] for Prosigna (see Table 21). Note that, for Oncotype DX, there would be no intermediate-risk postmenopausal patients, as these would be regarded as low risk for the purposes of considering whether to administer chemotherapy.

TABLE 21: Sensitivity analysis – proportion of patients assigned to each risk category by test, for node-negative pre- and postmenopausal patients

Risk category	Value (n)	
	Premenopausal	Postmenopausal
Oncotype DX		
Low risk	72% (n=2,387)	85% (n=5,429)
Intermediate risk	16% (n=514)	0%
High risk	12% (n=403)	15% (n=986)
Prosigna		
Low risk	60% (n=1,973)	61% (n=3,945)
Intermediate risk	26% (n=844)	25% (n=1,615)
High risk	15% (n=487)	13% (n=856)
No testing		
No risk category	48.96%	48.96%

n: number of patients

Price of Oncotype DX

To examine the impact of the price of Oncotype DX on the conclusions drawn from the analysis, this parameter was varied across plausible values with 15,000 Monte Carlo simulations carried out for each value.

Risk category stratification

Given the importance of the risk category stratification by test result, and the lack of a study that examines patient groups for both tests using Alberta cut-offs, further analysis was conducted to

examine the impact of this parameter on model results. Sestak et al.[46] conducted analysis of both tests applied to the same patient population. While this patient population only consisted of postmenopausal patients stratified by cut-offs that are different than those used in Alberta, this does allow further opportunity to examine the impact of this parameter on model results. The parameters used are shown in Table 22.

TABLE 22: Sensitivity analysis – risk category stratification for postmenopausal patients, by test

Parameter	% of patients (n)	Source and notes
Oncotype DX		
Low risk	63.3% (n=374)	Sestak et al. (2018)[46] (RS <18, 18–31, >31; postmenopausal)
Intermediate risk	26.4% (n=156)	
High risk	10.3% (n=61)	
Prosigna		
Low risk	53.8% (n=318)	Sestak et al. (2018)[46] (ROR <27, 27–68, >68; postmenopausal)
Intermediate risk	30.1% (n=178)	
High risk	16.1% (n=95)	

n: number of patients; ROR: risk of recurrence; RS: recurrence score

Discount rate

To examine the impact of the discount rate on model results, this value was taken to be 0% (no discounting) and 3%.

3.2. Results

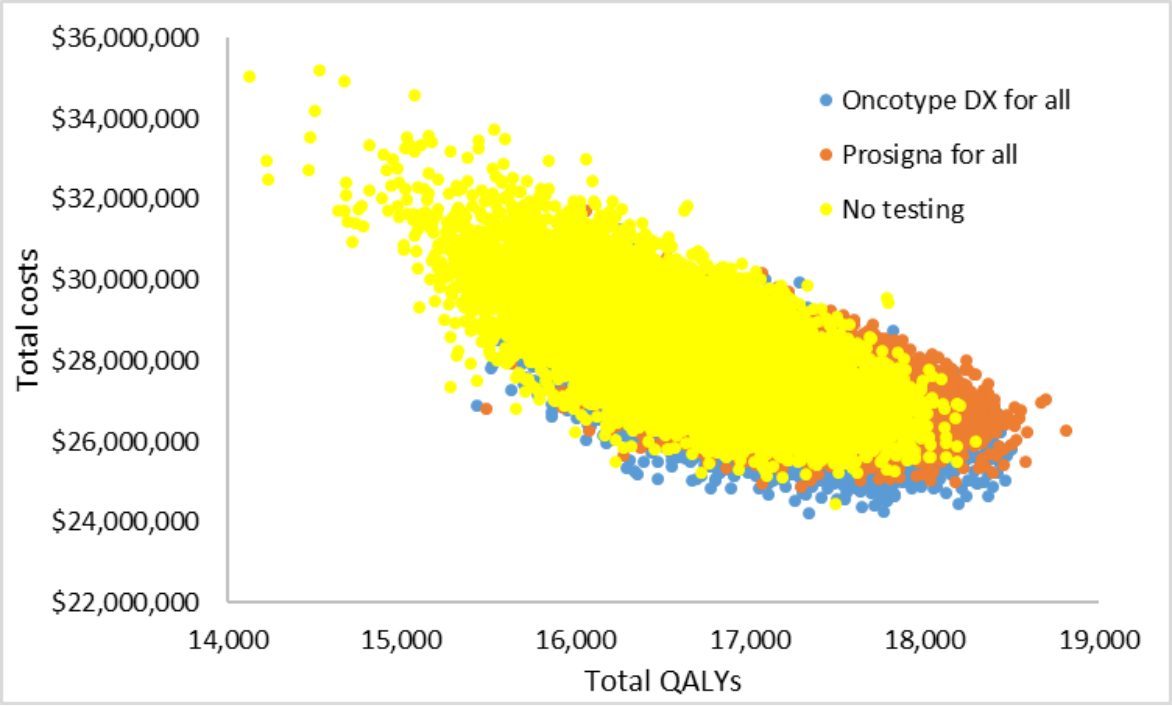
The results are presented for node-negative and node-positive patients. For the purposes of comparison, the impact of each strategy on 1,000 patients was examined. Following the baseline results, the results of the sensitivity analyses are presented.

3.2.1. Node-negative patients

The complete expected outcomes, costs, effectiveness and cost-effectiveness of the Prosigna strategy for node-negative patients compared with the Oncotype DX and "No testing" strategies are shown visually using a scatterplot in Figure 3 and a CEAC in Figure 4, and are summarized in Table 23. For further details, see Appendix K, Table K.1.

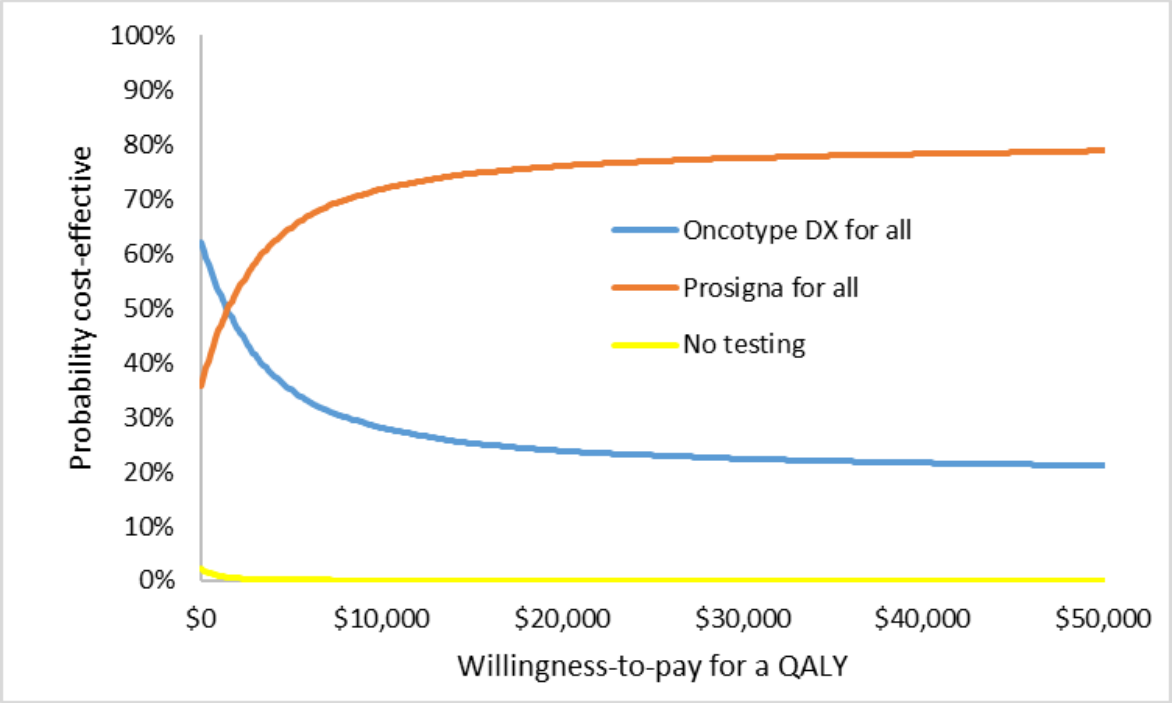
The expected cost of the Prosigna strategy would be approximately $200,000 greater per 1,000 patients than the Oncotype DX strategy (see Appendix K, Table K.1, which shows that these extra costs are mainly due to providing additional adjuvant chemotherapy compared to Oncotype DX). However, this leads to a gain of 171 QALYs per 1,000 patients compared with Oncotype DX. It is notable that the "No testing" strategy is more expensive than either of the testing strategies, but has the worst patient outcomes in terms of QALYs, cases of distant recurrence, and mortality. The additional costs due to "No testing" are a result of unnecessary chemotherapy and increased cases of distant recurrence. When considering parameter uncertainty, it can be seen that Prosigna is more than 76% likely to be cost-effective for WTP values for the QALY of $20,000 and above.

FIGURE 3: Scatterplot of 15,000 Monte Carlo iterations for 1,000 node-negative patients



QALY: quality-adjusted life year

FIGURE 4: Cost-effectiveness acceptability curve for 15,000 Monte Carlo iterations for node-negative patients



QALY: quality-adjusted life year

TABLE 23: Cost-effectiveness results for 1,000 node-negative patients

Test	Total lifetime costs	QALYs	ICER	Probability of cost-effectiveness		
				WTP $20,000/QALY	WTP $50,000/QALY	WTP $100,000/QALY
Oncotype DX	$27.0 million	17,066		23.8%	21.1%	20.0%
Prosigna	$27.2 million	17,237	$1,377.4	76.1%	78.9%	79.9%
No testing	$28.2 million	16,682	Dominated	0.1%	0.1%	0.1%

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness-to-pay

3.2.2. Node-positive patients

For node-positive patients, the scatterplot and CEAC are shown in Figures 5 and 6 respectively, with the results summarized in Table 24. For further details, see Appendix K, Table K.2.

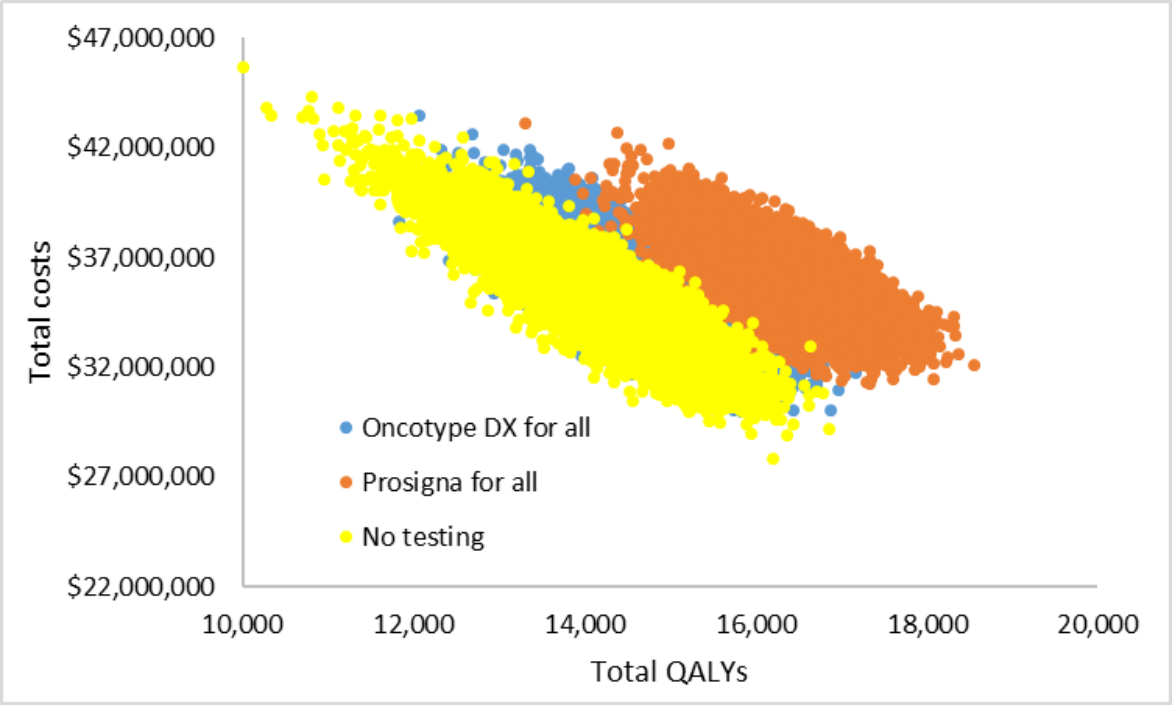
It is notable that the expected cost of the Prosigna strategy is greater than either the "No testing" or Oncotype DX strategy. However, Prosigna has much better patient outcomes in terms of QALYs gained and has reduced distant recurrence and mortality compared with either "No testing" or Oncotype DX. The incremental cost-effectiveness ratio (ICER) for Prosigna is $339 per QALY compared with "No testing". Oncotype DX is extendedly dominated compared with Prosigna. This means that the cost per QALY gained for Prosigna compared with "No testing" is lower than the cost per QALY gained for Oncotype DX compared with "No testing". When considering parameter uncertainty, it is notable that Prosigna is more than 99% likely to be cost-effective for WTP values for the QALY of $20,000 and above.

TABLE 24: Cost-effectiveness results for 1,000 node-positive patients

Test	Total lifetime costs	QALYs	ICER	Probability of cost-effectiveness		
				WTP $20,000/QALY	WTP $50,000/QALY	WTP $100,000/QALY
No testing	$34.9 million	14,263		0.0%	0.0%	0.0%
Oncotype DX	$35.5 million	14,715	Extendedly dominated	0.6%	0.4%	0.4%
Prosigna	$35.7 million	16,446	$339	99.4%	99.6%	99.6%

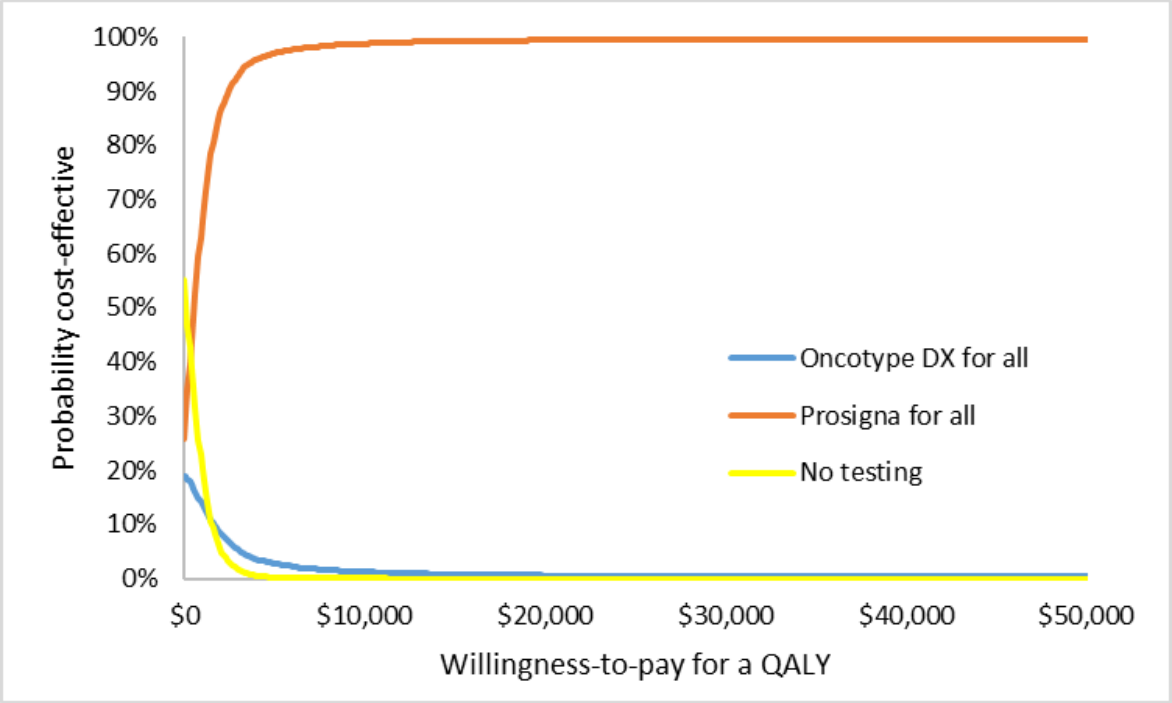
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness-to-pay

FIGURE 5: Scatterplot of 15,000 Monte Carlo iterations for 1,000 node-positive patients



QALY: quality-adjusted life year

FIGURE 6: Cost-effectiveness acceptability curve for 15,000 Monte Carlo iterations for node-positive patients



QALY: quality-adjusted life year

3.2.3. Sensitivity analyses

Node-negative patients by menopausal status

The impact of using risk category stratification by test result for node-negative pre- and postmenopausal patients can be seen in Tables 25 and 26.

For premenopausal patients, the Prosigna strategy is cheaper and more effective than the Oncotype DX and "No testing" strategies, and is 97% likely to be cost-effective across WTP values for the QALY of $20,000 and above. For postmenopausal patients, Prosigna is the most effective strategy, and is more expensive than Oncotype DX and less expensive than "No testing"; it is at least 63% likely to be cost-effective for WTP values for the QALY of $20,000 and above.

TABLE 25: Cost-effectiveness results for 1,000 node-negative premenopausal patients

Test	Total lifetime costs	QALYs	ICER	Probability of cost-effectiveness		
				WTP $20,000/QALY	WTP $50,000/QALY	WTP $100,000/QALY
Prosigna	$27.3 million	17,229		97.1%	97.1%	97.1%
Oncotype DX	$28.0 million	16,925	Dominated	2.9%	2.9%	2.9%
No testing	$28.5 million	16,567	Dominated	0%	0%	0%

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness-to-pay

TABLE 26: Cost-effectiveness results for 1,000 node-negative postmenopausal patients

Test	Total lifetime costs	QALYs	ICER	Probability of cost-effectiveness		
				WTP $20,000/QALY	WTP $50,000/QALY	WTP $100,000/QALY
Oncotype DX	$26.4 million	17,139		36.8%	32.9%	31.4%
Prosigna	$27.1 million	17,253	$5,325	63.1%	66.9%	68.5%
No testing	$28.0 million	16,742	Dominated	0.1%	0.2%	0.2%

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness-to-pay

Price of Oncotype DX

Even if the price of Oncotype DX is reduced to $500, the ICER is still approximately $20,394 per QALY for Prosigna compared to Oncotype DX, which would make Prosigna a cost-effective option compared to Oncotype DX. When considering parameter uncertainty, at this price, Prosigna becomes increasingly cost-effective at greater WTP values for the QALY (see Table 27).

TABLE 27: Cost-effectiveness for 1,000 node-negative patients, with variation in the price of Oncotype DX

Test	Total lifetime costs	QALYs	ICER	Probability of cost-effectiveness		
				WTP $20,000/QALY	WTP $50,000/QALY	WTP $100,000/QALY
Price of Oncotype DX = $500						
Oncotype DX	$23.7 million	17,066		51.6%	31.3%	25.1%
Prosigna	$27.2 million	17,237	$20,394	48.4%	68.6%	74.8%
No testing	$28.2 million	16,682		0.0%	0.1%	0.1%
Price of Oncotype DX = $1,000						
Oncotype DX	$24.2 million	17,066		46.9%	29.6%	24.4%
Prosigna	$27.2 million	17,237	$17,461	53.0%	70.4%	75.5%
No testing	$28.1 million	16,682		0.0%	0.1%	0.1%
Price of Oncotype DX = $3,742 (baseline)						
Oncotype DX	$27.0 million	17,066		23.8%	21.1%	20.0%
Prosigna	$27.2 million	17,237	$1377.4	76.1%	78.9%	79.9%
No testing	$28.2 million	16,682	Dominated	0.1%	0.1%	0.1%

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness-to-pay

Alternative risk category stratification

Using the alternative risk category stratification by test result informed by Sestak et al.,[46] the Prosigna strategy continues to be the more cost-effective option, and would be at least 76% likely to be cost-effective at WTP values for the QALY of $20,000 and above (see Table 28).

TABLE 28: Cost-effectiveness results for 1,000 node-negative postmenopausal patients, using risk category parameters informed by Sestak et al.

Test	Total lifetime costs	QALYs	ICER	Probability of cost-effectiveness		
				WTP $20,000/QALY	WTP $50,000/QALY	WTP $100,000/QALY
Oncotype DX	$27.0 million	17,066		23.8%	21.1%	20.0%
Prosigna	$27.2 million	17,237	$1,377	76.1%	78.9%	79.9%
No testing	$28.2 million	16,682	Dominated	0.1%	0.1%	0.1%

Sestak et al. (2018)[46]

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness-to-pay

Discount rate

As shown in Table 29, the impact of varying the discount rate across plausible values does not change the conclusions from the base case analysis. Prosigna continues to be the most effective strategy in terms of QALYs gained, and is at least 73.3% likely to be cost-effective for WTP values for the QALY of $20,000 and above across all the discount rates considered here.

TABLE 29: Cost-effectiveness results for 1,000 node-negative patients, with variation in discount rates

Test	Total lifetime costs	QALYs	ICER	Probability of cost-effectiveness		
				WTP $20,000/QALY	WTP $50,000/QALY	WTP $100,000/QALY
Discount rate = 0.0%						
Oncotype DX	$31.1 million	21,465		21.7%	19.6%	19.0%
Prosigna	$31.2 million	21,713	$373.67	78.3%	80.3%	81.0%
No testing	$32.6 million	20,933	Dominated	0.1%	0.1%	0.1%
Discount rate = 1.5%						
Oncotype DX	$27.0 million	17,066		23.8%	21.1%	20.0%
Prosigna	$27.2 million	17,237	$1,377.4	76.1%	78.9%	79.9%
No testing	$28.2 million	16,682	Dominated	0.1%	0.1%	0.1%
Discount rate = 3.0%						
Oncotype DX	$24.0 million	13,931		26.7%	22.9%	21.4%
Prosigna	$24.3 million	14,050	$2,806.7	73.3%	77.1%	78.5%
No testing	$24.9 million	13,644	Dominated	0.1%	0.1%	0.0%

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness-to-pay

SECTION 4: Discussion and Conclusions

4.1. Key Findings from Clinical Review

For prognostic and predictive data, the level of evidence was graded as level 1A (highest level), 1B, 2, or 3 (lowest level), based on the number of category A (strongest design; that is, an RCT), B, or C (weak design; that is, an observational study) studies contributing data.

Prognostic ability

Level 1B to level 3 evidence from nine category B and C studies supported the prognostic ability of both Oncotype DX and Prosigna, with lower-risk patients generally, but not always, experiencing better 5- to 15-year outcomes than higher-risk patients. The prognostic ability of both tests was observed in various patient groups, including node-negative and node-positive (N1) patients, pre- and postmenopausal patients, and patients receiving endocrine or chemoendocrine therapy, and results were consistent regardless of the risk cut-off used in the study.

There are important limitations and gaps in the evidence base. First, for both Oncotype DX and Prosigna, results were most pronounced when comparing low- and high-risk patients. Differences were not always reported or observed when comparing low- and intermediate-risk patients, or intermediate- and high-risk patients, so uncertainty remains about the prognostic ability of both tests for intermediate-risk patients. Second, for Prosigna, data were lacking for premenopausal women. For Oncotype DX, most of the studies conducted in premenopausal patients included treatment with chemotherapy, and the percentage of patients receiving chemotherapy increased across the risk categories (that is, more high-risk compared with low-risk patients received chemotherapy). Because chemotherapy treatment directly affects rates of long-term distant recurrence and mortality, the prognostic ability of Oncotype DX is confounded with systematic differences in treatment decisions across risk categories. Lastly, for both Oncotype DX and Prosigna, there was less and lower-quality evidence available for node-positive (N1) patients. Further, only three studies reported on patients with micrometastatic disease. These three studies combined micrometastatic disease with node-positive patients and did not report outcome data separately for the patients with micrometastatic disease. No ongoing clinical trials were identified to address the above-described gaps in evidence. Therefore, no firm conclusions can be drawn based on the limited evidence for the prognostic ability of Oncotype DX and Prosigna for intermediate-risk patients, premenopausal patients, and patients with micrometastatic disease.

Level 2 evidence from one category B study[46] indicated that Prosigna was more prognostic than Oncotype DX in node-negative, postmenopausal patients receiving endocrine therapy only. This retrospective analysis of the TransATAC trial may be prone to selection bias: tissue samples in the TransATAC trial were originally assessed using Oncotype DX, and retrospective Prosigna testing was dependent on the presence of enough remaining tissue to run the assay. This means that patients with smaller tumours, who may have differed systematically from those with larger tumours, were likely under-represented. There were no other comparative data available for any other patient groups, and no ongoing clinical trials were identified to address these gaps. Though out of the scope of the current review, the prognostic ability of both genetic tests has also been compared with the prognostic ability of using clinical features (for example, patient and tumour characteristics) with or without immunohistochemical markers (for example, ER, PR, HER2, and Ki67 markers). Evidence suggests that for node-negative and node-positive (N1) postmenopausal patients receiving endocrine therapy only, Prosigna is more prognostic[43, 46, 47] and Oncotype DX is often (but not always) more

prognostic[46, 47] than using clinical features with or without immunohistochemical markers. Further, when both genetic tests are given to the same group of patients, using both tests together contributes more prognostic information than using Oncotype DX alone, but not Prosigna alone.[47] This indirect evidence helps lend further support to the conclusion that Prosigna may be more prognostic than Oncotype DX in post-menopausal patients.

Predictive ability

Sparano et al.'s clinical trial, TAILORx,[13] contributed level 1A evidence indicating that Oncotype DX is predictive of a lack of adjuvant chemotherapy benefit at nine years in most node-negative patients at intermediate risk of distant recurrence. This finding was supported by additional level 1B evidence from three category B and C studies that used variable risk cut-offs and assessed outcomes at time points ranging from 5 to 10 years. An intermediate-risk RS cut-off of between 11 to 25 was used in TAILORx, which differed from the standard cut-off of between 18 to 30 recommended by Genomic Health. Changing the risk cut-off helped mitigate the potential for undertreatment by reducing the number of low-risk patients treated with endocrine therapy only and increasing the number of intermediate-risk patients treated with chemoendocrine therapy.[88]

Exploratory, post-hoc subgroup analyses from TAILORx showed a benefit of chemotherapy in node-negative patients aged 50 years or younger with intermediate-risk scores between 21 and 25. These analyses were not pre-planned, and no benefit of chemotherapy was observed in a subgroup of premenopausal patients. The amount of overlap between the patients aged 50 years or less and the premenopausal patients is unknown, as is the menopausal status of the premenopausal patients at nine-year follow up.

While the publication of the TAILORx results significantly increased clinician and patient confidence in using Oncotype DX test results to guide treatment decisions, it is important to note that the results apply only to node-negative patients receiving Oncotype DX testing. No conclusions can be drawn regarding the predictive ability of Oncotype DX in node-positive (N1) patients, due to conflicting level 3 evidence from two category C studies. Similarly, no conclusions can be drawn regarding the predictive ability of Prosigna in node-negative or node-positive (N1) patients, due to a lack of evidence. The results of two ongoing clinical trials (RxPONDER and OPTIMA) are expected to contribute level 1A evidence (in 2022 and 2023, respectively) regarding the predictive ability of the individual tests in patient populations for which there are currently gaps in evidence.

No conclusions can be drawn regarding the comparative predictive ability of both genetic tests due to a lack of comparative data. A well-designed prospective trial that gives both tests to the same patients, or that randomizes tests to different patients, could help resolve existing uncertainties. However, this type of comparative trial may be difficult to conduct as Prosigna is used in a narrower patient population than Oncotype DX. To the best of our knowledge, no ongoing comparative trials are currently underway. Thus, the comparative predictive ability of both genetic tests will likely continue to remain unknown.

Clinician and patient treatment decisions

Data from prospective observational studies examining the impact of genetic testing on clinician and patient treatment choices were generally consistent for both node-negative and node-positive (N1) patients. After receiving test results, clinician treatment recommendations changed for about one-third of patients tested with Oncotype DX and one-fifth of patients tested with Prosigna. Oncotype DX led to a net decrease in the use of adjuvant chemotherapy in a greater number of

lower-risk patients. Prosigna testing led to a net increase in the use of adjuvant chemotherapy in a greater number of higher-risk patients. Based on the above findings, Oncotype DX testing tends to classify more patients into low-risk groups who are likely to avoid chemotherapy. This may increase the likelihood of false negatives, where a clinician fails to offer chemotherapy when it is likely to have been beneficial for patients. On the other hand, Prosigna testing tends to classify more patients into high-risk groups who are likely to receive chemotherapy. This may increase the likelihood of false positives, where a clinician provides chemotherapy when it is unlikely to have been beneficial for patients. Limited evidence suggests that both genetic tests help support clinician and patient decision-making.

Risk category cut-offs and stratifications

Most of the above-described studies used standard risk cut-offs to define intermediate-risk patients, for both genetic tests (that is, an RS between 18 and 30 or 31 for Oncotype DX, and an ROR between 41 and 60 for Prosigna). However, two studies (including TAILORx) used a lower RS cut-off (between 11 or 12 and 25) for Oncotype DX, and three studies used ROR cut-offs that varied by node status for Prosigna. Overall, the risk stratifications differed across the tests for both node-negative and node-positive patients, with more patients classified as low risk by Oncotype DX and as high risk by Prosigna. For Oncotype DX, more node-negative and node-positive patients were classified as low risk when using the standard cut-offs compared to the TAILORx cut-offs.

Health-related quality of life

Primary studies with variable study designs found that chemotherapy treatment, as well as different chemotherapy regimens (for example, different types and dosing of chemotherapy), had variable effects on quality of life, as measured using two generic instruments (EQ-5D, SF-36). It is generally accepted, based on the larger body of literature using cancer- or breast-cancer-specific instruments, that adjuvant chemotherapy in breast cancer patients leads to short-term decreases in quality of life.[89-92]

Limitations of the clinical review

Although this clinical review followed a systematic and transparent process, there are some limitations due to time and resource constraints. First, only English-language studies were eligible for inclusion due to lack of translation resources, though many international studies were published in English-language journals and few studies were excluded on the basis of language. Second, a single reviewer was used to screen titles and abstracts, select studies for inclusion, and extract data, though a second reviewer was available to help resolve some uncertainties. Third, study authors were not contacted to request data or analyses not reported in the study publication, meaning that our analysis was hampered by a lack of uniform reporting of outcome data across the studies. Fourth, no formal assessment of the quality of the included studies was conducted, and limitations in study designs likely introduced bias as almost all were observational studies with retrospective designs. Lastly, approximately two-thirds of the studies examining the genetic tests received funding from, and were conducted by authors who were affiliated with, the test manufacturers.

4.2. Key Findings from Economic Evaluation

Prosigna testing of node-negative patients is more than 76% likely to be cost-effective compared with Oncotype DX testing and "No testing" for WTP values for the QALY of approximately $20,000 and above. For node-negative patients, it was found that Prosigna is likely to be more costly

on average per patient (approximately $90; see Table 29, 0% discount rate) over a lifetime compared with Oncotype DX but also more effective in terms of QALYs gained. "No testing" is likely to be more costly than either test, and less effective. The extra cost of Prosigna is driven by the additional patients given chemotherapy based on the test results compared with Oncotype DX, although these costs are to some extent outset by the reduced costs due to testing and lower costs associated with distant recurrence. The greater effectiveness (QALYs gained) of Prosigna compared with Oncotype DX is due to additional cases of distant recurrence being averted and, consequently, lower distant recurrence-related mortality. Interestingly, although Prosigna leads to an increased number of patients being given chemotherapy and a resulting temporary worse health state, this is more than offset by the health gains from the lower risk of future distant recurrence.

For node-positive patients, allowing for parameter uncertainty, Prosigna is more than 99% likely to be cost-effective compared with Oncotype DX and "No testing" for WTP values of the QALY of $12,000 and above (see Figure 6). Again, Prosigna is likely to be more costly and more effective than either Oncotype DX and "No Testing", with additional chemotherapy being the major driver of the extra costs. As with the node-negative patients, this is offset by the reduced testing costs and costs associated with distant recurrence.

A variety of sensitivity analyses were conducted (including menopausal status, price of Oncotype DX, risk category stratification, and discount rate), and in all cases the conclusions from the model remain robust. That is, Prosigna is more effective in terms of QALYs gained than Oncotype DX, and, while it is more expensive in terms of the cost incurred per patient over a lifetime, Prosigna is cost-effective compared with Oncotype DX. Limitations in the availability of data meant that it was not possible to examine the impact of other factors such as node status on the model results.

The clinical review revealed a major limitation in the evidence base for the economic model, in that the key parameters driving the model results were not well informed. For the stratification of patients by risk category for Oncotype DX and Prosigna, no studies were identified that applied both tests to the same patient population using the RS and ROR cut-offs used in Alberta. The clinical trial, TAILORx,[13] has been influential in the practice of using Oncotype DX in Alberta, and, as this study provides risk categories with Alberta cut-offs, it was used to inform these parameter values for Oncotype DX. However, TAILORx did not consider Prosigna, and it is not known how Prosigna would have risk categorized the patient group in the trial. Therefore, it was necessary to identify another source to inform the risk categories for Prosigna. Concordance data from Dowsett et al.[47] was then used to estimate the Prosigna risk categories, based on these Oncotype DX risk categories. However, this concordance data was obtained from postmenopausal patients using RS and ROR cut-offs quite different from those used in Alberta (RS low: <10%; RS intermediate: 10-20%; RS high: >20%; and ROR low: <10%; ROR intermediate: 10%-20%; ROR high: >20%). Despite these shortcomings, the conclusions from the model were found to be robust to plausible variations in these parameters.

In the case of chemotherapy uptake by risk category, the randomization by chemotherapy treatment used in TAILORx made it an inappropriate source to inform chemotherapy uptake for Oncotype DX, and there was no information available for chemotherapy uptake using appropriate cut-offs or patient groups for Prosigna. This parameter was informed by expert opinion from the Expert Advisory Group, based on the experience of having made chemotherapy decisions in Alberta for 1,000 to 1,500 patients since 2014. It was also assumed that chemotherapy uptake by risk

category would be same for both Oncotype DX and Prosigna, and, while this may not be strictly true in practice given that some clinicians may have their own views about the utility of the test results, this was felt to be the best approach to assess the cost-effectiveness of each test.

For the future risk of distant recurrence in patients without chemotherapy by risk category stratifications, the ideal study would examine the use of both tests in the same patient group for risk of distant recurrence, as well as the risk categorization for both tests. No such study was found, and thus it was necessary to inform these parameter values using studies that examined different patient populations. Sestak et al.[46] provides this information for both node-negative and node-positive patients, although, again, the cut-offs used to define the risk categories for each test are not the same as those used in Alberta (RS less than 18, between 18 and 31, and over 31; and ROR less than 27, between 27 and 68, and over 68). The potential shortcoming of using this approach is that the risk of distant recurrence estimates among patients without chemotherapy in Sestak et al. may not have been the same as the patient group in TAILORx. However, risk of distant recurrence for patients without chemotherapy was only reported in the intermediate-risk group in TAILORx, meaning that an alternative study had to be used. While such shortcomings in the parameterization may have impacted the results obtained from the model, the conclusions from the model were found to be robust to reasonable changes in the model parameters.

This economic evaluation takes forward the University of Alberta health economic assessment published in October 2016 examining the clinical effectiveness and cost-effectiveness of Oncotype DX and Prosigna.[21] In that assessment, risk category classification for Prosigna and Oncotype DX was based on 40 patients, and then chemotherapy uptake was informed by the chemotherapy status of 39 of these 40 patients. Some of the parameters used in this original analysis have been used here, but, notably, risk category stratification has been updated with its impact being subject to extensive sensitivity analysis. While both analyses found that Prosigna is likely to be cost-effectiveness compared with Oncotype DX, the 2016 University of Alberta analysis found that Prosigna leads to better health outcomes at lower cost. This is in contrast to the findings here, which suggest that the better health outcomes associated with Prosigna will come at increased cost. The explanations for this may be the prices of Oncotype DX and Prosigna now compared with those used in the 2016 assessment, with Oncotype DX now being slightly cheaper ($3,742 versus $3,942 in 2015) and Prosigna being slightly more expensive ($2,870 versus $2,500 in 2015), and also the lower discount rate used here (1.5%) compared with that in 2016 (5%).

4.3. Implications for Alberta

Like many health technology assessments, a main challenge in this report is finding reliable evidence that both answers the main research questions and is reasonably applicable to the Alberta context. Though few of the included studies were conducted in Canada, many of the studies were conducted in countries with large developed economies, similar levels of resources to devote to health care, comparable patient populations, and comparable use of the genetic test results in making treatment decisions.[77] Quality improvement data from Alberta on clinician treatment choices were generally consistent with the findings in the published literature. In addition, expert opinion from Alberta medical oncologists and pathologists helped inform key clinical and cost parameters of the economic model.

Oncotype DX and Prosigna genetic tests are intended to supplement clinical judgement in cases where clinical, pathological, and/or patient-related factors lead to uncertainty in the decision-making process. The clinical review found that, despite remaining uncertainties, evidence generally supports

the additional prognostic ability of both genetic tests and the predictive ability of Oncotype DX. Importantly, both tests tend to support different treatment decisions for a small proportion of patients. Oncotype DX testing tends to classify more patients into low-risk groups who are likely to avoid chemotherapy, while Prosigna testing tends to classify more patients into high-risk groups who are likely to receive chemotherapy. This may lead to potentially undertreating some patients based on Oncotype DX test results or overtreating some patients based on Prosigna test results.

The economic evaluation found that Prosigna was likely to be more cost-effective than Oncotype DX across a range of scenarios. In Alberta, using Oncotype DX to avoid potentially unnecessary adjuvant chemotherapy would result in greater costs of testing, reduced costs of chemotherapy, and higher short-term quality of life, but may also be associated with an increased risk of future long-term distant recurrence with its associated morbidity, mortality, and increased treatment costs. On the other hand, using Prosigna to offer potentially unnecessary adjuvant chemotherapy would result in lower costs of genetic testing, greater costs of chemotherapy, lower short-term quality of life, and a decreased risk of long-term distant recurrence and its associated treatment costs. The budget impact of using Prosigna in Alberta would be approximately $1,000 extra per patient in the first year after testing due to the extra costs associated with testing and chemotherapy. Given that approximately 300 patients require testing in Alberta each year (personal communication, Expert Advisory Group, March 2019), Prosigna testing of this population would require an initial extra $300,000. There may also be additional impacts on individual patients' HRQoL due to chemotherapy treatment. However, these shorter-term impacts may be offset by long-term future cost savings and QALYs gained as a result of averting cases of distant recurrence.

Relevant regulatory and operational factors should also be considered when determining the optimal use of the tests in Alberta. First, Oncotype DX does not currently have Health Canada approval. This has generated some controversy in the scientific community, though many laboratory-developed tests that do not have regulatory approval are commonly used in practice. In contrast, Prosigna has Health Canada approval for postmenopausal patients only, and the clinical evidence base supporting the use of Prosigna is restricted to postmenopausal patients. Second, Oncotype DX testing requires tissue samples to be shipped to a state-licensed central laboratory in California, meaning that Alberta Public Laboratories has no control, oversight, or input into the processing of the test results. Prosigna testing, on the other hand, is conducted locally by Alberta Public Laboratories using the University of Alberta's nCounter Analysis System. This multipurpose technology requires servicing on a yearly basis but can also be used to run other genetic tests. Third, Oncotype DX guarantees a two-week delivery of results from the date of the tissue sample's arrival at the testing facility. Because Prosigna tests are batched and must still be shipped within the province, Prosigna results are often delivered in slightly shorter or similar length of time. Lastly, anecdotal evidence suggests that medical oncologists may find the Oncotype DX results compared to the Prosigna results easier to read and interpret (personal communication, Expert Advisory Group, March 2019).

Due to an absence of clinical data comparing both genetic tests, Alberta may benefit from collecting prospective and comparative administrative data for both tests in patients with node-negative disease, and may also consider developing a risk prediction model that can assist with treatment decisions in cases of clinical and pathological discordance. Because the clinical evidence suggests a potential, but uncertain, benefit of testing patients with node-positive (N1) disease, Alberta may consider collecting prospective data in this population on a conditional basis and for a predetermined period of time. Though few studies explicitly reported on patients with

micrometastatic disease, it seems reasonable to offer genetic testing to this subset of patients as they are often formally classified as node-positive but treated as node-negative when making clinical treatment decisions.

4.4. Conclusions

Overall, results from our clinical review and economic evaluation generally support the additional prognostic ability of both Oncotype DX and Prosigna, the predictive ability of Oncotype DX, and the likely cost-effectiveness of Prosigna compared with Oncotype DX across a range of scenarios. While the publication of the TAILORx results significantly increased clinician and patient confidence in using Oncotype DX test results to guide treatment decisions, there are important evidence gaps regarding the predictive ability of the individual tests in certain patient populations and the comparative predictive ability of the two genetic tests. Decision-makers must weigh the availability of evidence for the predictive ability of Oncotype DX in certain populations with the increased cost-effectiveness of Prosigna when determining how the tests can be optimally used in Alberta. A decision regarding which test to use for which patient subgroups requires careful consideration of the remaining uncertainties in the clinical evidence base, the consequences of potentially undertreating patients based on Oncotype DX test results or overtreating patients based on Prosigna test results, and the potential agreements that may be reached between test manufacturers and laboratory services.

Appendix A: Expert Advisory Group

Expert Advisory Group Members

- Dr. Gilbert Bigras – Medical Lead, Edmonton Zone IHC Laboratory, Cross Cancer Institute
- Dr. Judith Hugh – Divisional Director, Anatomical Pathology, University of Alberta Hospital
- Dr. Karen King – Lead, Northern Alberta Breast Tumour Team, Cross Cancer Institute
- Dr. Sasha Lupichuk – Lead, Alberta Breast Tumour Team, Tom Baker Cancer Centre
- Dr. Marc Webster – Lead, Southern Alberta Breast Tumour Team, Tom Baker Cancer Centre

Alberta Health Representatives

- Mr. Scott Fulmer – Manager, Health Evidence and Policy
- Ms. Kate Wagontall – Policy Advisor, Research and Innovation Branch

Appendix B: Clinical Practice Guidelines

TABLE B.1: Summary of clinical practice guidelines for Oncotype DX and Prosigna testing

Organization, year	Scope of CPG	Intended user of CPG	Target population	CPG development methods	Conflicts of interest
Canada					
Alberta Health Services, 2018 (version 5)[23] (provincial guideline)	Adjuvant chemotherapy for early-stage BC	Presumed clinicians	Patients with N0 or N1, early-stage BC	Developed by consensus of the Alberta Provincial Breast Tumour Team based on a review of current best evidence	Some members of Alberta Provincial Breast Tumour Team are involved in research funded by industry; no details were provided
Alberta Health Services, 2017 (version 1)[22] (provincial guideline)	Process for ordering BC molecular tests	Oncologist personnel of AHS, Lamont Health Centre and Covenant Health	Patients with BC	NR	NR
British Columbia Cancer Agency, 2017[24] (provincial guideline)	Chemotherapy for early-stage BC	Presumed clinicians	Patients with HR+, N0, early BC	NR	NR
Cancer Care Ontario, 2016[25] (provincial guideline)	Utility of various multigene profiling assays in early-stage BC	Clinicians, policy-makers, Ontario Ministry of Health and Long-Term Care	Patients with invasive early-stage BC	Involved a systematic review, review and interpretation of the evidence by a working group, review by an internal methodology expert, and approval by sponsoring committee	All members of the working group disclosed potential conflicts of interest; 2 members received funding from Genomic Health
Princess Margaret Cancer Centre, 2015[93] (local guideline)	BC prevention, screening, diagnosis, pathology, management, supportive care and follow up	Presumed clinicians and medical staff at Princess Margaret Cancer Centre	Patients with ER+ and/or PR+, HER2−, N0 or N1, early-stage (I–II) BC	NR	NR

Organization, year	Scope of CPG	Intended user of CPG	Target population	CPG development methods	Conflicts of interest
Institut national d'excellence en santé et en services sociaux, 2016 and 2018[26-28] (provincial guideline)	Use of Oncotype DX, Prosigna, and EndoPredict for early invasive BC	Presumed clinicians, policy-makers	Patients with invasive early BC	Guideline development involved a review of the literature and evaluation from an expert advisory committee consisting of oncologists, epidemiologists, and a pathologist.	All members of the advisory committee declared any potential conflicts of interest; several members received funding from Genomic Health (4 members) or EndoPredict (1 member)
United States					
American Society of Clinical Oncology, 2017[29]	Use of biomarkers to guide adjuvant chemotherapy decision-making	Oncologists, clinician assistants, oncology nurses, pathologists, general practitioners, patients	Patients with ER+ and/or PR+, HER2−, invasive early-stage BC	An expert panel met to update previous guidelines based on newly published, potentially practice-changing evidence identified in routine literature searches	All panel members disclosed any potential conflicts; the majority of members did not disclose relationships that were deemed to be a conflict of interest for this subject matter, according to ASCO policy
National Comprehensive Cancer Network, 2019[30]	Workup, treatment, and follow up for non-invasive and invasive BC	Clinicians	Patients with non-invasive and invasive BC	Guidelines were based on the highest level available evidence and represent uniform consensus from an expert panel that the recommendations are appropriate	All panel members disclosed any potential conflicts of interest; 5 members disclosed relationships with Genomic Health
United Kingdom					
National Institute for Health and Care Excellence, 2018[31]	Tumour profiling tests to guide decision-making of adjuvant chemotherapy	Healthcare professionals, providers, commissioners	Patients with early-stage BC	An independent diagnostic advisory committee carefully considered evidence from several sources, including manufacturer data sets, to inform the development of consensus recommendations	All committee members disclosed any potential conflicts of interest; no member disclosed relationships with Genomic Health or NanoString Technologies

ASCO: American Society of Clinical Oncology; BC: breast cancer; CPG: clinical practice guideline; ER+ estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; N0: node-negative; N1: node-positive (1–3 nodes); NR: not reported; PR+: progesterone receptor positive

TABLE B.2: Summary of relevant recommendations from clinical practice guidelines

Organization, year	Recommendations related to Oncotype DX and Prosigna genetic testing
Canada	
Alberta Health Services, 2018 (version 5)[23] (provincial guideline)	To be eligible for Prosigna or Oncotype DX testing to inform chemotherapy decision-making, patients must: (a) be medically fit to receive adjuvant CT; (b) have resected, early-stage N0 (including N0i+) or N1mi disease; AND (c) have grade 2 or 3 invasive BC. Patients are not eligible for genomic testing if they: (a) are medically unfit or unwilling to consider receiving adjuvant CT; (b) have node-positive disease; or (c) have metastatic, HER2+, or grade 1 invasive BC. However, special considerations may apply and are subject to review by a multidisciplinary BC tumour board. (Table 2, Page 4)
Alberta Health Services, 2017 (version 1)[22] (provincial guideline)	Effective 2 October 2017 to October 2018, medical oncologists in Alberta can request Oncotype DX testing, but each request requires written approval from the *Oncotype Approval Committee*, which must be included with the requisition submitted to the laboratory. Ordering Prosigna testing does not require approval. Duplicate Oncotype DX and Prosigna testing is not permitted. *Note:* As of March 2019, committee approval of every Oncotype DX test ordered continues to be a requirement until further notice from the Laboratory Formulary Committee. (Personal communication, Expert Advisory Group, March 2019)
British Columbia Cancer Agency, 2017[24] (provincial guideline)	Effective 1 July 2017, Prosigna is available as a tool for decision-making regarding need of adjuvant CT. Patients can only be funded for either Prosigna or Oncotype DX. Patient eligibility criteria for both tests are as follows: (a) less than 80 years of age AND fit to receive CT; (b) ER+ and/or PR+ AND HER2−; (c) N0 or N0i+ (i. grade 1–2 AND less than 40 years of age; or ii. grade 2 AND pT1b or larger; or iii. grade 3) OR N1mi (0.3–2 mm micrometastases in one node only) of any grade. Approval from Compassionate Access Program is required for Prosigna testing. (Pages 4–5)
Cancer Care Ontario, 2016[25] (provincial guideline)	*Recommendation 1.* Clinicians may use multigene profile assay testing for patients with ER+, HER2− invasive BC who are potential candidates for CT (evidence-based; quality of evidence: level IB; strength of recommendation: moderate). *Recommendation 2.* In patients with N0, ER+, HER2− BC, clinicians may withhold CT based on a low-risk Oncotype DX, Prosigna, or EndoPredict score (evidence-based; quality of evidence: level IB; strength of recommendation: moderate). *Recommendation 3.* In patients with N0, ER+, HER2− BC, clinicians may offer CT based on a high-risk Oncotype DX score. Within this subpopulation, a high-risk Oncotype DX score has been associated with poor prognosis without CT and is predictive of benefit from CT (evidence-based; quality of evidence: level IB–II; strength of recommendation: weak). *Recommendation 4.* In certain patients with ER+, HER2−, N1 BC, clinicians may withhold CT on the basis of a low-risk Oncotype DX or Prosigna score when additional clinical, pathological, or patient-related variables support this decision (consensus-based; quality of evidence: level II; strength of recommendation: weak). *Recommendation 5.* Evidence is insufficient to recommend using multigene profiling assays for decision-making for late risk of recurrence in patients with ER+ BC. A high-risk Prosigna or EndoPredict score is associated risk of late recurrence; however, there is no evidence regarding whether the tests predict benefit of extended endocrine therapy after 5 years (consensus-based; quality of evidence: lack of evidence; strength of recommendation: weak). (Pages 1–4)
Princess Margaret Cancer Centre, 2015[93] (local guideline)	In patients with ER+ and/or PR+, N0, intermediate-risk BC, Oncotype DX may be considered to identify those who may not benefit from CT in addition to endocrine therapy (low RS).

Organization, year	Recommendations related to Oncotype DX and Prosigna genetic testing
Institut national d'excellence en santé et en services sociaux, 2016 and 2018[26-28] (provincial guideline)	INESSS recommends Oncotype DX for patients with ER+, HER2-, N0 or N1mi early-stage BC in situations when decision-making is difficult. Clinicians should consider the appropriateness and feasibility of chemotherapy and consult with patients prior to ordering the test. The results of the Oncotype DX test should be interpreted in conjunction with standard clinicopathological parameters and clinical judgement. The ordering and approval process of Oncotype DX should be closely monitored due to the high cost of Oncotype DX testing and likely limited added value in some circumstances. INESSS does not consider any other genomic test to be equivalent to Oncotype DX, and recommends that Prosigna and EndoPredict not be included in the *Répertoire québécois et système de mesure des procedures de biologie médicale.*
United States	
American Society of Clinical Oncology, 2017[29]	*Recommendation 1.1.* For patients with ER+/PR+, HER2−, N0 BC, clinicians may use Oncotype DX to guide decision-making on adjuvant CT (evidence-based; quality of evidence: high; strength of recommendation: strong). *Recommendation 1.2*. For patients with ER+/PR+, HER2−, node-positive BC, clinicians should not use Oncotype DX to guide decision-making on adjuvant CT (evidence-based; quality of evidence: intermediate; strength of recommendation: moderate). *Recommendation 1.3.* For patients with HER2+ BC or TN BC, clinicians should not use Oncotype DX to guide decision-making on adjuvant chemotherapy (informal consensus; quality of evidence: insufficient; strength of recommendation: strong). *Recommendation 1.10.* For patients with ER+/PR+, HER2−, N0 BC, clinicians may use Prosigna together with additional clinicopathologic variables to guide decision-making on adjuvant chemotherapy (evidence-based; quality of evidence: high; strength of recommendation: strong). *Recommendation 1.11.* For patients with ER+/PR+, HER2−, node-positive BC, clinicians should not use Prosigna to guide decision-making on adjuvant chemotherapy (evidence-based; quality of evidence: intermediate; strength of recommendation: moderate). *Recommendation 1.12.* For patients with HER2+ BC, clinicians should not use Prosigna to guide decision-making on adjuvant chemotherapy (informal consensus; quality of evidence: insufficient; strength of recommendation: strong). *Recommendation 1.13.* For patients with TN BC, clinicians should not use Prosigna to guide decision-making on adjuvant chemotherapy (informal consensus; quality of evidence: insufficient; strength of recommendation: strong). Recommendation 1.27. For patients with ER+/PR+, HER2−, N0 BC who have had endocrine therapy for 5 years without evidence of recurrence, clinicians should not use Oncotype DX, Prosigna, EndoPredict, Breast Cancer Index, or IHC4 assay to guide decision-making on extending endocrine therapy (evidence-based; quality of evidence: intermediate; strength of recommendation: moderate). (Table 1, Pages 2842–3)
National Comprehensive Cancer Network, 2019[30]	For patients with HR+, HER2−, N0 BC and a tumour >0.5 cm, Oncotype DX should be strongly considered. Oncotype DX is the NCCN-preferred multigene assay for N0 BC. Evidence supports its prognostic and predictive ability. For patients aged 50 years or younger who have RS 16–25, CT should be considered in addition to endocrine therapy. For patients with RS 26–30, clinical and pathological factors should be considered in decision-making regarding addition of CT to endocrine therapy. Combined treatment of CT and endocrine therapy is recommended for patients with RS ≥31. (Pages 15, 58) For patients with HR+, HER2−, N1mi and N1, Oncotype DX may be used for prognostic purposes. The results of the ongoing RxPONDER trial may inform the predictive ability of Oncotype DX in N1 patients, though a secondary analysis of another trial has shown Oncotype DX to be predictive of CT benefit for patients with 1–3 positive ipsilateral axillary lymph nodes. Patients with N1 and RS ≥31 should be considered for combination CT and endocrine therapy. (Pages 15, 58) For patients with HR+, HER2−, N0 and N1 BC, Prosigna may be considered in predicting risk of recurrence. However, the predictive ability of Prosigna has not been determined. (Pages 15, 58)

Organization, year	Recommendations related to Oncotype DX and Prosigna genetic testing
United Kingdom	
National Institute for Health and Care Excellence, 2018[31]	In patients with ER+, HER2−, N0 and N1mi early-stage BC, NICE recommends Oncotype DX, Prosigna, and EndoPredict as options for use in guiding decision-making on adjuvant CT, under the following conditions: (a) patients' risk of distant recurrence is assessed to be intermediate based on validated tool (e.g., Predict, Nottingham Prognostic index); (b) information from the test results would assist patients, together with their clinicians, in decision-making regarding adjuvant CT, considering patients' preferences; (c) manufacturers provide the tests to National Health Services at the previously agreed upon discounted rates; and (d) both clinicians and manufacturers make test data available to the National Cancer Registration and Analysis Service (described in the NICE data collection agreements). (Page 4)

BC: breast cancer; CT: chemotherapy; ER+ estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; HER2+: human epidermal growth factor receptor 2 positive; INESSS: Institut national d'excellence en santé et en services sociaux; N0: node-negative; N0i+: node-negative but presence of isolated tumour cells; N1: node-positive (1–3 nodes); N1mi: micrometastases in nodes; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence; PR+: progesterone receptor positive; ROR: risk of recurrence score (calculated using Prosigna); RS: recurrence score (calculated using Oncotype DX); TN: triple negative (negative for ER, PR, and excess HER2 protein)

Appendix C: Clinical Review – Methods

C.1. Rapid Review 1: Clinical Validity and Utility

Rapid review 1 examined the clinical validity and utility of Oncotype DX and Prosigna in early-stage (I–III), ER+ (and/or PR+), HER2−, node-negative or node-positive (N1) breast cancer. It included primary studies published from 2002 onward.

C.1.1. Literature search

Information specialists working on the 2016 CCO systematic review[25] and 2018 update (internal document)[32] conducted database searches of MEDLINE and Embase to identify full-text, English-language studies published from 2002 to 20 April 2018. An information specialist from Health Quality Ontario (MW) updated these searches on 28 November 2018 (as part of a collaboration agreement). We also searched reference lists of included studies and other relevant reports (including the 2018 CCO update) and consulted experts to help identify additional relevant studies. For the complete search strategies, see Appendix D, Table D.1.

An IHE information specialist (LT) searched the following trial registers to identify ongoing studies: ClinicalTrials.gov, Health Canada Clinical Trial Search, ISRCTN registry, and European Union Clinical Trials register. The searches were conducted on 12 February 2019 (ClinicalTrials.gov) and 8 March 2019 (all other registers). One reviewer (JS) screened the search results and summarized the ongoing studies relevant to rapid review 1. For the complete search strategy, see Appendix D, Table D.4.

C.1.2. Study selection

One reviewer (MP) screened the titles and abstracts of all citations retrieved by the searches and assessed the full text of each potentially relevant paper for inclusion. A second reviewer (JS) helped resolve uncertainties as needed.

Relevant primary studies were those reporting data from prospectively enrolled patients and prospectively collected tumour specimens or from retrospective analyses of tumour specimens from completed RCTs or prospective studies. We excluded retrospective cohort studies, case-control studies, and theoretical comparisons (for example, scenarios involving decision analytic models), as well as narrative reviews, case series or case reports, letters, editorials, protocols, conference abstracts, and studies not published in English.

Study eligibility was determined using the PICO criteria (Population, Intervention, Comparator, Outcome) outlined in section 2.1 (Table 3), with the following additional considerations:

- Studies were considered eligible for inclusion if at least 80% of the patient sample met the eligibility criteria; an appropriate subgroup analysis of eligible patients was provided; or the results for relevant patient groups could be separated from the aggregate data.
- The genetic test must have been used to help inform decision-making for adjuvant chemotherapy (post-surgical) but not neoadjuvant (pre-surgical) chemotherapy.
- Outcome data for node-negative or node-positive (N1) patients must have been presented separately or in an appropriate subgroup analysis.

C.1.3. Quality assessments

One reviewer (MP) assessed the study category of each included primary study, and the level of evidence supporting the prognostic and predictive ability of Oncotype DX and Prosigna, using the tumour marker utility grading system (see section 2.1, Table 4).[35] Major methodological issues of the evidence base were also identified and described.

C.1.4. Data extraction

One reviewer (MP) extracted data from each included primary study into predeveloped and piloted data extraction forms or tables. Data were extracted on study characteristics (including sources of funding and conflicts of interest), patient demographic and clinical characteristics, index tests, interventions and comparators, and outcomes. One reviewer (MYW) from Health Quality Ontario verified the outcome data and helped resolve discrepancies as needed (as part of a collaboration agreement).

The four pre-specified outcomes of interest were as follows:

- **Freedom from distant recurrence (primary outcome)**: Freedom from breast cancer recurrence at any distant site.
- **Freedom from distant or locoregional recurrence (secondary outcome)**: Freedom from breast cancer recurrence at any distant site, regional site, or local site.
- **Overall survival (secondary outcome)**: Freedom from death due to any cause.
- **Disease-free survival (secondary outcome)**: Freedom from breast cancer recurrence, second primary cancer, or death without evidence of recurrence.

Outcome data must have been collected beginning at the time point immediately after the start of adjuvant therapy (0 years) and reported at any long-term follow-up period (5 years or more). When multiple long-term time points were reported, endpoint data were extracted. Data on late recurrence or survival were excluded (for example, 5- to 10-year data, where events occurring from 0 to 5 years were censored). All outcome data were extracted as event rates (percentages) with standard errors or 95% confidence intervals. The data were extracted as *freedom from recurrence* (as opposed to *recurrence*) and *survival* (as opposed to *mortality*); when necessary, events and non-events were "flipped" using the formula: 100-x. Comparative studies that examined multiple genetic tests (for example, Oncotype DX, Prosigna, EndoPredict, and MammaPrint), were included if data for Oncotype DX and Prosigna could be extracted separately.

Outcome data were used to assess the prognostic and predictive ability of the genetic tests:

- *Prognostic ability* relates to a test's clinical validity (that is, the ability of a test to correctly identify patients who do and do not have a disease),[94] and refers to a test's ability to accurately predict the risk of an event and to accurately discriminate between patients with different event rates. Assessing prognostic ability involves comparing patients across risk categories (for example, low-risk compared with high-risk patients), irrespective of adjuvant therapy received.[12]
- *Predictive ability* relates to a test's clinical utility (that is, the benefits and harms associated with using a test),[95] and refers to a test's ability to accurately discriminate between patients who will have more or less benefit from chemotherapy, according to the test score and corresponding risk categories. Assessing predictive ability involves comparing patients within

the same risk category who receive different adjuvant therapies (for example, intermediate-risk patients who receive endocrine therapy only compared with chemoendocrine therapy).[12]

Prognostic and predictive data were extracted as unadjusted or adjusted hazard ratios with 95% confidence intervals. Hazard ratios compare the probability of an event (recurrence or death) in the intervention and the comparator groups at a specific point in time. They are *unadjusted* when they include only adjuvant therapy as a covariate; they are *adjusted* when they contain other covariates in addition to adjuvant therapy. All hazard ratios were presented such that the lower-risk patients were compared with the higher-risk patients (low versus high risk, low versus intermediate risk, intermediate versus high risk), and the endocrine therapy group was compared with the chemoendocrine therapy group; when necessary, the intervention and comparator groups were flipped using the formula: 1/x. Hazard ratios are interpreted as shown in Table C.1.[96]

TABLE C.1: Interpretation of hazard ratios

Hazard ratio	Interpretation	Example
=1	The event rate is **the same** in both the intervention and comparator groups.	HR=1.0: The risk of experiencing an event (recurrence or death) is the same in both groups.
<1	There are **less events** in the intervention group.	HR=0.5: Patients in the intervention group have a 50% lower risk of experiencing an event (recurrence or death) compared with patients in the comparator group.
>1	There are **more events** in the intervention group.	HR=2.0: Patients in the intervention group are twice as likely to experience an event (recurrence or death) compared with patients in the comparator group.

HR: hazard ratio

C.1.5. Data analysis and synthesis

Data were summarized narratively and presented in evidence tables. Meta-analysis was not appropriate due to clinical and methodological heterogeneity (for example, differences in patient populations, treatment regimens, risk cut-offs, and outcome measures). Results were stratified according to node status (node-negative, node-positive [N1]), genetic test (Oncotype DX, Prosigna), and clinical utility outcome (prognostic ability, predictive ability). Within each table, study results were presented by study category (A, B, C), followed by publication year. When available, subgroup data were extracted for risk subgroups within the intermediate-risk category, for age subgroups, and by menopausal status.

C.2. Rapid Review 2: Clinician and Patient Treatment Choices

Rapid review 2 examined the impact of Oncotype DX and Prosigna testing on clinician and patient treatment decisions for adjuvant chemotherapy in early-stage (I–III), ER+ (and/or PR+), HER2−, node-negative or node-positive (N1) breast cancer. It included the 2016 CCO systematic review[25] and all primary studies published subsequent to its literature search.

C.2.1. Literature search

Information specialists working on the 2016 CCO systematic review[25] conducted database searches of MEDLINE and Embase to identify full-text, English-language systematic reviews and primary studies published from 2002 to week 7 of 2016. An IHE information specialist (LT) updated these searches on 3 December 2018. We also searched reference lists of included studies and other

relevant reports (including the 2018 CCO update) and consulted experts to help identify additional relevant studies. For the complete search strategies, see Appendix D, Table D.2.

An IHE information specialist (LT) searched the following trial registers to identify ongoing studies: ClinicalTrials.gov, Health Canada Clinical Trial Search, ISRCTN registry, and European Union Clinical Trials register. The searches were conducted on 12 February 2019 (ClinicalTrials.gov) and 8 March 2019 (all other registers). One reviewer (JS) screened the search results and summarized the ongoing studies relevant to rapid review 2. For the complete search strategy, see Appendix D, Table D.4.

C.2.2. Study selection

One reviewer (ASc) screened the titles and abstracts of all citations retrieved by the searches and assessed the full text of each potentially relevant paper for inclusion. A second reviewer (MP) helped resolve uncertainties as needed.

Relevant studies were those reporting data from prospectively enrolled patients and prospectively collected tumour specimens or from retrospective analyses of tumour specimens from completed RCTs or prospective studies. *Prospective collection of data* was defined as the availability of data on pre-test decisions before the genetic test results were received. Studies were excluded if they applied post hoc assumptions to determine any aspect of the test ordering or decision process related to treatment recommendations (for example, reassessing medical records to determine why a genetic test was ordered or retrospectively formulating a pre-test recommendation in order to compare it with the recorded post-test recommendation). This was done to generate a more homogeneous data set and to better reflect current practice. We excluded retrospective cohort studies, case-control studies, and theoretical comparisons (for example, scenarios involving decision analytic models), as well as narrative reviews, case series or case reports, letters, editorials, protocols, conference abstracts, and studies not published in English. In cases of multiple publications on the same patient population, only the most comprehensive version was included.

Study eligibility was determined using the PICO criteria outlined in section 2.1 (Table 3), with the same additional considerations as rapid review 1 (see section C.1.2).[6]

C.2.3. Quality assessments

Due to time constraints, no formal quality assessments using validated tools were conducted. Study designs and major methodological issues of the evidence base were identified and described.

C.2.4. Data extraction

One reviewer (ASc) extracted data from each included primary study into predeveloped data extraction forms or tables. Data were extracted on study characteristics (including sources of funding and conflicts of interest), patient demographic and clinical characteristics, and outcomes. Where applicable, data extraction was cross-checked with the results data tabulated in the 2018 CCO update.[32] Data extracted from relevant primary studies included in the 2016 CCO systematic review[25] were limited to the outcomes reported in the tables and text of that review. The full texts of the primary studies were not retrieved.

[6] Though studies were considered eligible for inclusion if at least 90% (not 80%) of the patient sample met the eligibility criteria.

Treatment change outcomes were calculated as follows:

- **Total treatment change (decision impact)**: The number of patients whose treatment decision regarding chemotherapy changed after the test, calculated as a proportion of the entire patient sample. Changes in degree of treatment, such as alterations in chemotherapy intensity, were not included.
- **Net change in chemotherapy use**: The difference in the number of patients assigned to chemotherapy before and after the test, calculated as a proportion of the entire patient sample. Where possible, the net change in chemotherapy use was also calculated for the risk categories of each genetic test, using the entire patient sample as the denominator (this was done to better assess the contribution of changes in each risk category to the overall treatment change, but it should be noted that when the proportion of patients in a particular risk category is small, the estimated net change can never be large).[97]

C.2.5. Data analysis and synthesis

Data were summarized narratively and presented in evidence tables. Meta-analysis was not appropriate due to clinical and methodological heterogeneity. Results were stratified according to node status (node-negative or node-positive [N1]) and genetic test (Oncotype DX, Prosigna). Within each table, study results were presented by study design followed by publication year.

We used McNemar's test[7] to calculate the statistical significance of changes in chemotherapy decisions before and after the test, when appropriate, in studies where this statistic was not reported. A probability value (p-value) of 0.05 or lower was considered statistically significant.

C.3. Rapid Review 3: Health-Related Quality of Life

Rapid review 3 examined the HRQoL of patients with early-stage (I–III) breast cancer in the presence or absence of chemotherapy. It included systematic reviews and primary studies published from 2007 onward (though no systematic reviews were identified).

C.3.1. Literature search

An IHE information specialist (LT) conducted database searches of MEDLINE and Embase to identify full-text, English-language publications. A focused search for quality of life in breast cancer patients in the presence of chemotherapy was conducted from 2013 onward on 30 November 2018. Broader searches for quality of life in breast cancer patients were conducted from 2007 onward, as this was the publication date of the primary study that provided HRQoL information for the economic analysis included in the 2016 University of Alberta report.[21] These searches were conducted on 13 December and 14 December 2018. We also searched reference lists of included studies and other relevant reports, and consulted experts to help identify additional relevant studies. For complete search strategies, see Appendix D, Table D.3.

C.3.2. Study selection

One of two reviewers (JS, PC) screened the titles and abstracts of all citations retrieved by the searches and assessed the full text of each potentially relevant paper for inclusion. A second reviewer (MP) helped resolve uncertainties as needed.

[7] Calculated online at: https://www2.ccrb.cuhk.edu.hk/stat/confidence%20interval/McNemar%20Test.htm .

Systematic reviews and experimental and observational primary studies were eligible for inclusion. We excluded narrative reviews, case series or case reports, letters, editorials, protocols, conference abstracts, and studies not published in English.

Study eligibility was determined using the PICO criteria outlined in section 2.1 (Table 3), with the following additional considerations:

- In contrast to rapid reviews 1 and 2, HRQoL studies rarely reported ER (and/or PR) status, HER2 status, or regional lymph node involvement. Therefore, these parameters were not used in assessing study eligibility, except for studies that focused specifically on populations that were HR−, HER2+, or that had four or more positive nodes; these studies were excluded.
- Studies were considered eligible for inclusion if: at least 80% of the patient sample met the clinical and treatment eligibility criteria; an appropriate subgroup analysis of eligible patients was provided; or the results for relevant patient groups could be separated from the aggregate data.
- Based on standard clinical care, we considered all chemotherapy to be adjuvant unless otherwise specified.

C.3.3. Quality assessments

Due to time constraints, no formal quality assessments using validated tools were conducted. Study designs and major methodological issues of the evidence base were identified and described.

C.3.4. Data extraction

One of two reviewers (JS, PC) extracted data from each included primary study into predeveloped and piloted data extraction tables. Relevant data were extracted on study characteristics (including sources of funding and conflicts of interest), patient demographic and clinical characteristics, interventions, comparators, and HRQoL outcome data. When multiple time points were reported, endpoint data were extracted.

The EQ-5D,[98-100] SF-36,[101, 102] SF-12,[103] and SF-6D[104] were selected as HRQoL measures of interest because they are standardized, validated, generic instruments that allow for comparison across diseases in describing and valuing health states. The items, scoring, and interpretation of these instruments is described below:

- **EQ-5D**: Is a non-disease-specific measure consisting of a descriptive system and a visual analogue scale (EQ-VAS) that is used to describe and value HRQoL.[99] The descriptive system is composed of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, which are each rated with three (EQ-5D-3L) or five (EQ-5D-5L) levels of severity. The scores across these dimensions are converted to a single summary index score using a set of value weights, indicating preferability in comparison to other health states. Index scores range from 0 (dead) to 1 (perfect health). The EQ-VAS is a self-rated vertical scale numbered 0 to 100, with endpoints defined as "worst health you can imagine" and "best health you can imagine," respectively.
- **SF-36**: Is a generic measure composed of 36 items measuring eight domains or scales: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health.[105] Each scale is transformed into a score ranging from 0 to 100, with 0 representing worst health status to 100 representing

best health status. The scales also contribute in different proportions to a calculation of a Physical Component Summary and a Mental Component Summary using special algorithms. Some studies combine the scales or summary measures into a single total score, though the SF-36 scoring manual does not support this practice.[106]

- **SF-12**: Is an abbreviated version of the SF-36 composed of 12 items. This questionnaire addresses the same eight domains as the SF-36 but with only one or two items per domain, and is similarly scored to provide a Physical Component Summary and Mental Component Summary.[107]
- **SF-6D**: Is a health state measure that is derived by scoring and valuing 11 items from the SF-36 to produce a single utility index for use in economic evaluation. The score incorporates seven of the eight domains of the SF-36 (general health is omitted) and combines role physical and role emotional domains, for a total of six dimensions. The SF-6D index scores range from 0.0 (worst health state) to 1.0 (best health state).[107]

These instruments are described variously in the literature as measuring "health-related quality of life or "perceived health status," and there is little agreement on the definitions of these terms.[108] For simplicity, these instruments will be described as measures of HRQoL throughout this report.

C.3.5. Data analysis and synthesis

Data were summarized narratively and presented in evidence tables. Meta-analysis was not appropriate due to clinical and methodological heterogeneity. Results were stratified by the comparison and outcome measures of the included studies.

Appendix D: Search Strategies

TABLE D.1: Clinical review – search strategy for rapid review 1

Database	Search date	Search terms
Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Daily <1946 to Present>	2016 CCO review:[25] Feb 2016 2018 CCO update:[32] 20 Apr 2018 IHE update search:[a] 27 Nov 2018 (conducted by MW, an information specialist at Health Quality Ontario, based on a collaboration agreement)	1 exp breast cancer/ 2 breast cancer.mp. 3 breast adj2 (cancer$ or neoplasm$ or carcinoma$ or malignan$ or tumo?r)).mp. 4 or/1-3 5 (oncotype or 21 gene or recurrence score).mp. 6 (prosigna or PAM50).mp. 7 (mammaprint or 70 gene).mp. 8 endopredict.mp. 9 or/5-8 10 TAILORx.mp. 11 rxponder.mp. 12 (swog adj (S1007 or "8814")).mp. 13 (nsabp adj (b20 or b-20 or b 20)).mp. 14 (nsabp adj (b14 or b-14 or b 14)).mp. 15 transatac.mp. 16 ((ma17 or ma 17 or ma-17 or ma12 or ma 12 or ma-12) adj (trial or study)).mp. 17 (ABCSG-6 or ABCSG 6 or ABCSG-8 or ABCSG 8).mp. 18 mindact.mp. 19 (raster adj2 study).mp. 20 (geicam 9906 or geicam-9906 or geicam9906).mp. (21 (OPTIMA adj2 study).mp. 22 or/10-21 23 exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/ 24 (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt. 25 random allocation/ or double blind method/ or single blind method/ 26 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. 27 or/23-26 28 (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/ 29 (clinical trial or clinical trial, phase II or controlled clinical trial).pt. 30 (28 or 29) and random$.tw. 31 (clinic$ adj trial$1).tw. 32 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw. 33 placebos/

Database	Search date	Search terms
		34 (placebo? or random allocation or randomly allocated or allocated randomly).tw. 35 (allocated adj2 random).tw. 36 Prospective study/ 37 Retrospective study/ 38 Cohort study/ 39 or/30-38 40 27 or 39 41 (4 and 9 and 40) or 22 42 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. 43 41 not 42 44 exp animal/ not human/ 45 43 not 44 46 limit 45 to english language 47 limit 46 to yr="2018 -Current"
Embase <1996 to 2016 Week 7>	2016 CCO review:[25] Feb 2016 2018 CCO update:[32] 20 Apr 2018 IHE update search:[a] 27 Nov 2018 (conducted by MW, an information specialist at Health Quality Ontario, based on a collaboration agreement)	1 breast cancer/ 2 breast cancer.mp. 3 (breast adj2 (cancer$ or neoplasm$ or carcinoma$ or malignan$ or tumo?r)).mp. 4 or/1-3 5 (oncotype or 21 gene or recurrence score).mp. 6 (prosigna or PAM50).mp. 7 (mammaprint or 70 gene).mp. 8 endopredict.mp. 9 or/5-8 10 TAILORx.mp. 11 rxponder.mp. 12 (SWOG adj (S1007 or "8814")).mp. 13 (nsabp adj (b20 or b-20)).mp. 14 (nsabp adj (b14 or b-14)).mp. 15 transatac.mp. 16 ((ma17 or ma 17 or ma-17 or ma12 or ma 12 or ma-12) adj (trial or study)).mp. 17 (ABCSG-6 or ABCSG 6 or ABCSG-8 or ABCSG 8).mp. 18 mindact.mp. 19 (raster adj2 study).mp. 20 (geicam 9906 or geicam-9906 or geicam9906).mp. 21 (OPTIMA adj2 study).mp. 22 or/10-21 23 exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/

Database	Search date	Search terms
		24 randomization/ or single blind procedure/ or double blind procedure/
		25 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
		26 or/23-25
		27 (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
		28 27 and random$.tw.
		29 (clinic$ adj trial$1).tw.
		30 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw
		31 placebo/
		32 (placebo? or random allocation or randomly allocated or allocated randomly).tw.
		33 (allocated adj2 random).tw.
		34 Prospective study/
		35 Retrospective study/
		36 Cohort study/
		37 or/29-36
		38 26 or 28 or 37
		39 (4 and 9 and 38) or 22
		40 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
		41 39 not 40
		42 animal/ not human/
		43 41 not 42
		44 limit 43 to english language
		45 limit 44 to exclude medline journals
		46 limit 44 to yr="2018 -Current"

Note: "*", and "$" are truncation characters that retrieve all possible suffix variations of the root word, e.g., Surg* retrieves surgery, surgical, surgeon, etc.

[a] The second update search was similar to the original search, except for the following changes: added '$' after 'tum?r' in line 3 (both searches), added '$' after 'oncotype' in line 5 (both searches), and added 'exp' to 'breast cancer/' in line 1 (Embase search only).

TABLE D.2: Clinical review – search strategy for rapid review 2

Database	Search date	Search terms
Ovid MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to December 3, 2018>	3 Dec 2018 (conducted by LT, an IHE information specialist)	1 exp breast neoplasms/ 2 Carcinoma, Intraductal, Noninfiltrating/ or Carcinoma, Lobular/ 3 ((breast* or mammary) adj3 (cancer* or neoplasm* or carcinoma* or adenocarcinoma* or sarcoma* or carcinoid or tumor* or tumour* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or tubular or metasta* or malignan*)).tw,kw. 4 or/1-3 5 exp drug therapy/ or exp Antibodies, Monoclonal/ or exp Antineoplastic Agents/ 6 (Chemo* or 5-fluorouracil or "5 fluorouracil" or doxorubicin or paclitaxel or nab-paclitaxel or capecitabine or gemcitabine or vinorelbine or cyclophosphamide or carboplatin or docetaxel or cisplatin or epirubicin or trastuzumab or pertuzumab or Ixabepilone or Eribulin).tw,kw. 7 (CMF or (TC adj2 (chemo* or therap*))).tw,kw. 8 or/5-7 9 4 and 8 10 exp Gene Expression Profiling/ or exp gene expression/ or exp gene expression regulation/ 11 ((gene* or genom*) adj3 (test* or profil* or assay or score*)).mp. 12 (oncotype$ or 21 gene or recurrence score).mp. 13 (prosigna or PAM50).mp. 14 or/10-13 15 TAILORx.mp. 16 rxponder.mp. 17 (swog adj (S1007 or "8814")).mp. 18 (nsabp adj (b20 or b-20 or b 20)).mp. 19 (nsabp adj (b14 or b-14 or b 14)).mp. 20 transatac.mp. 21 mindact.mp. 22 (OPTIMA adj2 study).mp. 23 or/15-22 24 9 and 14 25 23 or 24 26 exp Clinical Decision-Making/ 27 exp Practice Patterns, Clinicians'/ 28 exp Patient Preference/ 29 Decision Making/ 30 (choice* or decid* or decision* or prefer* or choose*).tw,kw. 31 exp decision support techniques/ 32 Decision Trees/ 33 or/26-32

Database	Search date	Search terms	
		34	9 and 33
		35	25 and 33
		36	((Chemo* or 5-fluorouracil or "5 fluorouracil" or doxorubicin or paclitaxel or nab-paclitaxel or capecitabine or gemcitabine or vinorelbine or cyclophosphamide or carboplatin or docetaxel or cisplatin or epirubicin or trastuzumab or pertuzumab or Ixabepilone or Eribulin or (CMF or (TC adj2 (chemo* or therap*)))) adj5 (choice* or decid* or decision* or prefer* or choose* or guide* or guidance)).tw,kw.
		37	4 and 36
		38	((treatment* or therap*) adj5 (choice* or decid* or decision* or prefer* or choose* or guide* or guidance)).tw,kw.
		39	9 and 38
		40	35 or 37 or 39
		41	limit 40 to (english language and yr="2013 -Current")
		42	(addresses or autobiography or bibliography or biography or case report or comment or dataset or dictionary or directory or duplicate publication or editorial or historical article or interactive tutorial or lectures or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or video-audio media or webcasts).pt.
		43	(trial or review or study or studies or evaluation or research).pt.
		44	42 not 43
		45	41 not 44
		46	randomized controlled trial.pt.
		47	clinical trial.pt.
		48	randomi?ed.ti,ab.
		49	placebo.ti,ab.
		50	dt.fs.
		51	randomly.ti,ab.
		52	trial.ti,ab.
		53	groups.ti,ab.
		54	or/46-53
		55	Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Cross-sectional studies/
		56	((Case or cases) adj2 (control or controls or series)).tw.
		57	(cohort adj (study or studies or analy*)).tw.
		58	((Follow up or observational or prevalence or prospective) adj (study or studies)).tw.
		59	(Longitudinal or Retrospective or Cross sectional).tw.
		60	(Longitudinal or Retrospective or prospective or Cross sectional).tw.
		61	controlled clinical trial.pt.
		62	or/55-61
		63	(survey* or interview*).tw,kw,pt.

Database	Search date	Search terms
		64 54 or 62 or 63 65 animals/ not (animals/ and humans/) 66 64 not 65 67 meta-analysis.pt. 68 (meta-anal$ or metaanal$).mp. 69 ((quantitativ$ adj3 review$1) or (quantitativ$ adj3 overview$)).mp. 70 ((systematic$ adj3 review$) or (systematic adj3 overview$)).mp. 71 ((methodologic adj3 review$1) or (methodologic adj3 overview$)).mp. 72 (integrat$ adj5 research).mp. 73 (quantitativ$ adj3 synthes$).mp. 74 or/67-73 75 review.pt. or (review$ or overview$).mp. 76 (medline or medlars or pubmed or indexmedicus or embase or cochrane).mp. 77 (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 78 (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index or scopus).mp. 79 (hand search$ or manual search$).mp. 80 ((electronic adj3 database$) or (bibliographic adj3 database$) or periodical index$).mp. 81 (pooling or pooled or mantel haenszel).mp. 82 (peto or der simonian or dersimonian or fixed effect$).mp. 83 ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 84 or/76-83 85 75 and 84 86 74 or 85 87 (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 88 technology assessment, biomedical/ or biomedical technology assessment/ 89 87 or 88 90 86 or 89 91 45 and 66 [PRIMARY STUDIES] (1091) 92 45 and 90 [SYSTEMATIC REVIEWS] (117)
Embase <1996 to 2018 Week 48>	3 Dec 2018 (conducted by LT, an IHE information specialist)	1 exp breast tumor/ 2 ((breast* or mammary) adj3 (cancer* or neoplasm* or carcinoma* or adenocarcinoma* or sarcoma* or carcinoid or tumor* or tumour* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or tubular or metasta* or malignan*)).ti,kw. 3 or/1-2 4 exp chemotherapy/ or exp Antineoplastic agent/

Database	Search date	Search terms
		5 (Chemo* or 5-fluorouracil or "5 fluorouracil" or doxorubicin or paclitaxel or nab-paclitaxel or capecitabine or gemcitabine or vinorelbine or cyclophosphamide or carboplatin or docetaxel or cisplatin or epirubicin or trastuzumab or pertuzumab or Ixabepilone or Eribulin).ti,kw.
		6 (CMF or (TC adj2 (chemo* or therap*))).tw,kw.
		7 or/4-6
		8 3 and 7
		9 exp gene expression profiling/ or exp gene expression assay/ or exp gene expression/
		10 ((gene* or genom*) adj3 (test* or profil* or assay or score*)).mp.
		11 (oncotype$ or 21 gene or recurrence score).mp.
		12 (prosigna or PAM50).mp.
		13 or/9-12
		14 (TAILORx or rxponder or transatac or mindact).mp.
		15 (swog adj (S1007 or "8814")).mp.
		16 (nsabp adj (b20 or b-20 or b 20)).mp.
		17 (nsabp adj (b14 or b-14 or b 14)).mp.
		18 (OPTIMA adj2 study).mp.
		19 or/14-18
		20 8 and 13
		21 19 or 20
		22 exp decision making/
		23 exp patient attitude/
		24 exp decision trees/
		25 (choice* or decid* or decision* or prefer* or choose*).tw,kw.
		26 or/22-25
		27 21 and 26
		28 ((Chemo* or 5-fluorouracil or "5 fluorouracil" or doxorubicin or paclitaxel or nab-paclitaxel or capecitabine or gemcitabine or vinorelbine or cyclophosphamide or carboplatin or docetaxel or cisplatin or epirubicin or trastuzumab or pertuzumab or Ixabepilone or Eribulin or (CMF or (TC adj2 (chemo* or therap*)))) adj5 (choice* or decid* or decision* or prefer* or choose* or guide* or guidance)).tw,kw.
		29 3 and 28
		30 ((treatment* or therap*) adj5 (choice* or decid* or decision* or prefer* or choose* or guide* or guidance)).tw,kw.
		31 8 and 30
		32 27 or 29 or 31
		33 limit 32 to (english language and embase and yr="2013 -Current")
		34 meta-analysis.pt.
		35 (meta-anal$ or metaanal$).mp.
		36 ((quantitativ$ adj3 review$1) or (quantitativ$ adj3 overview$)).mp.
		37 ((systematic$ adj3 review$) or (systematic adj3 overview$)).mp.
		38 ((methodologic adj3 review$1) or (methodologic adj3 overview$)).mp.
		39 (integrat$ adj5 research).mp.
		40 (quantitativ$ adj3 synthes$).mp.
		41 or/34-40
		42 review.pt. or (review$ or overview$).mp.

Database	Search date	Search terms
		43 (medline or medlars or pubmed or indexmedicus or embase or cochrane).mp. 44 (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 45 (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index or scopus).mp. 46 (hand search$ or manual search$).mp. 47 ((electronic adj3 database$) or (bibliographic adj3 database$) or periodical index$).mp. 48 (pooling or pooled or mantel haenszel).mp. 49 (peto or der simonian or dersimonian or fixed effect$).mp. 50 ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 51 or/43-50 52 42 and 51 53 41 or 52 54 (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 55 technology assessment, biomedical/ or biomedical technology assessment/ 56 54 or 55 57 53 or 56 58 exp clinical trial/ 59 randomi?ed.ti,ab. 60 placebo.ti,ab. 61 dt.fs. 62 randomly.ti,ab. 63 trial.ti,ab. 64 groups.ti,ab. 65 or/58-64 66 (clin$ adj25 (trial$ or study or studies or design)).mp. 67 exp Placebo/ 68 (placebo$ or random$).mp. 69 (ae or co or ct or do or th).fs. 70 exp Methodology/ 71 exp Comparative Study/ 72 exp Evaluation/ 73 exp Follow Up/ 74 exp Prospective Study/ 75 clinical study/ 76 exp case control study/ 77 family study/ 78 exp longitudinal study/ 79 retrospective study/ 80 exp cohort analysis/ 81 exp Risk/ 82 ((allocat$ or compar$ or assign$ or treatment or control$ or interven$ or experiment$) and (group or groups)).mp. 83 (group or groups).ti,ab.

Database	Search date	Search terms
		84 ((control$ or prospectiv$ or retrospectiv$ or volunteer$ or participant$ or compar$) and (trial$ or study or studies or design)).ti,ab,sh. 85 cohort$.mp. 86 (case$ and control$).tw. 87 "Cross sectional".ti,ab. 88 (before adj2 after).ti,ab. 89 (observational adj5 (study or studies or design)).ti,ab. 90 Longitudinal.mp. 91 Retrospective.ti,ab. 92 "Relative risk".ti,ab. 93 "Odds ratio".ti,ab. 94 (Follow up adj5 (study or studies or design)).ti,ab. 95 (case adj (comparison or referent)).ti,ab. 96 (Causation or causal$).ti,ab. 97 (Analytic adj (study or studies)).ti,ab. 98 (epidemiologic$ adj (study or studies)).ti,ab. 99 single subject$.mp. or SSRD.ti,ab. 100 "n-of-1".ti,ab. 101 or/66-100 102 65 or 101 103 animal/ 104 human/ 105 103 not (103 and 104) 106 102 not 105 107 (survey* or interview*).tw,kw,pt. 108 106 or 107 109 33 and 108 [PRIMARY STUDIES] (1194) 110 33 and 57 [SYSTEMATIC REVIEWS] (129)

Note: "*", and "$" are truncation characters that retrieve all possible suffix variations of the root word, e.g., Surg* retrieves surgery, surgical, surgeon, etc.

TABLE D.3: Clinical review – search strategy for rapid review 3

Database	Search date	Search terms
Quality of life in breast cancer patients receiving chemotherapy		
Ovid MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to November 29, 2018>	30 Nov 2018 (conducted by LT, an IHE information specialist)	1 exp breast neoplasms/ 2 Carcinoma, Intraductal, Noninfiltrating/ or Carcinoma, Lobular/ 3 ((breast* or mammary) adj3 (cancer* or neoplasm* or carcinoma* or adenocarcinoma* or sarcoma* or carcinoid or tumor* or tumour* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or tubular or metasta*)).ti,kw. 4 or/1-3 5 exp drug therapy/ or exp Antibodies, Monoclonal/ or exp Antineoplastic Agents/ 6 (Chemotherap* or 5-fluorouracil or "5 fluorouracil" or doxorubicin or paclitaxel or nab-paclitaxel or capecitabine or gemcitabine or vinorelbine or cyclophosphamide or carboplatin or docetaxel or cisplatin or epirubicin or trastuzumab or pertuzumab or Ixabepilone or Eribulin).ti,kw. 7 (CMF or (TC adj2 (chemo* or therap*))).ti,kw. 8 or/5-7 9 exp "quality of life"/ 10 "value of life"/ 11 exp health status/ 12 exp satisfaction/ 13 exp "Activities of Daily Living"/ 14 exp quality-adjusted life years/ 15 exp sickness impact profile/ 16 (quality adj2 (life or wellbeing or well-being)).tw,kw. 17 (qol* or hql* or hqol* or h qol* or hrqol* or hr qol* or qal* or qtime* or qwb* or daly* or euroqol* or eq5d* or eq 5d* or sf20 or sf 20 or short form 20 or shortform 20 or shortform20 or rand12 or rand 12 or sf36 or sf 36 or short form 36 or shortform 36 or shortform36 or rand36 or rand 36 or sf12 or sf 12 or short form 12 or shortform 12 or shortform12 or sf8 or sf 8 or shortform 8 or shortform 8 or shortform8 or sf6 or sf 6 or short form 6 or shortform 6 or shortform6 or hui or hui1 or hui2 or hui3 or hye or hyes).tw,kw. 18 (disutilit* or "Magnitude estimation" or Quality adjusted life year* or QWB or "Health state" or Health status or "Life quality" or Wellbeing or "Well being" or "activities of daily living" or"personal satisfaction" or "self-rated health" or sickness impact profile or disability adjusted life or health* year* equivalent* or rosser).tw,kw. 19 (health adj3 (utilit* or status)).ti,ab,kf. 20 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. 21 or/9-20 22 4 and 8 and 21 23 limit 22 to yr="2013 -Current" 24 remove duplicates from 23 25 limit 24 to english language 26 limit 25 to (case reports or comment or editorial or letter or news) 27 (comparative study or review or research or trial).pt. 28 26 not 27 29 25 not 28

Database	Search date	Search terms
		30 limit 29 to "review articles" 31 limit 29 to systematic reviews 32 30 or 31 [REVIEWS] (211) 33 29 not 32 [PRIMARY STUDIES] (737)
Embase <1996 to 2018 Week 48>	30 Nov 2018 (conducted by LT, an IHE information specialist)	1 exp breast tumor/ 2 ((breast* or mammary) adj3 (cancer* or neoplasm* or carcinoma* or adenocarcinoma* or sarcoma* or carcinoid or tumor* or tumour* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or tubular or metasta*)).ti,kw. 3 or/1-2 4 exp chemotherapy/ or exp Antineoplastic agent/ 5 (Chemotherap* or 5-fluorouracil or "5 fluorouracil" or doxorubicin or paclitaxel or nab-paclitaxel or capecitabine or gemcitabine or vinorelbine or cyclophosphamide or carboplatin or docetaxel or cisplatin or epirubicin or trastuzumab or pertuzumab or Ixabepilone or Eribulin).ti,kw. 6 (CMF or (TC adj2 (chemo* or therap*))).tw,kw. 7 or/4-6 8 exp *"quality of life"/ 9 *"value of life"/ 10 exp *health status/ 11 exp *satisfaction/ 12 exp *"Activities of Daily Living"/ 13 exp *quality-adjusted life years/ 14 exp *"activity of daily living assessment"/ or *nottingham health profile/ or exp *"quality of life assessment"/ or exp *sickness impact profile/ 15 (quality adj2 (life or wellbeing or well-being)).ti,kw. 16 (quality adj2 (life or wellbeing or well-being)).ab. /freq=2 17 (qol* or hql* or hqol* or h qol* or hrqol* or hr qol* or qal* or qtime* or qwb* or daly* or euroqol* or eq5d* or eq 5d* or sf20 or sf 20 or short form 20 or shortform 20 or shortform20 or rand12 or rand 12 or sf36 or sf 36 or short form 36 or shortform 36 or shortform36 or rand36 or rand 36 or sf12 or sf 12 or short form 12 or shortform 12 or shortform12 or sf8 or sf 8 or short form 8 or shortform 8 or shortform8 or sf6 or sf 6 or short form 6 or shortform 6 or shortform6 or hui or hui1 or hui2 or hui3 or hye or hyes).ti,kw. 18 (qol* or hql* or hqol* or h qol* or hrqol* or hr qol* or qal* or qtime* or qwb* or daly* or euroqol* or eq5d* or eq 5d* or sf20 or sf 20 or short form 20 or shortform 20 or shortform20 or rand12 or rand 12 or sf36 or sf 36 or short form 36 or shortform 36 or shortform36 or rand36 or rand 36 or sf12 or sf 12 or short form 12 or shortform 12 or shortform12 or sf8 or sf 8 or short form 8 or shortform 8 or shortform8 or sf6 or sf 6 or short form 6 or shortform 6 or shortform6 or hui or hui1 or hui2 or hui3 or hye or hyes).ab. /freq=2 19 (disutilit* or "Magnitude estimation" or Quality adjusted life year* or QWB or "Health state" or Health status or "Life quality" or Wellbeing or "Well being" or "activities of daily living" or "personal satisfaction" or "self-rated health" or sickness impact profile or disability adjusted life or health* year* equivalent* or rosser).ti,kw. 20 (health adj3 (utilit* or status)).ti,ab,kw. 21 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.

Database	Search date	Search terms
		22 (disutilit* or "Magnitude estimation" or Quality adjusted life year* or QWB or "Health state" or Health status or "Life quality" or Wellbeing or "Well being" or "activities of daily living" or personal satisfaction" or "self-rated health" or sickness impact profile or disability adjusted life or health* year* equivalent* or rosser).ab. /freq=2 23 or/8-22 24 3 and 7 and 23 25 remove duplicates from 24 26 limit 25 to (english language and embase and yr="2013 -Current") [RESULTS BEFORE STUDY DESIGNS] 27 exp clinical trial/ 28 randomi?ed.ti,ab. 29 placebo.ti,ab. 30 dt.fs. 31 randomly.ti,ab. 32 trial.ti,ab. 33 groups.ti,ab. 34 or/27-33 35 (clin$ adj25 (trial$ or study or studies or design)).mp. 36 exp Placebo/ 37 (placebo$ or random$).mp. 38 (ae or co or ct or do or th).fs. 39 exp Methodology/ 40 exp Comparative Study/ 41 exp Evaluation/ 42 exp Follow Up/ 43 exp Prospective Study/ 44 clinical study/ 45 exp case control study/ 46 family study/ 47 exp longitudinal study/ 48 retrospective study/ 49 exp cohort analysis/ 50 exp Risk/ 51 ((allocat$ or compar$ or assign$ or treatment or control$ or interven$ or experiment$) and (group or groups)).mp. 52 (group or groups).ti,ab. 53 ((control$ or prospectiv$ or retrospectiv$ or volunteer$ or participant$ or compar$) and (trial$ or study or studies or design)).ti,ab,sh. 54 cohort$.mp. 55 (case$ and control$).tw. 56 "Cross sectional".ti,ab. 57 (before adj2 after).ti,ab. 58 (observational adj5 (study or studies or design)).ti,ab. 59 Longitudinal.mp. 60 Retrospective.ti,ab. 61 "Relative risk".ti,ab. 62 "Odds ratio".ti,ab. 63 (Follow up adj5 (study or studies or design)).ti,ab.

Database	Search date	Search terms
		64 (case adj (comparison or referent)).ti,ab. 65 (Causation or causal$).ti,ab. 66 (Analytic adj (study or studies)).ti,ab. 67 (epidemiologic$ adj (study or studies)).ti,ab. 68 single subject$.mp. or SSRD.ti,ab. 69 "n-of-1".ti,ab. 70 or/35-69 71 34 or 70 72 animal/ 73 human/ 74 72 not (72 and 73) 75 71 not 74 76 26 and 75 [PRIMARY STUDIES] 77 meta-analysis.pt. 78 (meta-anal$ or metaanal$).mp. 79 ((quantitativ$ adj3 review$1) or (quantitativ$ adj3 overview$)).mp. 80 ((systematic$ adj3 review$) or (systematic adj3 overview$)).mp. 81 ((methodologic adj3 review$1) or (methodologic adj3 overview$)).mp. 82 (integrat$ adj5 research).mp. 83 (quantitativ$ adj3 synthes$).mp. 84 or/77-83 85 review.pt. or (review$ or overview$).mp. 86 (medline or medlars or pubmed or index medicus or embase or cochrane).mp. 87 (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 88 (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index or scopus).mp. 89 (hand search$ or manual search$).mp. 90 ((electronic adj3 database$) or (bibliographic adj3 database$) or periodical index$).mp. 91 (pooling or pooled or mantel haenszel).mp. 92 (peto or der simonian or dersimonian or fixed effect$).mp. 93 ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 94 or/86-93 95 85 and 94 96 84 or 95 97 (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 98 technology assessment, biomedical/ or biomedical technology assessment/ 99 97 or 98 100 96 or 99 101 26 and 75 [PRIMARY STUDIES] (1115) 102 26 and 100 [SYSTEMATIC REVIEWS] (115)
Quality of life in breast cancer patients		
Ovid MEDLINE (R) and Epub	13 Dec 2018 (conducted by LT,	1 exp breast neoplasms/ 2 Carcinoma, Intraductal, Noninfiltrating/ or Carcinoma, Lobular/

Database	Search date	Search terms
Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to December 12, 2018>	an IHE information specialist)	3 ((breast* or mammary) adj3 (cancer* or neoplasm* or carcinoma* or adenocarcinoma* or sarcoma* or carcinoid or tumor* or tumour* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or tubular or metasta*)).ti,kw. 4 or/1-3 5 exp "quality of life"/ 6 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. 7 (quality adj2 (life or wellbeing or well-being)).ti,kw. 8 4 and (5 or 6 or 7) 9 limit 8 to (english language and yr="2007 -Current") 10 remove duplicates from 9 11 limit 10 to (case reports or comment or editorial or letter or news) 12 (comparative study or review or research or trial).pt. 13 11 not 12 14 10 not 13 15 meta-analysis.pt. 16 (meta-anal$ or metaanal$).mp. 17 ((quantitativ$ adj3 review$1) or (quantitativ$ adj3 overview$)).mp. 18 ((systematic$ adj3 review$) or (systematic adj3 overview$)).mp. 19 ((methodologic adj3 review$1) or (methodologic adj3 overview$)).mp. 20 (integrat$ adj5 research).mp. 21 (quantitativ$ adj3 synthes$).mp. 22 or/15-21 23 review.pt. or (review$ or overview$).mp. 24 (medline or medlars or pubmed or indexmedicus or embase or cochrane).mp. 25 (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 26 (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index or scopus).mp. 27 (hand search$ or manual search$).mp. 28 ((electronic adj3 database$) or (bibliographic adj3 database$) or periodical index$).mp. 29 (pooling or pooled or mantel haenszel).mp. 30 (peto or der simonian or dersimonian or fixed effect$).mp. 31 ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 32 or/24-31 33 23 and 32 34 22 or 33 35 (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 36 technology assessment, biomedical/ or biomedical technology assessment/ 37 35 or 36 38 34 or 37 39 14 and 38 40 limit 14 to systematic reviews 41 39 or 40 [REVIEWS] (314)

Database	Search date	Search terms
		42 14 not 41 [ALL OTHER STUDIES] (3234)
Embase <1974 to 2018 December 14>	14 Dec 2018 (conducted by LT, an IHE information specialist)	1 exp breast tumor/ 2 ((breast* or mammary) adj3 (cancer* or neoplasm* or carcinoma* or adenocarcinoma* or sarcoma* or carcinoid or tumor* or tumour* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or tubular or metasta*)).ti,kw. 3 or/1-2 4 exp chemotherapy/ or exp Antineoplastic agent/ 5 (Chemotherap* or 5-fluorouracil or "5 fluorouracil" or doxorubicin or paclitaxel or nab-paclitaxel or capecitabine or gemcitabine or vinorelbine or cyclophosphamide or carboplatin or docetaxel or cisplatin or epirubicin or trastuzumab or pertuzumab or Ixabepilone or Eribulin).ti,kw. 6 (CMF or (TC adj2 (chemo* or therap*))).tw,kw. 7 or/4-6 8 exp *"quality of life"/ 9 *"value of life"/ 10 exp *health status/ 11 exp *satisfaction/ 12 exp *"Activities of Daily Living"/ 13 exp *quality-adjusted life years/ 14 exp *"activity of daily living assessment"/ or *nottingham health profile/ or exp *"quality of life assessment"/ or exp *sickness impact profile/ 15 (quality adj2 (life or wellbeing or well-being)).ti,kw. 16 (quality adj2 (life or wellbeing or well-being)).ab. /freq=2 17 (qol* or hql* or hqol* or h qol* or hrqol* or hr qol* or qal* or qtime* or qwb* or daly* or euroqol* or eq5d* or eq 5d* or sf20 or sf 20 or short form 20 or shortform 20 or shortform20 or rand12 or rand 12 or sf36 or sf 36 or short form 36 or shortform 36 or shortform36 or rand36 or rand 36 or sf12 or sf 12 or short form 12 or shortform 12 or shortform12 or sf8 or sf 8 or short form 8 or shortform 8 or shortform8 or sf6 or sf 6 or short form 6 or shortform 6 or shortform6 or hui or hui1 or hui2 or hui3 or hye or hyes).ti,kw. 18 (qol* or hql* or hqol* or h qol* or hrqol* or hr qol* or qal* or qtime* or qwb* or daly* or euroqol* or eq5d* or eq 5d* or sf20 or sf 20 or short form 20 or shortform 20 or shortform20 or rand12 or rand 12 or sf36 or sf 36 or short form 36 or shortform 36 or shortform36 or rand36 or rand 36 or sf12 or sf 12 or short form 12 or shortform 12 or shortform12 or sf8 or sf 8 or short form 8 or shortform 8 or shortform8 or sf6 or sf 6 or short form 6 or shortform 6 or shortform6 or hui or hui1 or hui2 or hui3 or hye or hyes).ab. /freq=2 19 (disutilit* or "Magnitude estimation" or Quality adjusted life year* or QWB or "Health state" or Health status or "Life quality" or Wellbeing or "Well being" or "activities of daily living" or "personal satisfaction" or "self-rated health" or sickness impact profile or disability adjusted life or health* year* equivalent* or rosser).ti,kw. 20 (health adj3 (utilit* or status)).ti,ab,kw.

Database	Search date	Search terms
		21 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw. 22 (disutilit* or "Magnitude estimation" or Quality adjusted life year* or QWB or "Health state" or Health status or "Life quality" or Wellbeing or "Well being" or "activities of daily living" or "personal satisfaction" or "self-rated health" or sickness impact profile or disability adjusted life or health* year* equivalent* or rosser).ab. /freq=2 23 or/8-22 24 3 and 23 25 3 and (8 or 15 or 20 or 21) 26 exp clinical trial/ 27 randomi?ed.ti,ab. 28 placebo.ti,ab. 29 dt.fs. 30 randomly.ti,ab. 31 trial.ti,ab. 32 groups.ti,ab. 33 or/26-32 34 (clin$ adj25 (trial$ or study or studies or design)).mp. 35 exp Placebo/ 36 (placebo$ or random$).mp. 37 (ae or co or ct or do or th).fs. 38 exp Methodology/ 39 exp Comparative Study/ 40 exp Evaluation/ 41 exp Follow Up/ 42 exp Prospective Study/ 43 clinical study/ 44 exp case control study/ 45 family study/ 46 exp longitudinal study/ 47 retrospective study/ 48 exp cohort analysis/ 49 exp Risk/ 50 ((allocat$ or compar$ or assign$ or treatment or control$ or interven$ or experiment$) and (group or groups)).mp. 51 (group or groups).ti,ab. 52 ((control$ or prospectiv$ or retrospectiv$ or volunteer$ or participant$ or compar$) and (trial$ or study or studies or design)).ti,ab,sh. 53 cohort$.mp. 54 (case$ and control$).tw.

Database	Search date	Search terms
		55 "Cross sectional".ti,ab. 56 (before adj2 after).ti,ab. 57 (observational adj5 (study or studies or design)).ti,ab. 58 Longitudinal.mp. 59 Retrospective.ti,ab. 60 "Relative risk".ti,ab. 61 "Odds ratio".ti,ab. 62 (Follow up adj5 (study or studies or design)).ti,ab. 63 (case adj (comparison or referent)).ti,ab. 64 (Causation or causal$).ti,ab. 65 (Analytic adj (study or studies)).ti,ab. 66 (epidemiologic$ adj (study or studies)).ti,ab. 67 single subject$.mp. or SSRD.ti,ab. 68 "n-of-1".ti,ab. 69 or/34-68 70 33 or 69 71 animal/ 72 human/ 73 71 not (71 and 72) 74 70 not 73 75 meta-analysis.pt. 76 (meta-anal$ or metaanal$).mp. 77 ((quantitativ$ adj3 review$1) or (quantitativ$ adj3 overview$)).mp. 78 ((systematic$ adj3 review$) or (systematic adj3 overview$)).mp. 79 ((methodologic adj3 review$1) or (methodologic adj3 overview$)).mp. 80 (integrat$ adj5 research).mp. 81 (quantitativ$ adj3 synthes$).mp. 82 or/75-81 83 review.pt. or (review$ or overview$).mp. 84 (medline or medlars or pubmed or index medicus or embase or cochrane).mp. 85 (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp. 86 (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index or scopus).mp. 87 (hand search$ or manual search$).mp. 88 ((electronic adj3 database$) or (bibliographic adj3 database$) or periodical index$).mp. 89 (pooling or pooled or mantel haenszel).mp. 90 (peto or der simonian or dersimonian or fixed effect$).mp.

Database	Search date	Search terms
		91 ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp. 92 or/84-91 93 83 and 92 94 82 or 93 95 (hta$ or health technology assessment$ or biomedical technology assessment$).mp. 96 technology assessment, biomedical/ or biomedical technology assessment/ 97 95 or 96 98 94 or 97 99 25 and 74 100 24 and 98 101 limit 99 to (english language and embase and yr="2007 -Current") [PRIMARY STUDIES] (2739) 102 limit 100 to (english language and embase and yr="2007 -Current") [REVIEWS] (476)

Note: "*", and "$" are truncation characters that retrieve all possible suffix variations of the root word, e.g., Surg* retrieves surgery, surgical, surgeon, etc.

TABLE D.4: Clinical review – search strategy for clinical trial registers

Database	Search date	Search terms
ClinicalTrials.gov *www.clinicaltrials.gov*	12 Feb 2019	TAILORx OR Transatac OR RxPonder OR Oncotype (22 results) Prosigna OR PAM50 (16 results)
Health Canada Clinical Trials Search *health-products.canada.ca/ctdb-bdec/newSearch-nouvelleRecherche.do*	8 Mar 2019	TAILORx OR Transatac OR RxPonder OR Oncotype (0 results) Prosigna OR PAM50 (0 results)
ISRCTN registry *www.isrctn.com/search?q=*	8 Mar 2019	oncotype OR PAM50 OR prosigna OR TAILORx OR RxPonder OR Transatac OR "Optimal Personalised Treatment of early breast cancer" (4 results)
EU Clinical Trials Register *www.clinicaltrialsregister.eu/ctr-search/*	8 Mar 2019	oncotype OR PAM50 OR prosigna OR TAILORx OR RxPonder OR Transatac (16 results) "Optimal Personalised Treatment of early breast cancer" OR OPTIMA (0 results)

TABLE D.5: Background section – grey literature searches for regulatory status information and clinical practice guidelines

Database	Search date	Search terms
Regulatory status information		
Health Canada Medical Devices Active License Listing (MDALL) *health-products.canada.ca/mdall-limh/dispatch-repartition.do?type=active*	12 Feb 2019	Device name: Oncotype (0 results) Device name: Prosigna (1 result)
Alberta Health Standards and Guidelines *www.alberta.ca/health-standards-and-guidelines.aspx*	12 Feb 2019	Browsed guidelines (0 results)
US Food and Drug Administration, FDA Premarket Approval 510(K) database *www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm*	12 Feb 2019	Device name: Prosigna (2 result) Device name: Oncotype (0 results)
US Food and Drug Administration, FDA Medical Device Recalls *www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm*	12 Feb 2019	Prosigna (0 results)
US Food and Drug Administration, FDA MAUDE (Manufacturer and User Facility Device Experience; reports of adverse events) *www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Search.cfm*	12 Feb 2019	Oncotype (22 results) Prosigna (0 results)
Clinical practice guidelines		
CPG Infobase *joulecma.ca/cpg/homepage*	12 Feb 2019	Prosigna OR PAM50 (2 results) Oncotype OR TAILORx OR RxPonder OR Transatac(3 results) Selected “Include full text in search”
Cancer Care Ontario *www.cancercareontario.ca*	12 Feb 2019	Prosigna (0 results) Oncotype (3 results)
Alberta Health Services *www.albertahealthservices.ca/info/cancerguidelines.aspx*	12 Feb 2019	Browsed cancer guidelines (1 result)
Towards Optimized Practice *www.topalbertadoctors.org/cpgs/*	12 Feb 2019	Browsed guidelines (0 results)
BC Cancer Agency *www.bccancer.bc.ca/screening/health-professionals/breast/guidance*	12 Feb 2019	Browsed breast guidance for health professionals (1 result)
Google *www.google.ca/*	14 Feb 2019	oncotype OR RxPonder OR TAILORx OR Transatac OR prosigna OR PAM50 "practice guideline" site:.ca (38 results)

Appendix E: Clinical Review – Flow Diagrams

FIGURE E.1: Rapid review 1 flow diagram

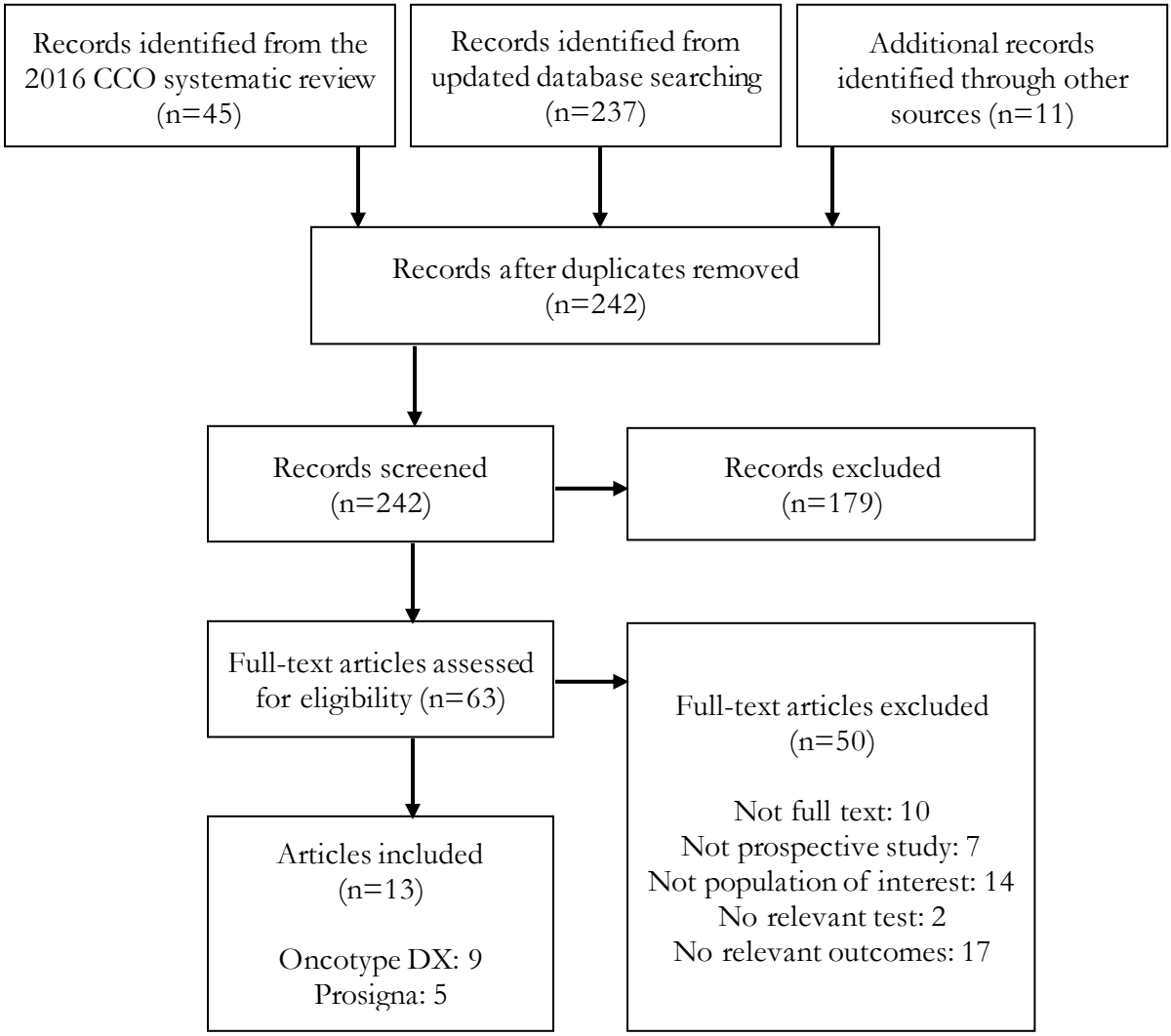
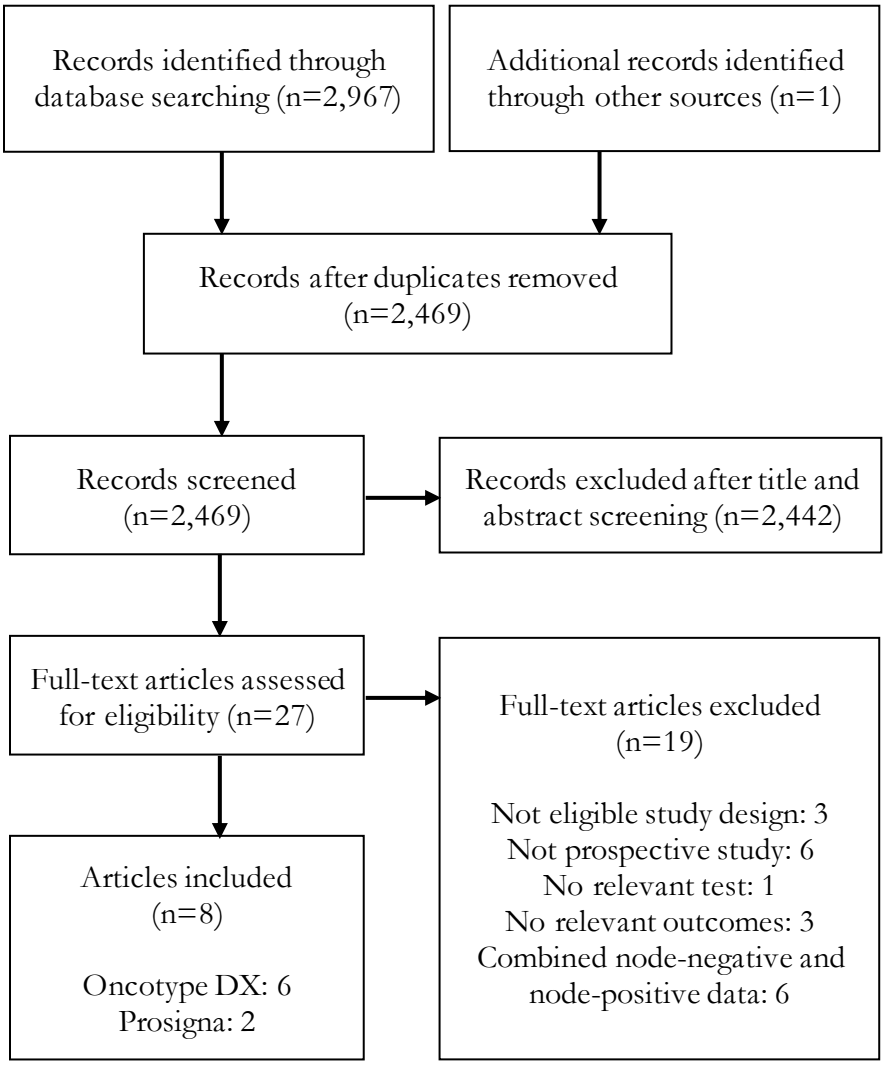
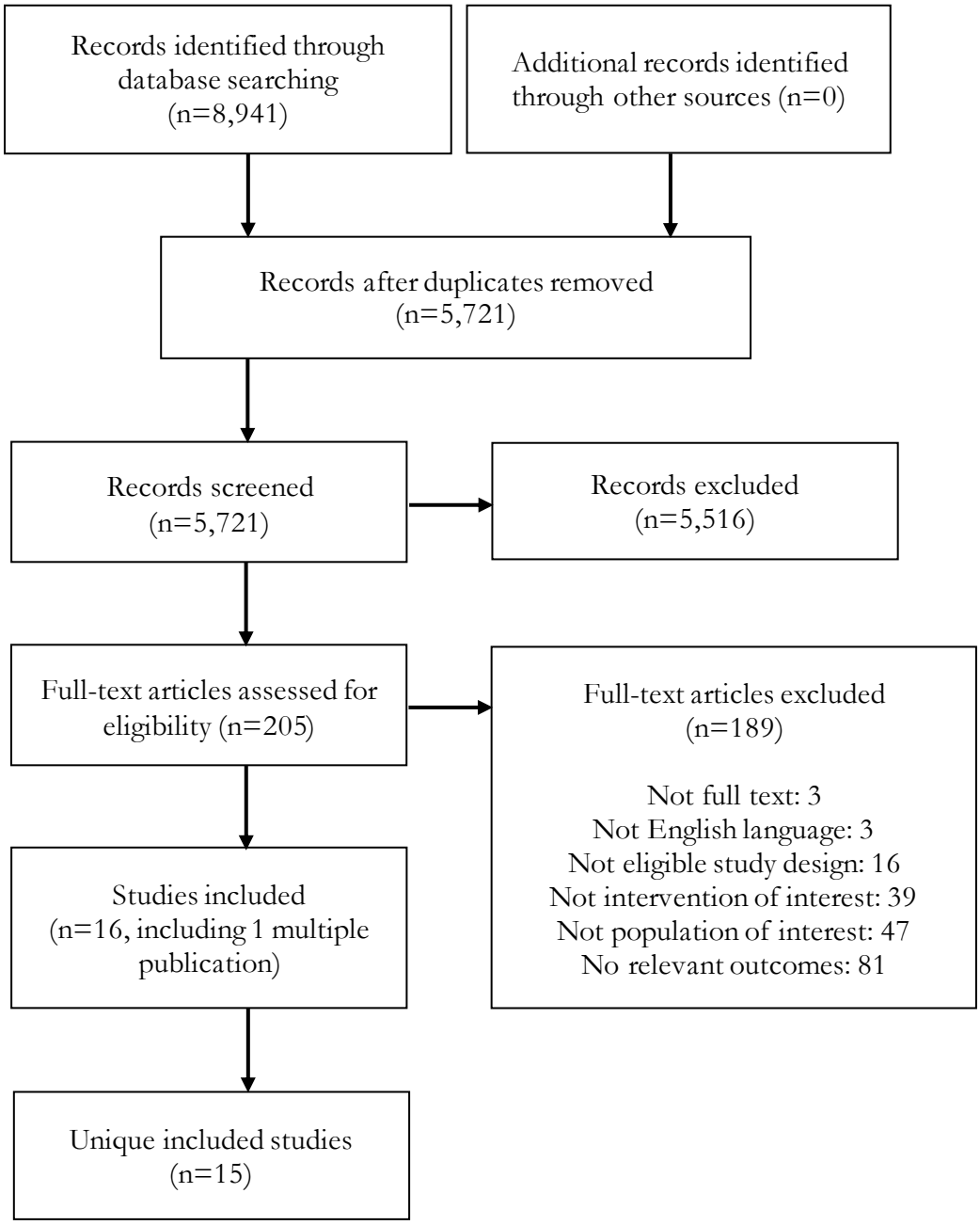


FIGURE E.2: Rapid review 2 flow diagram for primary studies



Note: The 2016 CCO systematic review[25] was also included, which contained five relevant primary studies.[72-76]

FIGURE E.3: Rapid review 3 flow diagram



Appendix F: Clinical Review – Excluded Studies

BOX F.1: Rapid review 1 excluded studies

Not full text (n=10)

Anonymous. MINDACT study results show low risk of local recurrence after 5 years for patients with early breast cancer. *Cancer* 2018;124(17):3466-7.

Beca F, Tsang J, Jensen KC, Allison K, Tse G. The clinicopathologic and genomic features of fibrotic foci in breast cancer-results from the TCGA cohort. *Lab Invest* 2018;98 Suppl 1:50.

Brock J, Lester S, Iorgulescu JB. Filling the TAILORx gap: Survival benefit from chemotherapy using data from the NCDB. *Lab Invest* 2018;98 Suppl 1:52-3.

Dabbs D, Clark B, Serdy K, Bhargava R, Smalley S, Perkins S, et al. The health care value of Oncotype DX for patients with recurrence scores of 10 or less: A value based pathology study of tumor biology with outcomes. *Lab Invest* 2018;98 Suppl 1:56.

Iwata H, Masuda N, Yamamoto Y, Fujisawa T, Toyama T, Kashiwaba M, et al. Association of 21-gene recurrence score results with surgical intervention received after neoadjuvant hormonal therapy: Secondary endpoints of the TransNEOS validation study. *Ann Surg Oncol* 2018;25(2 Suppl 1):35-6.

Lange S, Scheibler F, Fleer D, Windeler J. Interpretation of the results of the MINDACT study and consequent recommendations in the updated ASCO clinical practice guideline. *J Clin Oncol* 2018;36(4):429-30.

Mutai R, Goldvaser H, Shochat T, Peretz I, Sulkes A, Yerushalmi R. Prognostic value of the detection of lymphovascular invasion in hormone receptor-positive early breast cancer in the era of molecular profiling. *Oncology* 2018.

Riba L, Gruner R, Tung N, James T. Oncotype DX recurrence score as a predictor of response to neoadjuvant chemotherapy. *Ann Surg Oncol* 2018;25(2 Suppl 1):34.

Tevis S, Bedrosian I, Bassett R, FitzSullivan E, Barcenas C, Meric-Bernstam F, et al. Evaluation of Oncotype DX as a predictor of nodal burden in clinically node negative breast cancer patients. *Ann Surg Oncol* 2018;25(2 Suppl 1):59.

Veeratterapillay J, Mahtab N, Cresti N, Lee D. Audit of Oncotype DX in the north east-can we improve our practice? *Breast Cancer Res Treat* 2018;167(1):327.

Not prospective study (n=7)

Barcenas CH, Raghavendra A, Sinha AK, Syed MP, Hsu L, Patangan MG Jr, et al. Outcomes in patients with early-stage breast cancer who underwent a 21-gene expression assay. *Cancer* 2017;123(13):2422-31.

Gong C, Tan W, Chen K, You N, Zhu S, Liang G, et al. Prognostic value of a BCSC-associated microRNA signature in hormone receptor-positive HER2-negative breast cancer. *EBioMedicine* 2016;11:199-209.

Meisel J, Zhang C, Neely C, Mendoza P, You S, Han T, et al. Evaluation of prognosis in hormone receptor-positive/HER2-negative and lymph node-negative breast cancer with low Oncotype DX recurrence score. *Clin Breast Cancer* 2018;18(5):347-52.

Natsuhara KH, Losk K, King TA, Lin NU, Camuso K, Golshan M, et al. Impact of genomic assay testing and clinical factors on chemotherapy use after implementation of standardized testing criteria. *Oncologist* 2018.

Rath MG, Uhlmann L, Fiedler M, Heil J, Golatta M, Dinkic C, et al. Oncotype DX® in breast cancer patients: Clinical experience, outcome and follow-up-a case-control study. *Arch Gynecol Obstet* 2018;297(2):443-7.

Wang W, Chen X, Lin L, Fei X, Garfield DH, Hong J, et al. Distribution and clinical utility of the 21-gene Recurrence Score in pure mucinous breast cancer patients: A case-control study. *J Cancer* 2018;9(18):3216-24.

Wen HY, Krystel-Whittemore M, Patil S, Pareja F, Bowser ZL, Dickler MN, et al. Breast carcinoma with an Oncotype Dx recurrence score <18: Rate of distant metastases in a large series with clinical follow-up. *Cancer* 2017;123(1):131-7.

Not population of interest (n=14)

Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, et al. Prognostic and predictive value of the 21-gene Recurrence Score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial. *Lancet Oncol* 2010;11(1):55-65.

Dowsett M, Cuzick J, Wale C, Forbes J, Mallon EA, Salter J, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: A TransATAC study. *J Clin Oncol* 2010;28(11):1829-34.

Filipits M, Nielsen TO, Rudas M, Greil R, Stoger H, Jakesz R, et al. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. *Clin Cancer Res* 2014;20(5):1298-305.

Jensen MB, Lænkholm AV, Nielsen TO, Eriksen JO, Wehn P, Hood T, et al. The Prosigna gene expression assay and responsiveness to adjuvant cyclophosphamide-based chemotherapy in premenopausal high-risk patients with breast cancer. *Breast Cancer Res* 2018;20(1):79.

King TA, Lyman JP, Gonen M, Voci A, De Brot M, Boafo C, et al. Prognostic impact of 21-gene recurrence score in patients with stage IV breast cancer: TBCRC 013. *J Clin Oncol* 2016;34(20):2359-65.

Liu MC, Pitcher BN, Mardis ER, Davies SR, Friedman PN, Snider JE, et al. PAM50 gene signatures and breast cancer prognosis with adjuvant anthracycline- and taxane-based chemotherapy: Correlative analysis of C9741 (Alliance). *NPJ Breast Cancer* 2016;2.

Liu S, Chapman JA, Burnell MJ, Levine MN, Pritchard KI, Whelan TJ, et al. Prognostic and predictive investigation of PAM50 intrinsic subtypes in the NCIC CTG MA.21 phase III chemotherapy trial. *Breast Cancer Res Treat* 2015;149(2):439-48.

Mamounas EP, Tang G, Fisher B, Paik S, Shak S, Costantino JP, et al. Association between the 21-gene Recurrence Score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol* 2010;28(10):1677-83.

Martin M, Brase JC, Ruiz A, Prat A, Kronenwett R, Calvo L, et al. Prognostic ability of EndoPredict compared to research-based versions of the PAM50 risk of recurrence (ROR) scores in node-positive, estrogen receptor-positive, and HER2-negative breast cancer. A GEICAM/9906 sub-study. *Breast Cancer Res Treat* 2016;156(1):81-9.

Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351(27):2817-26.

Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006;24(23):3726-34.

Park KU, Chen Y, Chitale D, Choi S, Ali H, Nathanson SD, et al. Utilization of the 21-gene recurrence score in a diverse breast cancer patient population: Development of a clinicopathologic model to predict high-risk scores and response to neoadjuvant chemotherapy. *Ann Surg Oncol* 2018;25(7):1921-7.

Tamez-Pena JG, Rodriguez-Rojas JA, Gomez-Rueda H, Celaya-Padilla JM, Rivera-Prieto RA, Palacios-Corona R, et al. Radiogenomics analysis identifies correlations of digital mammography with clinical molecular signatures in breast cancer. *PLoS ONE* 2018;13(3):e0193871.

Wolmark N, Mamounas EP, Baehner FL, Butler SM, Tang G, Jamshidian F, et al. Prognostic impact of the combination of recurrence score and quantitative estrogen receptor expression (ESR1) on predicting late distant recurrence risk in estrogen receptor-positive breast cancer after 5 years of tamoxifen: Results from NRG Oncology/National Surgical Adjuvant Breast and Bowel Project B-28 and B-14. *J Clin Oncol* 2016;34(20):2350-8.

No relevant test (n=2)

Asleh K, Gao D, Tu D, Shepherd L, Levine MN, Pritchard K, et al. Basal biomarkers nestin and INPP4b accurately identify intrinsic breast cancer subtype and predict benefit from anthracycline vs. non-anthracycline based treatment in the CCTG MA.5 phase III randomized clinical trial. *Lab Invest* 2018;98 Suppl 1:46.

Goodman CR, Seagle BLL, Kocherginsky M, Donnelly ED, Shahabi S, Strauss JB. 21-gene recurrence score assay predicts benefit of post-mastectomy radiotherapy in T1-2 N1 breast cancer. *Clin Cancer Res* 2018;24(16):3878-87.

No relevant outcomes (n=17)

Bello DM, Russell C, McCullough D, Tierno M, Morrow M. Lymph node status in breast cancer does not predict tumor biology. *Ann Surg Oncol* 2018;25(10):2884-9. Erratum in: *Ann Surg Oncol* 2018 Jul 19, PMID: 30027458.

Dieci MV, Guarneri V, Giarratano T, Mion M, Tortora G, De Rossi C, et al. First prospective multicenter Italian study on the impact of the 21-gene recurrence score in adjuvant clinical decisions for patients with ER positive/HER2 negative breast cancer. *Oncologist* 2018;23(3):297-305.

Ding S, Wu J, Lin C, Chen W, Li Y, Shen K, et al. Predictors for survival and distribution of 21-gene recurrence score in patients with pure mucinous breast cancer: A SEER population-based retrospective analysis. *Clin Breast Cancer* 2018.

Gluz O, Nitz UA, Christgen M, Kates RE, Shak S, Clemens M, et al. West German study group phase III PlanB trial: First prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. *J Clin Oncol* 2016;34(20):2341-9.

Iwata H, Masuda N, Yamamoto Y, Fujisawa T, Toyama T, Kashiwaba M, et al. Validation of the 21-gene test as a predictor of clinical response to neoadjuvant hormonal therapy for ER+, HER2-negative breast cancer: The TransNEOS study. *Breast Cancer Res Treat* 2018;21:21.

Khan MA, Henderson L, Clarke D, Harries S, Jones L. The Warwick experience of the Oncotype DX® Breast Recurrence Score® assay as a predictor of chemotherapy administration. *Breast Care* 2018;13(5):369-72.

Lænkholm AV, Jensen MB, Eriksen JO, Buckingham W, Ferree S, Nielsen TO, et al. The ability of PAM50 risk of recurrence score to predict 10-year distant recurrence in hormone receptor-positive postmenopausal women with special histological subtypes. *Acta Oncol* 2018;57(1):44-50.

Larson KE, Valente SA, Shah C, Tendulkar RD, Cherian S, Abraham J, et al. Oncotype testing in patients undergoing intraoperative radiation for breast cancer. *Mol Clin Oncol* 2018;9(5):535-8.

Mamounas EP, Liu Q, Paik S, Baehner FL, Tang G, Jeong JH, et al. 21-gene recurrence score and locoregional recurrence in node-positive/ER-positive breast cancer treated with chemo-endocrine therapy. *J Natl Cancer Inst* 2017;109(4).

Penault-Llorca F, Filleron T, Asselain B, Baehner FL, Fumoleau P, Lacroix-Triki M, et al. The 21-gene recurrence score® assay predicts distant recurrence in lymph node-positive, hormone receptor-positive, breast cancer patients treated with adjuvant sequential epirubicin- and docetaxel-based or epirubicin-based chemotherapy (PACS-01 trial). *BMC Cancer* 2018;18(1):526.

Schwartzberg BS, Chin DT, Dorn PL, Herron DS, Howell KT, Kemmis TJ, et al. Application of 21-gene recurrence score results and ASTRO suitability criteria in breast cancer patients treated with intraoperative radiation therapy (IORT). *Am J Surg* 2018;216(4):689-93.

Sestak I, Cuzick J, Dowsett M, Lopez-Knowles E, Filipits M, Dubsky P, et al. Prediction of late distant recurrence after 5 years of endocrine treatment: A combined analysis of patients from the Austrian breast and colorectal cancer study group 8 and arimidex, tamoxifen alone or in combination randomized trials using the PAM50 risk of recurrence score. *J Clin Oncol* 2015;33(8):916-22.

Sestak I, Dowsett M, Zabaglo L, Lopez-Knowles E, Ferree S, Cowens J.W., Cuzik K. Factors predicting late recurrence for estrogen receptor-positive breast cancer. *J Natl Cancer Inst* 2013;105:1504-11.

Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med* 2015;373(21):2005-14.

Tadros AB, Wen HY, Morrow M. Breast cancers of special histologic subtypes are biologically diverse. *Ann Surg Oncol* 2018;25(11):3158-64.

Torres S, Trudeau M, Gandhi S, Warner E, Verma S, Pritchard KI, et al. Prospective evaluation of the impact of the 21-gene recurrence score assay on adjuvant treatment decisions for women with node-positive breast cancer in Ontario, Canada. *Oncologist* 2018;23(7):768-75.

Williams AD, Reyes SA, Arlow RL, Tchou J, De La Cruz LM. Is age trumping genetic profiling in clinical practice? Relationship of chemotherapy recommendation and Oncotype DX recurrence score in patients aged < 50 years versus ≥ 50 years, and trends over time. *Ann Surg Oncol* 2018;25(10):2875-83.

BOX F.2: Rapid review 2 excluded studies

Not eligible study design (n=3)

Harris LN, Ismaila N, McShane LM, Andre F, Collyar DE, Gonzalez-Angulo AM, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2016;34(10):1134-50.

McVeigh TP, Kerin MJ. Clinical use of the Oncotype DX genomic test to guide treatment decisions for patients with invasive breast cancer. *Breast Cancer* 2017 29;9:393-400.

Siow ZR, De Boer RH, Lindeman GJ, Mann GB. Spotlight on the utility of the Oncotype DX® breast cancer assay. *Int J Womens Health* 2018;10:89-100.

Primary study: not prospective (n=6)

Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, Duijm-de Carpentier M, Putter H, Liefers G-J, et al. Treatment decisions and the impact of adverse events before and during extended endocrine therapy in postmenopausal early breast cancer. *Eur J Cancer* 2018;95:59-67.

Bonneterre J, Prat A, Galvan P, Morel P, Giard S. Value of a gene signature assay in patients with early breast cancer and intermediate risk: A single institution retrospective study. *Curr Med Res Opin* 2016;32(5):835-9.

Chin-Lenn L, De Boer RH, Segelov E, Marx GM, Hughes TM, McCarthy NJ, et al. The impact and indications for Oncotype DX on adjuvant treatment recommendations when third-party funding is unavailable. *Asia Pac J Clin Oncol* 2018;14(6):410-6.

Khan MA, Henderson L, Clarke D, Harries S, Jones L. The Warwick experience of the Oncotype DX® Breast Recurrence Score® assay as a predictor of chemotherapy administration. *Breast Care* 2018;13(5):369-72.

Obley A, Mosbaek C, King V, Shaffer W. *Coverage guidance: Genome expression profiling for breast cancer*. Portland (OR): Center for Evidence-Based Policy, Oregon Health & Science University; 2017.

Panattoni L, Lieu TA, Jayasekera J, O'Neill S, Mandelblatt JS, Etzioni R, et al. The impact of gene expression profile testing on confidence in chemotherapy decisions and prognostic expectations. *Breast Cancer Res Treat* 2018. doi: 10.1007/s10549-018-4988-3.

No relevant test (n=1)

Zeng Y, Li Q, Qin T, Li S, Jin L, Wu J, et al. Impact of a 21-gene recurrence score test on the choice of adjuvant chemotherapy for hormone receptor-positive early-stage breast cancer: A prospective study. *Anticancer Res* 2017;37(8):4539-47.

No relevant outcomes (n=3)

Bartlett JMS, Bayani J, Marshall A, Dunn JA, Campbell A, Cunningham C, et al. Comparing breast cancer multiparameter tests in the OPTIMA prelim trial: No test is more equal than the others. *J Natl Cancer Inst* 2016;108(9). doi: 10.1093/jnci/djw050.

Narain T, Adcock L. *Gene expression tests for women with early stage breast cancer: A review of clinical utility and cost-effectiveness*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2017.

Partridge AH, Sepucha K, O'Neill A, Miller KD, Baker E, Dang CT, et al. Does biomarker information impact breast cancer patients' preferences and physician recommendation for adjuvant chemotherapy? *Breast Cancer Res Treat* 2017;165(3):545-53.

Combined node-negative and node-positive data (n=6) (see Appendix I)

Evans CN, Brewer NT, Vadaparampil ST, Boisvert M, Ottaviano Y, Lee MC, et al. Impact of genomic testing and patient-reported outcomes on receipt of adjuvant chemotherapy. *Breast Cancer Res Treat* 2016;156(3):549-55.

Kuchel A, Robinson T, Comins C, Shere M, Varughese M, Sparrow G, et al. The impact of the 21-gene assay on adjuvant treatment decisions in oestrogen receptor-positive early breast cancer: A prospective study. *Br J Cancer* 2016;114(7):731-6.

Leung RCY, Yau TCC, Chan MCM, Chan SWW, Chan TWC, Tsang YY, et al. The impact of the Oncotype DX breast cancer assay on treatment decisions for women with estrogen receptor-positive, node-negative breast carcinoma in Hong Kong. *Clin Breast Cancer* 2016;16(5):372-8.

Martínez del Prado P, Alvarez-López I, Domínguez-Fernández S, Plazaola A, Ibarrondo O, Galve-Calvo E, et al. Clinical and economic impact of the 21-gene recurrence score assay in adjuvant therapy decision making in patients with early-stage breast cancer: Pooled analysis in 4 Basque Country university hospitals. *Clinicoecon Outcomes Res* 2018;10:189-99.

Pestalozzi BC, Tausch C, Dedes KJ, Rochlitz C, Zimmermann S, von Moos R, et al. Adjuvant treatment recommendations for patients with ER-positive/HER2-negative early breast cancer by Swiss tumor boards using the 21-gene recurrence score (SAKK 26/10). *BMC Cancer* 2017;17(1):265.

Voelker HU, Frey L, Strehl A, Weigel M. Practical consequences resulting from the analysis of a 21-multigene array in the interdisciplinary conference of a breast cancer center. *Int J Breast Cancer* 2018;2047089.

BOX F.3: Rapid review 3 excluded studies

Not full text (n=3)

Hughes R, Mitchell CR, Bishop RS, Fotheringham I. Health-state utility values in breast and prostate cancer measured using the EQ-5D: A systematic review of the literature. *Value Health* 2014;17(7):A645-6.

Kunisawa S, Shimozuma K, Tange C, Maeda S, Imanaka Y, Watanabe T, et al. Effects of adverse events on quality of life scores in a randomized clinical trial of adjuvant chemotherapy for breast cancer: N-Sas Bc 02. *Value Health* 2015;18(7):A473.

Matisakova I, Bielik J, Kormancova R, Bystricky B, Melus V. Quality of life in patients with breast cancer in Slovakia. *Value Health* 2015;18(7):A475.

Not English language (n=3)

Buyukakincak O, Akyol Y, Ozen N, Ulus Y, Canturk F, Tander B, et al. Quality of life in patients with breast cancer at early postoperative period: Relationship to shoulder pain, handgrip strength, disability, and emotional status. *Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi* 2014;60(1):1-6.

Ruchalla E. Oncology - quality of life in women with early-stage breast cancer: Data from text and soft trials. *Geburtshilfe und Frauenheilkunde* 2016;76(1):10-1.

Trejo-Ochoa JL, Maffuz-Aziz A, Said-Lemus FM, Dominguez-Reyes CA, Hernandez-Hernandez B, Villegas-Carlos F, et al. Impact on quality of life after reconstructive surgery breast cancer treatment. *Ginecologia y Obstetricia de Mexico* 2013;81(9):510-8.

Not eligible study design (n=16)

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Appendix G: Rapid Review 1 – Evidence Summary Tables

TABLE G.1: Study characteristics

Study	Study category Study design	Country Enrolment Follow up	Treatment assignment by risk stratification	Treatment description	Source(s) of funding	Conflicts of interest
Oncotype DX						
Sparano et al. (2018)[13]	Category A RCT (TAILORx)	United States 2006–2010 9 years	LR patients received ET IR patients randomized ET or ET+CT HR patients received ET+CT	CT: Docetaxel/ cyclophosphamide (56%) and anthracycline-based regimens (36%); treatment length: NR ET: Median: 5.4 years; premenopausal: tamoxifen with/without aromatase inhibitor (78%) and ovarian suppression regimens (13%); postmenopausal: aromatase inhibitor regimens (91%)	NCI-NIH, Canadian Cancer Society Research Institute, Breast Cancer Research Foundation, Komen Foundation, Breast Cancer Research Stamp, Genomic Health	2 of 30 co-authors are consultants with and/or hold patents issued to Genomic Health
Geyer et al. (2018)[36]	Category B Retrospective analysis of an RCT (NSABP B-20)	United States 1988–1993 12 years	LR, IR, and HR patients received ET or ET+CT	CT: NR ET: 5 years of tamoxifen plus methotrexate and fluorouracil, with/without cyclophosphamide	NCI-NIH	4 of 11 co-authors are employees, consultants, shareholders, and/or have received honoraria from Genomic Health and/or Biotheranostrics
Nitz et al. (2017)[37]	Category C Prospective study (PlanB study)	Germany 2009–2011 5 years	LR patients received ET IR and HR patients received ET+CT	CT: Epirubicin/ cyclophosphamide with docetaxel, or docetaxel/ cyclophosphamide; treatment length: NR ET: NR	Genomic Health, Sanofi Aventis, Amgen	7 of 21 co-authors are employees, shareholders, and/or have received honoraria or grant support from Genomic Health, NanoString Technologies, Agendia, Amgen, AstraZeneca, Celegne, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi Aventis, and/or Western German Study Group

Study	Study category Study design	Country Enrolment Follow up	Treatment assignment by risk stratification	Treatment description	Source(s) of funding	Conflicts of interest
Ibraheem et al. (2018)[38]	Category C Retrospective analysis of prospective study (NCDB database)	United States 2010–2014 5 years	IR patients received ET or ET+CT	CT: NR ET: NR	Breast Cancer Research Foundation, National Institute on Aging	No authors declared conflicts
Roberts et al. (2017)[39]	Category C Retrospective analysis of prospective study (SEER database)	United States 2004–2012 5 years	LR, IR, and HR patients received ET or ET+CT	CT: NR ET: NR	NCI-NIH	2 of 4 co-authors are employees and shareholders of Genomic Health
Stemmer et al. (2017)[40, 41]	Category C Retrospective analysis of prospective study (TPIO database)	Israel 2006–2011 5 years	LR, IR, and HR patients received ET or ET+CT	CT: Predominantly anthracycline-based and taxane-based regimens; treatment length: NR ET: NR	Teva Pharmaceuticals	9 of 25 co-authors are employees, consultants, shareholders, have received honoraria or grant support from, and/or hold patents issued to Genomic Health and/or Teva Pharmaceuticals
Petkov et al. (2016)[42]	Category C Retrospective analysis of prospective study (SEER database)	United States 2004–2011 5 years	LR, IR, and HR patients received ET or ET+CT	CT: NR ET: NR	NCI-NIH	4 of 24 co-authors are employees of Genomic Health
Prosigna						
Gnant et al. (2015)[43]	Category B Retrospective analysis of RCTs (ABCSG-8 and TransATAC)	United Kingdom 1996–2015 10 years	LR, IR, and HR patients received ET	CT: NA ET: 5 years of tamoxifen or aromatase inhibitor (anastrozole)	AstraZeneca, NanoString Technologies	11 of 17 co-authors are employees, consultants, shareholders, have received honoraria, grant support, or other fees from, and/or hold patents issued to, Genomic Health, NanoString Technologies, Accelsiors, Agendia, AstraZeneca, Bioclassifier LLC, Breakthrough Breast Cancer, GlaxoSmithKline, Novartis, Pfizer, Roche, Sanofi-Aventis, Sividon Diagnostics, and/or Smith Medical

Study	Study category Study design	Country Enrolment Follow up	Treatment assignment by risk stratification	Treatment description	Source(s) of funding	Conflicts of interest
Lænkholm et al. (2018)[44]	Category C Retrospective analysis of prospective study (DBCG database)	Denmark 2000–2003 10 years	LR, IR, and HR patients received ET	CT: NA ET: 5 years of tamoxifen or aromatase inhibitor (anastrozole)	NanoString Technologies	13 of 15 co-authors are employees, consultants, shareholders, have received honoraria or grant support from and/or hold patents issued to NanoString Technologies, AcceleratedDX, AstraZeneca, Bioclassifier, Biomedical, Celegne, Dako/Agilent Technologies, Faxitron, Genopix, Guardant, Illumina, IncellDx, Kypha, Medivation, Novartis, Novo Nordisk, Pfizer, Pierre Fabre, Roche, SysMed, Visiopharm, and/or Verax
Ohnstad et al. (2017)[45]	Category C Retrospective analysis of prospective study (Oslo1 study)	Norway 1995–1998 15 years	LR, IR, and HR patients received no ET, ET, or ET+CT	CT: 5 months of cyclophosphamide, methotrexate, and fluorouracil ET: 5 years of tamoxifen	South-Eastern Norway Regional Health Authority, Norwegian Cancer Society	No authors declared conflicts
Both Oncotype DX and Prosigna						
Sestak et al. (2018)[46]	Category B Retrospective analysis of an RCT (TransATAC trial)	United Kingdom 2009–2015 10 years	LR, IR, and HR patients received ET	CT: NA ET: 5 years of tamoxifen or aromatase inhibitor (anastrozole)	Biomedical Research Centre-NIH, Royal Marsden, Breast Cancer Now, Cancer Research UK	7 of 12 co-authors are employees, consultants, shareholders, and/or have received honoraria or grant support from Genomic Health, NanoString Technologies, Agendia, Amgen, Biotheranostrics, Genoptix, Myriad Genetics, and/or Sividion
Dowsett et al. (2013)[47]	Category B Retrospective analysis of an RCT (TransATAC trial)	United Kingdom NR 10 years	LR, IR, and HR patients received ET	CT: NA ET: 5 years of tamoxifen (49%) or aromatase inhibitor (anastrozole) (51%)	Breakthrough Breast Cancer, Biomedical Research Centre-NIH, Cancer Research UK, NanoString Technologies	6 of 10 co-authors are employees, consultants, shareholders, and/or have received honoraria or grant support from or provided expert testimony to Genomic Health, NanoString Technologies, and/or AstraZeneca

ABCSG: Austrian Breast and Colorectal Cancer Study Group; CT: chemotherapy; DBCG: Danish Breast Cancer Group; ET: endocrine therapy; HR: high risk; IR: intermediate risk; LR: low risk; NA: not applicable; NCDB: National Cancer Database; NCI: National Cancer Institute; NIH: National Institutes of Health; NR: not reported; NSABP: National Surgical Adjuvant Breast and Bowel Project; RCT: randomized controlled trial; SEER: Surveillance, Epidemiology, and End Results; TAILORx: Trial Assigning Individualized Options for Treatment; TPIO: Teva Pharmaceutical Industries Oncotest; TransATAC: Translational Study of Anastrozole or Tamoxifen Alone or Combined

TABLE G.2: Patient characteristics

Study Risk categories and cut-offs	Patients analyzed, overall and by risk category, n (%)[a]	Patients who receive CT, overall and by risk category, n (%)	Age, years	Meno-pause status, %	Hormone receptor status, %	Node status, %	Tumour grade, %	Tumour size (cm), %	Mastect-omy type, %
Oncotype DX									
Sparano et al. (2018)[13] LR (RS ≤10) IR (RS 11–25) HR (RS ≥26)	n=9,719[b] 1,619 (17%) 6,711 (69%) 1,389 (14%)	n=4,197 (43%) 8 (1%) 2,889 (43%) 1,300 (94%)	Median: 56 (range: 23–75)	34% pre, 66% post	99% ER+, 88% PR+, 100% HER2−	100% N0	26% grade 1, 54% grade 2, 17% grade 3, 3% unknown	Median: 1.5 (IQR: 1.2–2.3)	72% partial, 28% total
Geyer et al. (2018)[36] LR (RS ≤17) IR (RS 18–30) HR (RS ≥31)	n=569 347 (61%) 125 (22%) 97 (17%)	n=365 (64%) 213 (61%) 83 (66%) 69 (71%)	Median: 51 (range: 28–74)	NR	100% ER+, ≥86% PR+, 100% HER2−	100% N0	13% grade 1, 52% grade 2, 24% grade 3, 11% unknown	17% ≤1.0, 50% 1.1–2.0, 30% 2.1–4.0, 3% ≥4.1, 1% unknown	NR
Nitz et al. (2017)[37] LR (RS ≤11) IR (RS 12–25) HR (RS ≥26) Unknown	n=2,642 459 (17%) 1,544 (58%) 550 (21%) 89 (3%)	n=1,970 (75%) NR (14%) NR (79%) NR (90%) NR	Median: 56 (range: 25–77)	NR	≥80% ER+, ≥66% PR+, 100% HER2−	59% N0, 35% N1	5% grade 1, 62% grade 2, 31% grade 3, 2% unknown	Median 1.9 (range 0.1–13.0)	NR
Ibraheem et al. (2018)[38] IR (RS 11–30)	n=73,185 73,185 (100%)	n=17,858 (24%) 17,858 (24%)	Mean: 58 (SD: 10.5)	NR	100% ER+, 92% PR+, 100% HER2−	82% N0 17% N1	27% grade 1, 54% grade 2, 14% grade 3, 5% unknown	24% ≤1.0, 51% 1.1–2.0, 24% 2.1–5.0, 1% ≥5.1	68% partial, 32% total
Roberts et al. (2017)[39] LR (RS ≤17) IR (RS 18–30) HR (RS ≥31)	n=6,483 3,790 (59%) 2,263 (35%) 430 (6%)	n=NR NR NR NR	22% <50, 78% ≥51	NR	100% ER+, 92% PR+, 100% HER2−	0% N0, 100% N1 (includes N1mi)	28% grade 1, 54% grade 2, 16% grade 3, 2% unknown	13% <1.0, 48% 1.0–1.9, 25% 2.0–2.9, 8% 3.0–3.9, 7% ≥4.0	NR
Stemmer et al. (2017)[40, 41] LR (RS ≤17) IR (RS 18–30) HR (RS ≥31)	n=2,510 1,259 (50%) 991 (40%) 260 (10%)	n=541 (22%) 39 (3%) 276 (28%) 226 (87%)	Median: 61 (IQR: 52-67)	NR	100% ER+, PR+ NR, 100% HER2−	72% N0, 28% N1 (includes N1mi)	14% grade 1, 51% grade 2, 16% grade 3, 18% unknown	Median: 1.6 (IQR: 1.2–2.1)	NR

Study Risk categories and cut-offs	Patients analyzed, overall and by risk category, n (%)[a]	Patients who receive CT, overall and by risk category, n (%)	Age, years	Meno-pause status, %	Hormone receptor status, %	Node status, %	Tumour grade, %	Tumour size (cm), %	Mastect-omy type, %
Petkov et al. (2016)[42] LR (RS ≤17) IR (RS 18–30) HR (RS ≥31)	n=44,825 24,454 (55%) 16,821 (38%) 3,550 (8%)	n=10,754 (24%) 2,162 (9%) 6,049 (36%) 2,487 (70%)	27% <50, 73% ≥51	NR	100% HR+,[c] 100% HER2−	90% N0, 10% N1 (includes N1mi)	28% grade 1, 53% grade 2, 17% grade 3, 3% unknown	55% ≤1.0, 52% 1.1–2.0, 20% 2.1–4.0, 3% >4.0	NR
Prosigna									
Gnant et al. (2015)[43] LR[d] IR[d] HR[d]	n=2,197 NR NR NR	n=0 (0%)	NR	100% post	100% HR+,[c] 93% HER2−	75% N0, 25% N1	22% grade 1, 79% grade 2	17% ≤1.0, 54% 1.0–2.0, 23% 2.0–3.0, 6% ≥3.0	NR
Lænkholm et al. (2018)[44] LR[e] IR[e] HR[e]	n=2,558 720 (28%) 763 (30%) 1,075 (42%)	n=0 (0%)	Median: 63 (range: 50–89)	100% post	100% ER+, PR+ NR, 100% HER2−	46% N0, 54% N1	25% grade 1, 52% grade 2, 12% grade 3, 10% unknown	9% ≤1.0, 43% 1.1–2.0, 34% 2.1–3.0, 14% >3.0	NR
Ohnstad et al. (2017)[45] LR (ROR ≤40) IR (ROR 41–60) HR (ROR ≥61)	n=653 180 (38%) 108 (23%) 188 (40%)	n=158 (24%)	Median: 58 (range: 28–93)	NR	73% ER+,[f] PR+ NR, 89% HER2−	64% N0, 32% N1	23% grade 1, 49% grade 2, 27% grade 3	58% ≤2.0, 36% 2.1–5.0, 4% >5.0, 3% unknown	NR
Both Oncotype DX and Prosigna									
Sestak et al. (2018)[46] <u>Oncotype DX</u> LR (RS ≤17) IR (RS 18–31) HR (RS ≥32) <u>Prosigna</u> LR (ROR ≤26) IR (ROR 27–68) HR (ROR ≥69)	n=774 479 (62%) 214 (28%) 81 (11%) 333 (43%) 236 (31%) 205 (27%)	n=0 (0%)	Mean: 64 (SD: 8.0)	100% post	100% ER+, PR+ NR, 100% HER2−	76% N0, 24% N1	23% grade 1, 59% grade 2, 18% grade 3	Mean: 1.9 (SD: 0.94)	NR

Study Risk categories and cut-offs	Patients analyzed, overall and by risk category, n (%)[a]	Patients who receive CT, overall and by risk category, n (%)	Age, years	Meno-pause status, %	Hormone receptor status, %	Node status, %	Tumour grade, %	Tumour size (cm), %	Mastect-omy type, %
Dowsett et al. (2013)[47]	n=739	n=0 (0%)	Mean: 64 (SD: 8.3)	100% post	100% ER+, PR+ NR, 88% HER2−	100% N0	21% grade 1, 60% grade 2, 19% grade 3	14% ≤1.0, 52% 1.0–2.0, 25% 2.0–3.0, 9% >3.0	59% partial, 41% total
Oncotype DX									
LR (RS NR)	434 (59%)								
IR (RS NR)	243 (33%)								
HR (RS NR)	62 (8%)								
Prosigna									
LR (ROR NR)	428 (59%)								
IR (ROR NR)	192 (26%)								
HR (ROR NR)	119 (16%)								

[a] Only N0 or N1 patients were counted.

[b] 10,273 patients were enrolled.

[c] ER and PR status not reported.

[d] Risk cut-offs differed by node status: LR (N0: ROR ≤48; N1: ROR ≤29), IR (N0: ROR 49–67; N1: ROR 30–49), HR (N0: ROR ≥68; N1: ROR ≥50).

[e] Risk cut-offs differed by node status: LR (N0: ROR ≤40; 1 node: ROR ≤35; 2 nodes: ROR ≤25; 3 nodes: NA), IR (N0: ROR 41–60; 1 node: ROR 36–55; 2 nodes: ROR 26–45; 3 nodes: ROR ≤25), HR (N0: ROR ≥61; 1 node: ROR ≥56; 2 nodes: ROR ≥46; 3 nodes: ROR ≥26).

[f] Outcome data were extracted only for the subgroup of HR+ patients.

cm: centimetres; CT: chemotherapy; ER+ estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; HR: high risk; HR+: hormone receptor positive (ER+ or PR+); IQR: interquartile range; IR: intermediate risk; LR: low risk; n: number; N0: node-negative; N1: node-positive (1–3 nodes); N1mi: micrometastases in nodes; NA: not applicable; NR: not reported; post: postmenopausal; PR+: progesterone receptor positive; pre: premenopausal; ROR: risk of recurrence (calculated using Prosigna); RS: recurrence score (calculated using Oncotype DX); SD: standard deviation

TABLE G.3: Prognostic ability of Oncotype DX in node-negative patients

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or loco-regional recurrence, %	Overall survival, %	Disease-free survival, %
Category B study: Sestak et al. (2018)[46]						
RS ≤17: ET RS 18–31: ET RS ≥32: ET	374 156 61	10 years	94.1 [90.9, 96.2] 83.3 [76.0, 88.5] *p*=NR 72.8 [58.5, 82.7]	--	--	--
RS ≤17 vs. 18–31 or ≥32[a]			HR=0.59 [0.49, 0.71], *p*<0.05	--	--	--
RS 18–31 vs. ≥32			HR=NR	--	--	--
Category B study: Dowsett et al. (2013)[47]						
Low RS (NR): ET Intermediate RS (NR): ET High RS (NR): ET	434 243 62	10 years	94.5% (NR)[b] 83.6% (NR)[b] *p*=NR 69.1% (NR)[b]	--	--	--
RS ≤17 vs. ≥32			HR=0.15 (NR), *p*=NR	--	--	--
RS ≤17 vs. 18–31			HR=NR	--	--	--
RS 18–31 vs. ≥32			HR=NR	--	--	--
Category C study: Nitz et al. (2017)[37]						
RS ≤11: ET RS 12–25: ET+CT RS ≥26: ET+CT	248 661 283	5 years	--	--	99.2 [98.0, 100.0] 98.3 [97.0, 99.5] *p*=NR 96.7 [94.4, 99.0]	94.0 (NR)[b] 95.3 (NR)[b] *p*=NR 88.3[b]
RS ≤11 vs. ≥26			--	--	HR=NR, *p*<0.05	HR=NR, *p*<0.05
RS ≤11 vs. 12–25			--	--	HR=NR, NS	HR=NR, NS
RS 12–25 vs. ≥26			--	--	HR=NR, *p*<0.05	HR=NR, *p*<0.05
Category C study: Stemmer et al. (2017)[40]						
RS ≤10: ET RS 11–25: ET	304 1,037	5 years	99.0 [96.9, 99.7] 98.7 [97.8, 99.2] *p*=NS	--	100.0 [100.0, 100.0] 99.6 [98.1, 99.8] *p*=NS	--
RS ≤10 vs. 11–25			HR=NR, NS	--	HR=NR, NS	--

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or loco-regional recurrence, %	Overall survival, %	Disease-free survival, %
RS ≤17: ET or ET+CT RS 18–30: ET or ET+CT RS ≥31: ET or ET+CT	880 733 188	5 years	99.2 [98.3, 99.6] 97.0 [95.5, 98.0] p<0.001 91.4 [86.3, 94.6]	--	100.0 [100.0, 100.0] 99.1 [98.1, 99.6] p<0.001 93.8 [89.1, 96.5]	--
RS ≤17 vs. ≥31			Adjusted HR=0.17 [0.08, 0.39], p<0.05	--	HR=NR	--
RS ≤17 vs. 18-30			Adjusted HR=0.50 [0.23, 1.03], NS	--	HR=NR	--
RS 18–30 vs. ≥31			HR=NR	--	HR=NR	--
Category C study: Petkov et al. (2016)[42]						
RS ≤11: ET or ET+CT RS 12–25: ET or ET+CT RS ≥26: ET or ET+CT	7,281 26,462 6,391	5 years	--	--	--	99.6 [99.4, 99.8] 99.3 [99.2, 99.4] p<0.001 96.4 [95.6, 97.0]
RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
RS ≤17: ET or CET RS 18–30: ET or CET RS ≥31: ET or CET	20,123 14,494 3,051	5 years	--	--	--	99.6 [99.4, 99.7] 98.6 [98.3, 98.9] p<0.001 95.6 [94.4, 96.6]
RS ≤17 vs. ≥31			--	--	--	HR=0.09 [0.07, 0.13], p<0.05 (adjusted HR=0.13 [0.09, 0.19], p<0.05)
RS ≤17 vs. 18–30			--	--	--	HR=0.32 [0.23, 0.43], p<0.05 (adjusted HR=0.33 [0.24, 0.48], p<0.05)
RS 18–30 vs. ≥31			--	--	--	HR=NR

Note: All measures of variance are 95% confidence intervals.

[a] Comparator group unclear.

[b] One researcher extracted these data from the paper's figure using WebPlotDigitizer v4.1.

CT: chemotherapy; ET: endocrine therapy; HR: hazard ratio; NR: not reported; NS: not significant; p: p-value statistic; RS: recurrence score

TABLE G.4: Prognostic ability of Oncotype DX in node-negative patients (subgroup analysis: age)

Sub-group	Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Category C study: Petkov et al. (2016)[42]							
Age <40 years	RS ≤11: ET or ET+CT RS 12–25: ET or ET+CT RS ≥26: ET or ET+CT	682 637 161	5 years	--	--	--	100 ± 0.0 99.8 ± 0.2 94.8 ± 3.2 *p*=0.001
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age 40–49 years	RS ≤11: ET or ET+CT RS 12–25: ET or ET+CT RS ≥26: ET or ET+CT	5,185 3,550 615	5 years	--	--	--	99.8 ± 0.1 98.9 ± 0.3 98.0 ± 0.8 *p*<0.001
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age 50–59 years	RS ≤11: ET or ET+CT RS 12–25: ET or ET+CT RS ≥26: ET or ET+CT	6,799 4,924 1,021	5 years	--	--	--	99.8 ± 0.1 98.7 ± 0.3 96.9 ± 0.8 *p*<0.001
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age 60–69 years	RS ≤11: ET or ET+CT RS 12–25: ET or ET+CT RS ≥26: ET or ET+CT	6,471 4,438 1,004	5 years	--	--	--	99.4 ± 0.1 98.7 ± 0.3 94.8 ± 1.0 *p*<0.001
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age 70–79 years	RS ≤11: ET or ET+CT RS 12–25: ET or ET+CT RS ≥26: ET or ET+CT	2,360 1,439 374	5 years	--	--	--	98.8 ± 0.4 97.7 ± 0.6 89.6 ± 3.1 *p*<0.001
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age ≥80 years	RS ≤11: ET or ET+CT RS 12–25: ET or ET+CT RS ≥26: ET or ET+CT	263 164 47	5 years	--	--	--	99.6 ± 0.4 92.7 ± 2.5 78.4 ± 8.8 *p*=0.001
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR

Note: All measures of variance are standard errors.

CT: chemotherapy; ET: endocrine therapy; HR: hazard ratio; NR: not reported; *p*: *p*-value statistic; RS: recurrence score

TABLE G.5: Prognostic ability of Prosigna in node-negative patients

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Category B study: Sestak et al. (2018)[46]						
ROR ≤26: ET ROR 27–68: ET ROR ≥69: ET	318 178 95	10 years	97.0 [94.2, 98.4] 85.9 [79.2, 90.6] *p*=NR 67.6 [56.2, 76.6]	--	--	--
ROR ≤26 vs. 27–68 or ≥69[a]			HR=0.39 [0.30, 0.51], *p*<0.05	--	--	--
ROR 27–68 vs. ≥69			HR=NR	--	--	--
Category B study: Dowsett et al. (2013)[47]						
Low ROR (NR): ET Intermediate ROR (NR): ET High ROR (NR): ET	428 192 119	10 years	95.0% (NR)[b] 86.8% (NR)[b] *p*=NR 69.6% (NR)[b]	--	--	--
Low vs. high ROR			HR=0.14 (NR), *p*=NR	--	--	--
Low vs. intermediate ROR			HR=NR	--	--	--
Intermediate vs. high ROR			HR=NR	--	--	--
Category B study: Gnant et al. (2015)[43]						
ROR ≤48: ET ROR 49–67: ET ROR ≥68: ET	NR NR NR	10 years	95.1 [93.6, 96.3] 85.0 [80.8, 88.4] *p=NR* 79.9 [72.3, 85.3]	--	--	--
ROR ≤48 vs. ≥68			HR=NR, *p<0.001*	--	--	--
ROR ≤48 vs. 49–67			HR=NR	--	--	--
ROR 49–67 vs. ≥68			HR=NR	--	--	--
Category C study: Lænkholm et al. (2018)[44]						
ROR ≤40: ET ROR 41–60: ET ROR ≥61: ET	361 375 427	10 years	95.0 [92.0, 97.1] 92.7 [89.4, 95.2] *p*=NR 82.2 [78.0, 86.0]	--	--	--
ROR ≤40 vs. ≥61			HR=NR, *p*<0.001	--	--	--
ROR ≤40 vs. 41–60			HR=NR	--	--	--
ROR 41–60 vs. ≥61			HR=NR	--	--	--

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Category C study: Ohnstad et al. (2017)[45]						
ROR ≤40: ET ROR 41–60: ET ROR ≥61: ET	17 27 22	8 years	88% (NR)[b] 77% (NR)[b] *p*=NS 74% (NR)[b]	--	--	--
ROR ≤40 vs. ≥61			HR=NR	--	--	--
ROR ≤40 vs. 41–60			HR=NR	--	--	--
ROR 41–60 vs. ≥61			HR=NR	--	--	--
ROR ≤40: ET ROR 41–60: ET ROR ≥61: ET	17 29 23	15 years	--	--	--	93% (NR)[b] 88% (NR)[b] *p*=0.03 63% (NR)[b]
ROR ≤40 vs. ≥61			--	--	--	HR=NR, *p*<0.05
ROR ≤40 vs. 41–60			--	--	--	HR=NR
ROR 41–60 vs. ≥61			--	--	--	HR=NR, *p*<0.05

Note: All measures of variance are 95% confidence intervals.

[a] Comparator group unclear.

[b] One researcher extracted these data from the paper's figure using WebPlotDigitizer v4.1.

ET: endocrine therapy; HR: hazard ratio; NR: not reported; NS: not significant; *p*: *p*-value statistic; ROR: risk of recurrence

TABLE G.6: Prognostic ability of Oncotype DX compared with Prosigna in node-negative patients

Comparison	# of patients	Follow up	Freedom from distant recurrence	Freedom from distant or locoregional recurrence	Overall survival	Disease-free survival
Category B study: Sestak et al. (2018)[46]						
Oncotype DX vs. Prosigna	591	10 years	$p<0.05$[a]	--	--	--

[a] Prosigna significantly more prognostic than Oncotype DX.

p: *p*-value statistic

TABLE G.7: Prognostic ability of Oncotype DX in node-positive (N1) patients

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Category B study: Sestak et al. (2018)[46]						
RS ≤17: ET RS 18–31: ET RS ≥32: ET	105 58 20	10 years	80.6 [70.5, 87.5] 70.9 [56.9, 81.1] *p*=NR 62.0 [35.9, 80.0]	--	--	--
RS ≤17 vs. 18–31 or ≥32[a]			HR=0.72 [0.54, 0.95], *p*<0.05	--	--	--
RS 18–31 vs. ≥32			HR=NR	--	--	--
Category C study: Roberts et al. (2017)[39]						
RS ≤17: ET or ET+CT RS 18–30: ET or ET+CT RS ≥31: ET or ET+CT	3,790 2,263 430	5 years	--	--	92.1 ± 0.8 90.9 ± 1.0 *p*<0.001 81.7 ± 2.8	98.8 ± 0.3 97.3 ± 0.6 *p*<0.001 88.5 ± 2.4
RS ≤17 vs. 18–30 vs. ≥31			--	--	HR=NR	HR=NR
Category C study: Stemmer et al. (2017)[41]						
RS ≤17: ET or ET+CT RS 18–30: ET or ET+CT RS ≥31: ET or ET+CT	379 258 72	5 years	96.8 [94.4, 98.2] 93.7 [89.9, 96.1] *p*<0.001 83.1 [72.1, 90.0]	--	99.5 [97.9, 99.9] 96.6 [93.3, 98.3] *p*<0.001 94.3 [85.6, 97.8]	--
RS ≤17 vs. ≥31			HR=0.19 [0.09, 0.40], *p*<0.05 (adjusted HR=0.23 [0.11, 0.50], *p*<0.05)	--	HR=NR	--
RS ≤17 vs. 18–30			HR=0.39 [0.20, 0.79], *p*<0.05 (adjusted HR=0.42 [0.20, 0.86], *p*<0.05)	--	HR=NR	--
RS 18–30 vs. ≥31			HR=NR	--	HR=NR	--
RS ≤17: ET RS 18–30: ET	342 153	5 years	97.3 [94.9, 98.6] 90.1 [84.1, 93.9] *p*<0.001	--	99.4 [97.7, 99.9] 95.1 [89.8, 97.6] *p*=0.002	--
RS ≤17 vs. 18–30			HR=NR, *p*<0.001	--	HR=NR, *p*=0.002	--
RS ≤10: ET RS 11–25: ET	109 379	5 years	96.3 [90.5, 98.6] 95.4 [92.8, 97.1] *p*=NS	--	99.1 [93.7, 99.9] 98.6 [96.6, 99.4] *p*=NS	--
RS ≤10 vs. 11–25			HR=NR	--	HR=NR	--

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
RS ≤25: ET or ET+CT RS ≥26: ET or ET+CT	577 132	5 years	96.0 [94.0, 97.3] 86.9 [79.7, 91.6] *p*<0.001	--	98.5 [97.5, 99.5] 93.5 [87.4, 96.7] *p*<0.001	--
RS ≤25 vs. ≥26			HR=NR, *p*<0.001	--	HR=NR, *p*<0.001	--
Category C study: Petkov et al. (2016)[42]						
RS ≤17: ET or ET+CT RS 18–30: ET or ET+CT RS ≥31: ET or ET+CT	2,694 1,669 328	5 years	--	--	--	99.0 [98.0, 99.5] 97.7 [95.9, 98.7] *p*<0.001 85.7 [76.2, 91.6]
RS ≤17 vs. 18–30 vs. ≥31			--	--	--	HR=NR

Note: All measures of variance are 95% confidence intervals or standard errors.

[a] Comparator group unclear.

CT: chemotherapy; ET: endocrine therapy only; HR: hazard ratio; N1: 1–3 nodes; NR: not reported; NS: not significant; *p*: *p*-value statistic; RS: recurrence score

TABLE G.8: Prognostic ability of Oncotype DX in node-positive (N1) patients (subgroup analysis: age)

Sub-group	Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Category C study: Petkov et al. (2016)[42]							
Age <40 years	RS ≤11: ET or ET+CT	82	5 years	--	--	--	98.4 ± 1.6
	RS 12–25: ET or ET+CT	62					100 ± 0.0 *p*=0.035
	RS ≥26: ET or ET+CT	21					84.9 ± 9.9
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age 40–49 years	RS ≤11: ET or ET+CT	507	5 years	--	--	--	99.0 ± 1.0
	RS 12–25: ET or ET+CT	285					99.5 ± 0.5 *p*<0.001
	RS ≥26: ET or ET+CT	61					88.0 ± 7.3
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age 50–59 years	RS ≤11: ET or ET+CT	757	5 years	--	--	--	98.6 ± 0.8
	RS 12–25: ET or ET+CT	515					95.4 ± 1.8 *p*=NS
	RS ≥26: ET or ET+CT	103					90.5 ± 9.1
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age 60–69 years	RS ≤11: ET or ET+CT	827	5 years	--	--	--	99.7 ± 0.2
	RS 12–25: ET or ET+CT	501					98.0 ± 1.1 *p*<0.001
	RS ≥26: ET or ET+CT	90					84.5 ± 7.6
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age 70–79 years	RS ≤11: ET or ET+CT	464	5 years	--	--	--	98.4 ± 0.9
	RS 12–25: ET or ET+CT	267					99.2 ± 0.5 *p*<0.001
	RS ≥26: ET or ET+CT	47					84.6 ± 7.4
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR
Age ≥80 years	RS ≤11: ET or ET+CT	57	5 years	--	--	--	100 ± 0.0
	RS 12–25: ET or ET+CT	39					96.8 ± 3.2 *p*=0.012
	RS ≥26: ET or ET+CT	6					66.7 ± 19.3
	RS ≤11 vs. 12–25 vs. ≥26			--	--	--	HR=NR

Note: All measures of variance are standard errors.

CT: chemotherapy; ET: endocrine therapy; HR: hazard ratio; N1: 1–3 nodes; NR: not reported; NS: not significant; *p*: *p*-value statistic; RS: recurrence score

TABLE G.9: Prognostic ability of Prosigna in node-positive (N1) patients

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Category B study: Sestak et al. (2018)[46]						
ROR ≤26: ET ROR 27–68: ET ROR ≥69: ET	15 58 110	10 years	100.0 [100.0, 100.0] 79.3 [65.6, 88.0] *p*=NR 69.3 [58.7, 77.8]	--	--	--
ROR ≤26 vs. 27–68 or ≥69[a]			HR=0.63 [0.47, 0.86], *p*<0.05	--	--	--
ROR 27–68 vs. ≥69			HR=NR	--	--	--
Category C study: Lænkholm et al. (2018)[44]						
Low ROR: ET[b] Intermediate ROR: ET[b] High ROR: ET[b]	359 388 648	10 years	96.5 [93.9, 98.1] 88.5 [84.4, 92.0] *p*<0.001 77.9 [74.2, 81.4]	--	--	--
Low vs. high ROR			HR=NR, *p*<0.05	--	--	--
Low vs. intermediate ROR			Adjusted HR=0.39 [0.20, 0.77], *p*<0.05	--	--	--
Intermediate vs. high ROR			Adjusted HR=0.65 [0.44, 0.96], *p*<0.05	--	--	--

Note: All measures of variance are 95% confidence intervals.

[a] Comparator group unclear.

[b] Risk cut-offs differed by node status: low risk (1 node: ROR ≤35; 2 nodes: ROR ≤25; 3 nodes: NA), intermediate risk (1 node: ROR 36–55; 2 nodes: ROR 26–45; 3 nodes: ROR ≤25), high risk (1 node: ROR ≥56; 2 nodes: ROR ≥46; 3 nodes: ROR ≥26).

ET: endocrine therapy; HR: hazard ratio; N1: 1–3 nodes; NA: not applicable; NR: not reported; *p*: *p*-value statistic; ROR: risk of recurrence

TABLE G.10: Predictive ability of Oncotype DX in node-negative patients

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Category A study: Sparano et al. (2018)[13]						
RS ≤10: ET RS 11–25: ET RS 11–25: ET+CT RS ≥26: ET+CT	1,619 3,399 3,312 1,389	9 years	96.8 ± 0.7 94.5 ± 0.5 95.0 ± 0.5 86.8 ± 1.7 *p*<0.001	95.0 ± 0.8 92.2 ± 0.6 92.9 ± 0.6 84.8 ± 1.7 *p*<0.001	93.7 ± 0.8 93.9 ± 0.5 93.8 ± 0.5 89.3 ± 1.4 *p*<0.001	84.0 ± 1.3 83.3 ± 0.9 84.3 ± 0.8 75.7 ± 2.2 *p*<0.001
RS 11–25: ET vs. ET+CT			HR=1.10 [0.85, 1.41], NS	HR=1.11 [0.90, 1.37], NS	HR=0.99 [0.79, 1.22], NS	HR=1.08 [0.94, 1.24], NS
RS 11–15: ET vs. ET+CT			HR=1.08 [0.64, 1.82], NS	HR=0.92 [0.61, 1.38], NS	--	HR=0.95 [0.75, 1.22], NS
RS 16–20: ET vs. ET+CT			HR=0.95 [0.63, 1.43], NS	HR=1.09 [0.78, 1.52], NS	--	HR=1.04 [0.84, 1.29], NS
RS 20–25: ET vs. ET+CT			HR=1.27 [0.85, 1.90], NS	HR=1.29 [0.91, 1.83], NS	--	HR=1.32 [1.01, 1.71], *p*<0.05
RS 11–17: ET vs. ET+CT			HR=1.00 [0.67, 1.49], NS	HR=0.99 [0.72, 1.37], NS	--	HR=1.01 [0.82, 1.23], NS
RS 18–25: ET vs. ET+CT			HR=1.16 [0.84, 1.60], NS	HR=1.19 [0.91, 1.57], NS	--	HR=1.16 [0.96, 1.40], NS
Category B study: Geyer et al. (2018)[36]						
RS ≤10: ET RS ≤10: ET+CT RS 11–25: ET RS 11–25: ET+CT RS ≥26: ET RS ≥26: ET+CT	66 110 103 168 35 87	10 years	98.0 [95.0, 100.0] 95.0 [90.0, 99.0] 95.0 [90.0, 99.0] 94.0 [90.0, 98.0] 62.0 [48.0, 81.0] 88.0 [81.0, 95.0] *p*=0.014	--	--	--
RS ≤10: ET vs. ET+CT			Adjusted HR=0.84 [0.29, 2.44], NS	--	--	--
RS 11–25: ET vs. ET+CT			Adjusted HR=1.64 [0.74, 3.85], NS	--	--	--
RS ≥26: ET vs. ET+CT			Adjusted HR=3.70 [1.61, 8.33], *p*<0.001	--	--	--

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
RS ≤17: ET RS ≤17: ET+CT RS 18–30: ET RS 18–30: ET+CT RS ≥31: ET RS ≥31: ET+CT	134 213 42 83 28 69	10 years	97.0 [94.0, 100.0] 96.0 [93.0, 99.0] 93.0 [85.0, 100.0] 88.0 [82.0, 96.0] 56.7 [47.2, 66.2] 89.6 [85.9, 93.3] *p*=0.023	--	--	--
RS ≤17: ET vs. ET+CT			Adjusted HR=0.84 [0.29, 2.50], NS	--	--	--
RS 18–30: ET vs. ET+CT			Adjusted HR=1.56 [0.57, 4.35], NS	--	--	--
RS ≥31: ET vs. ET+CT			Adjusted HR=5.56 [2.13, 14.29], *p*<0.001	--	--	--
Category C study: Ibraheem et al. (2018)[38]						
RS 11–17: ET RS 11–17: ET+CT RS 18–25: ET RS 18–25: ET+CT RS 26–30: ET RS 26–30: ET+CT	29,412 1,534 16,013 7,133 2,085 3,845	5 years	--	--	97.4 (NR) 97.5 (NR) 96.4 (NR) 97.1 (NR) 94.0 (NR) 95.8 (NR) *p*=NS	--
RS 11–17: ET vs. ET+CT			--	--	Adjusted HR=1.03 [0.65, 1.64], NS	--
RS 18–25: ET vs. ET+CT			--	--	Adjusted HR=1.27 [1.00, 1.61], *p*=0.052	--
RS 26–30: ET vs. ET+CT			--	--	Adjusted HR=1.47 [1.04, 2.08], *p*=0.029	--
Category C study: Stemmer et al. (2017)[40]						
RS 18–25: ET RS 18–25: ET+CT RS 26–30: ET RS 26–30: ET+CT	473 89 8685	5 years	98.0 [96.2, 99.0] 96.4 [89.1, 99.8] 94.2 [86.6, 97.5] 95.0 [87.0, 98.1] *p*=NS	--	--	--
RS 18–25: ET vs. ET+CT			HR=NR	--	--	--

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
RS 26–30: ET vs. ET+CT			HR=NR	--	--	--

Note: All measures of variance are 95% confidence intervals or standard errors.

CT: chemotherapy; ET: endocrine therapy; HR: hazard ratio; IR: intermediate risk; NR: not reported; NS: not significant; *p*: *p*-value statistic; RS: recurrence score

TABLE G.11: Predictive ability of Oncotype DX in node-negative patients (subgroup analysis: age or menopausal status)

Sub-group	Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Category A study: Sparano et al. (2018)[13]							
Age ≤50 years	RS ≤10: ET	429	9 years	98.5 ± 0.8	95.4 ±1.3	--	87.4 ± 2.0
	RS 11–15: ET	1,214		97.2 ± 1.0	93.3 ± 1.6		85.7 ± 2.2
	RS 11–15: ET+CT	1,159		98.0 ± 0.8	94.4 ± 1.5		89.2 ± 1.9
	RS 16–20: ET	1,368		93.6 ± 1.4	89.6 ± 1.9		80.6 ± 2.5
	RS 16–20: ET+CT	1,344		95.2 ± 1.3 *p*=NR	93.0 ± 1.5 *p*=NR		89.6 ± 1.7 *p*=NR
	RS 21–25: ET	817		86.9 ± 2.9	82.0 ± 3.2		79.2 ± 3.3
	RS 21–25 ET+CT	809		93.4 ± 2.3	90.7 ± 2.5		85.5 ± 3.0
	RS ≥26: ET+CT	409		88.7 ± 2.1	86.1 ± 2.2		80.3 ± 2.9
	RS 11–25: ET vs. ET+CT			HR=1.51 [0.97, 2.33], NS	HR=1.56 [1.11, 2.18], *p*<0.05	--	HR=1.51 [1.17, 1.96], *p*<0.05
	RS 11–15: ET vs. ET+CT			HR=0.86 [0.31, 2.39], NS	HR=0.85 [0.43, 1.66], NS	--	HR=0.99 [0.62, 1.58], NS
	RS 16–20: ET vs. ET+CT			HR=1.36 [0.71, 2.62], NS	HR=1.69 [1.00, 2.83], NS	--	HR=1.90 [1.27, 2.84], *p*=0.0016
	RS 21–25: ET vs. ET+CT			HR=2.19 [1.06, 4.55], *p*<0.05	HR=2.17 [1.20, 3.92], *p*<0.05	--	HR=1.70 [1.03, 2.80], *p*=0.035
Age 51–64 years	RS 11–25: ET vs. ET+CT			HR=0.93 [0.65, 1.35], NS	HR=0.93 [0.68, 1.27], NS	--	HR=0.89 [0.73, 1.09], NS
	RS 11–15: ET vs. ET+CT			HR=1.10 [0.54, 2.22], NS	HR=0.96 [0.52, 1.77], NS	--	HR=0.74 [0.51, 1.08], NS
	RS 16–20: ET vs. ET+CT			HR=0.72 [0.39, 1.31], NS	HR=0.81 [0.49, 1.35], NS	--	HR=0.76 [0.56, 1.04], NS
	RS 21–25: ET vs. ET+CT			HR=1.09 [0.59, 1.99], NS	HR=1.04 [0.61, 1.75], NS	--	HR=1.38 [0.94, 2.03], NS
Age ≥65 years	RS 11–25: ET vs. ET+CT			HR=0.95 [0.48, 1.86], NS	HR=0.87 [0.49, 1.57], NS	--	HR=1.12 [0.81, 1.53], NS
	RS 11–15: ET vs. ET+CT			HR=0.73 [0.15, 3.44], NS	HR=0.60 [0.16, 2.22], NS	--	HR=1.36 [0.78, 2.39], NS
	RS 16–20: ET vs. ET+CT			HR=0.93 [0.29, 2.94], NS	HR=0.91 [0.37, 2.21], NS	--	HR=0.97 [0.58, 1.62], NS
	RS 21–25: ET vs. ET+CT			HR=1.07 [0.40, 2.86], NS	HR=1.02 [0.39, 2.70], NS	--	HR=1.07 [0.59, 1.95], NS

Sub-group	Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Pre-meno-pausal	RS 11–15: ET RS 11–15: ET+CT RS 16–20: ET RS 16–20: ET+CT RS 21–25: ET RS 21–25 ET+CT	472 415 497 517 243 271	9 years	--	--	--	88.4 (NR)[a] 88.7 (NR)[a] 83.5 (NR)[a] 90.8 (NR)[a] 80.7 (NR)[a] 85.9 (NR)[a] *p*=NR
	RS 11–25: ET vs. ET+CT			HR=1.42 [0.93, 2.19], NS	HR=1.35 [0.98, 1.86], NS	--	HR=1.36 [1.06, 1.75], *p*<0.05
	RS 11–15: ET vs. ET+CT			HR=0.88 [0.31, 2.54], NS	HR=0.76 [0.39, 1.46], NS	--	HR=0.85 [0.54, 1.35], NS
	RS 16–20: ET vs. ET+CT			HR=1.21 [0.64, 2.31], NS	HR=1.42 [0.86, 2.34], NS	--	HR=1.76 [1.20, 2.59], *p*=0.003
	RS 21–25: ET vs. ET+CT			HR=2.06 [1.03, 4.14], NS	HR=1.93 [1.09, 3.40], *p*<0.05	--	HR=1.50 [0.93, 2.42], NS
Post-meno-pausal	RS 11–25: ET vs. ET+CT			HR=0.97 [0.71, 1.34], NS	HR=0.98 [0.74, 1.29], NS	--	HR=0.99 [0.84, 1.17], NS
	RS 11–15: ET vs. ET+CT			HR=1.15 [0.62, 2.13], NS	HR=1.06 [0.62, 1.81], NS	--	HR=1.02 [0.76, 1.37], NS
	RS 16–20: ET vs. ET+CT			HR=0.83 [0.49, 1.42], NS	HR=0.92 [0.59, 1.44], NS	--	HR=0.84 [0.64, 1.09], NS
	RS 21–25: ET vs. ET+CT			HR=1.00 [0.60, 1.68], NS	HR=0.98 [0.62, 1.56], NS	--	HR=1.23 [0.90, 1.70], NS
Category B study: Geyer et al. (2018)[36]							
Age ≤50 years[b]	RS ≥26: ET vs. ET+CT			Adjusted HR=8.33 [2.04, 33.33], *p*<0.05	--	--	--
Age >50 years[b]	RS ≥26: ET vs. ET+CT			Adjusted HR=2.27 [0.73, 7.14], NS	--	--	--

Note: All measures of variance are 95% confidence intervals or standard errors.

[a] One researcher extracted these data from the paper's figure using WebPlotDigitizer v4.1.

[b] Number of patients not reported; length of follow up was 10 years.

CT: chemotherapy; ET: endocrine therapy; HR: hazard ratio; NR: not reported; NS: not significant; *p*: *p*-value statistic; RS: recurrence score

TABLE G.12: Predictive ability of Oncotype DX in node-positive (N1) patients

Intervention group	# of patients	Follow up	Freedom from distant recurrence, %	Freedom from distant or locoregional recurrence, %	Overall survival, %	Disease-free survival, %
Category C study: Ibraheem et al. (2018)[38]						
RS 11–17: ET RS 11–17: ET+CT RS 18–25: ET RS 18–25: ET+CT RS 26–30: ET RS 26–30: ET+CT	5,203 1,889 2,328 2,567 286 890	5 years	--	--	96.5 (NR) 97.7 (NR) 92.7 (NR) 96.0 (NR) 85.5 (NR) 92.2 (NR) *p*<0.001	--
RS 11–17: ET vs. ET+CT			--	--	Adjusted HR=1.59 [1.01, 2.50], *p*=0.044	--
RS 18–25: ET vs. ET+CT			--	--	Adjusted HR=1.89 [1.32, 2.70], *p*=0.001	--
RS 26–30: ET vs. ET+CT			--	--	Adjusted HR=2.00 [1.12, 3.57], *p*=0.018	--
Category C study: Stemmer et al. (2017)[40]						
RS ≤17: ET RS ≤17: ET+CT RS 18–30: ET RS 18–30: ET+CT	352 27 156 102	5 years	--	--	99.4 [97.7, 99.9] 100.0 [100.0, 100.0] 95.0 [89.8, 97.6] 98.9 [92.1, 98.8] *p*=NR	--
RS ≤17: ET vs. ET+CT			--	--	HR=NR, NS	--
RS 18–30: ET vs. ET+CT			--	--	HR=NR, NS	--
RS 18–25: ET RS 18–25: ET+CT RS 26–30: ET RS 26–30: ET+CT	136 62 20 40	5 years	--	--	96.8 [91.7, 98.8] 100.0 [100.0, 100.0] 84.0 [57.9, 94.6] 97.1 [80.9, 99.6] *p*=NR	--
RS 18–25: ET vs. ET+CT			--	--	HR=NR, NS	--
RS 26–30: ET vs. ET+CT			--	--	HR=NR, NS	--
RS ≤25: ET RS ≤25: ET+CT	488 89	5 years	--	--	98.7 [97.1, 99.4] 100.0 [100.0, 100.0] *p*=NS	--
RS ≤25: ET vs. ET+CT			--	--	HR=NR, NS	--

Note: All measures of variance are 95% confidence intervals.

CT: chemotherapy; ET: endocrine therapy; HR: hazard ratio; N1: 1–3 nodes; NR: not reported; NS: not significant; *p*: *p*-value statistic; RS: recurrence score

TABLE G.13: Relevant ongoing studies identified through clinical trial registers

Principal Investigator Identifier Acronym Country	Study design # of centres Enrolment	Start date Completion date Status	Purpose	Population	Outcomes	Sponsor/ collaborator
Kalinsky KM NCT01272037[a] RxPONDER United States	RCT Multicentre N=10,000[b]	Jan 2011 Feb 2022 In progress	To compare the effectiveness of ET with or without CT in treating patients (RS ≤25) with Oncotype DX	Patients with ER+ (and/or PR+), HER2−, N1 BC, who have completed surgery and are eligible for adjuvant CT	1. Disease-free survival 2. Overall survival 3. Distant recurrence-free survival 4. Local disease-free interval 5. Toxicities	National Cancer Institute
Stein R ISRCTN 42400492[c] OPTIMA United Kingdom	RCT Multicentre N=4,500[b]	Jul 2012 Sep 2023[b] In progress	To compare two management options: standard care (ET+CT) and Prosigna-directed treatment (where patients with an ROR more than 60 receive ET+CT and patients with an ROR 60 or less receive ET alone)	Patients aged ≥40 years with ER+, HER2− BC, N0 and tumour size ≥3.0 cm *or* 1–9 positive nodes, who have completed surgery and are eligible for adjuvant CT	1. Invasive disease-free survival 2. Cost-effectiveness 3. Distant and BC-specific disease-free survival 4. Quality of life and health resource use	National Institute for Health Research
Rouzier R NCT03080428[d] OPTIGEN France	RCT Multicentre N=0	May 2017 NA Withdrawn due to lack of funding	To compare the impact of four genetic tests (Oncotype DX, Prosigna, EndoPredict, Mammaprint) on adjuvant CT decision-making	Patients with ER+, HER2−, N0 or N1 BC, who have completed surgery and are eligible for adjuvant CT	1. Clinical utility 2. Distant disease-free survival 3. Changes in decision based on test result 4. Feasibility of test 5. Change in treatment based on test result 6. Cost-effectiveness	Unicancer

[a] Full study record available at: *https://clinicaltrials.gov/ct2/show/NCT01272037.*

[b] Expected, not actual.

[c] Full study record available at: *http://www.isrctn.com/ISRCTN42400492*.

[d] Full study record available at: *https://ClinicalTrials.gov/show/NCT03080428.*

BC: breast cancer; cm: centimetre; CT: chemotherapy; ER+: estrogen receptor positive; ET: endocrine therapy; HER2−: human epidermal growth factor receptor 2 negative; N: number; N1: node-positive (1–3 nodes); NA: not applicable; PR+: progesterone receptor positive; RCT: randomized controlled trial; ROR: risk of recurrence

Appendix H: Rapid Review 2 – Evidence Summary Tables

TABLE H.1: Systematic review characteristics and data summary

Study	Inclusion criteria	Exclusion criteria	Number of studies and patients[a]	Relevant results
Cancer Care Ontario (2016)[25]	Studies published from 2002 to week 7 of 2016, evaluating the clinical utility of the Oncotype DX, Prosigna, EndoPredict, or MammaPrint genetic test in early-stage breast cancer (ER+, HER2−) Prospectively enrolled patients and prospectively collected tumour samples	Studies only available in abstract form, retrospective cohort studies, case-control studies, case series, letters, editorials, and studies not published in English	Oncotype DX: N0: 5 studies (n=1,331)[72-76] N1: 2 studies (n=84)[73, 74] Prosigna: No studies identified	Oncotype DX: N0: Proportion of change in treatment recommendations ranged from 24 to 52% (5 studies).[72-76] Clinician confidence in treatment recommendations increased after receiving the test results (3 studies).[72, 73, 76] N1: Proportion of change in treatment recommendations ranged from 26 to 41% (2 studies).[73] Clinician confidence in treatment recommendations increased after receiving the test results (1 study).[73]

[a] Only information related to the decision impact of Oncotype DX and Prosigna was tabulated.

ER+: estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; n: number; N0: node-negative; N1: node-positive (1–3 nodes)

TABLE H.2: Primary study characteristics

Study	Study design	Country # of centres Time period	Patient sample	Pre-test treatment determination	Post-test treatment determination	Source(s) of funding	Conflicts of interest
Oncotype DX							
Albanell et al. (2016)[48]	Prospective cohort study	France, Germany, Spain, United Kingdom Multicentre NR	n=716 Consecutive patients with early-stage BC (ER+, HER2−, N0) and no micrometastases Participant losses: Ineligible (151)	Recommendation: Oncologist (clinicopathology results)	Recommendation: Oncologist (clinicopathology results and RS)	Genomic Health	7 of 9 co-authors are employees, consultants, and/or have received honoraria from Genomic Health
Dieci et al. (2018)[49]	Prospective cohort study	Italy Multicentre NR	n=361 Consecutive patients with early-stage BC (ER+, HER2−, N0 or N1) who had intermediate risk of recurrence based on clinicopathology Participant losses: Ineligible (72), no informed consent (39)	Recommendation: Oncologist (clinicopathology results)	Recommendation: Oncologist (clinicopathology results and RS) Decision: Oncologist and patient preference	Genomic Health, Regione Veneto	3 of 18 co-authors have received grant support from Genomic Health, Novartis, and/or Roche
Ozmen et al. (2016)[50]	Prospective cohort study	Turkey Multicentre NR	n=165 Consecutive patients with early-stage BC (ER+, HER2−, N0) and no evidence of distant metastases Participant losses: None	Recommendation: Multidisciplinary team meeting (clinicopathology results)	Recommendation: Multidisciplinary team meeting (clinicopathology results and RS)	Genomic Health	No authors declared conflicts

Study	Study design	Country # of centres Time period	Patient sample	Pre-test treatment determination	Post-test treatment determination	Source(s) of funding	Conflicts of interest
Torres et al. (2018)[51]	Prospective cohort study	Canada Multicentre Oct 2014–May 2016	n=72 Patients with early-stage BC (ER+, HER2−, N1) in whom the benefit of CT was uncertain Participant losses: Withdrew prior to receiving RS result (1), ineligible (2), withdrawn due to study protocol violation (2)	Recommendation: Oncologist (clinicopathology results)	Recommendation: Oncologist (clinicopathology results and RS) Decision: Oncologist and patient preference	Genomic Health	7 of 10 co-authors are employees, consultants, shareholders, and/or have received grant support and/or honoraria from Genomic Health, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Novartis, Merck, Pfizer, RNA Diagnostics, Roche, and/or Spectrum Health
Loncaster et al. (2017)[52]	Retrospective analysis of prospectively collected data	United Kingdom Multicentre May 2012–Mar 2015	n=201 Patients with early-stage BC (ER+, HER2−) who had intermediate risk of recurrence based on clinicopathology: N0 or N1 (postmenopausal only) and had been referred for CT Participant losses: None	Recommendation: Multidisciplinary team meeting (clinicopathology results and Predict calculation)	Decision: Multidisciplinary team meeting (clinicopathology results and RS) and patient preference	Greater Manchester Cancer Network, Genomic Health, Christie Hospital	3 of 8 co-authors are consultants for Genomic Health
Panousis et al. (2017)[53]	Retrospective analysis of prospectively collected data	Greece Single centre Jan 2009–Dec 2015	n=250 Patients with early-stage BC (ER+, HER2−) in whom the benefit of CT was uncertain Participant losses: Ineligible (130), non-valid RS result (1), HER2+ (5)	Recommendation: Multidisciplinary team meeting (clinicopathology results)	Recommendation: Multidisciplinary team meeting (clinicopathology results and RS)	NR	No authors declared conflicts

Study	Study design	Country # of centres Time period	Patient sample	Pre-test treatment determination	Post-test treatment determination	Source(s) of funding	Conflicts of interest
Prosigna							
Hequet et al. (2017)[54]	Prospective cohort study	France Multicentre Mar 2015–Jan 2016	n=210 Consecutive postmenopausal patients with early-stage BC (ER+, HER2−, N0) and no metastatic disease Participant losses: Withdrew (4), ineligible (2), not meeting tumour requirements (2), other reasons (2)	Recommendation: Multidisciplinary team meeting (clinicopathology results)	Recommendation: Multidisciplinary team meeting (clinicopathology results and ROR)	NanoString Technologies	4 of 23 co-authors are employees of NanoString Technologies or an organization funded by NanoString Technologies
Wuerstlein et al. (2016)[55]	Prospective cohort study	Germany Multicentre Oct 2013–Oct 2014	n=201 Consecutive postmenopausal patients with early-stage BC (ER+, HER2−, N0) and no metastatic disease Participant losses: Withdrew (2), insufficient tumour sample (1)	Recommendation: Oncologist (clinicopathology results)	Recommendation: Oncologist (clinicopathology results and ROR)	NanoString Technologies	7 of 20 co-authors are employees, consultants, and/or have received grant support from NanoString Technologies, Genomic Health, Agendia, or an organization funded by NanoString Technologies

BC: breast cancer; CT: chemotherapy; ER+ estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; HER2+: human epidermal growth factor receptor 2 positive; n: number; N0: node-negative; N1: node-positive (1–3 nodes); NR: not reported; PR+: progesterone receptor positive; ROR: risk of recurrence (calculated using Prosigna); RS: recurrence score (calculated using Oncotype DX)

TABLE H.3: Patient characteristics

Study Risk categories and cut-offs	Patients analyzed, overall and by risk category, n (%)	Risk score	Age, years	Meno-pause status, %	Receptor status, %	Node status, %	Tumour grade, %	Tumour size (cm), %	Mastect-omy type, %
Oncotype DX									
Albanell et al. (2016)[48] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=565 312 (55%) 199 (35%) 54 (10%)	Mean: 18 (SD: 10.1) Median: 16 (range: 0–81)	Mean: 56 (SD: 10.1; range: 25–85)	NR	100% ER+, 87% PR+, 100% HER2−	100% N0	17% grade 1, 69% grade 2, 13% grade 3, 1% unknown	Median: 1.8 (range: 0.5–9.0)	NR
Dieci et al. (2018)[49] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=250 152 (61%) 81 (32%) 17 (7%)	Median: 16 (range: 0–47)	Median: 55 (range: 27–83)	41% pre, 59% post	100% ER+, median 80% PR+ (range: 0–100%), 100% HER2−	50% N0, 50% N1	4% grade 1, 71% grade 2, 25% grade 3	Median: 1.6 (range: 0.3–5.4)	NR
Ozmen et al. (2016)[50] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=165 93 (56%) 58 (35%) 14 (9%)	Mean: 19 (SD: 14.0) Median: 16 (range: 0-64)	Median: 49 (range: 26–76)	NR	100% ER+, 67% PR+, 100% HER2−	93% N0, 7% N1	17% grade 1, 66% grade 2, 16% grade 3, 1% unknown	Median: 2.0 (range: 0.6–8.0)	NR
Torres et al. (2018)[51] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=67[a] 38 (57%) 23 (34%) 6 (9%)	n=69 Mean: 17 (SD: 8.0) Median: 16 (range: 1–37)	Mean: 61 (range: 37–84)	28% pre, 72% post	100% ER+, 93% PR+, 100% HER2−	99% N1, 1% unknown	21% grade 1, 61% grade 2, 18% grade 3	46% ≤2.0, 46% >2.0–5.0, 8% >5.0	77% partial, 23% total
Loncaster et al. (2017)[52] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=201 86 (43%) 89 (44%) 26 (13%)	Mean: 20.5 (range: 4–54)	Mean: 55 (SD: 10.0; range: 24–77)	NR	100% ER+, PR+ NR, 100% HER2−	68% N0, 32% N1	2% grade 1, 52% grade 2, 46% grade 3	Mean: 2.6 (range: 0.2–8.0)	NR
Panousis et al. (2017)[53] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=114 68 (60%) 43 (38%) 3 (2%)	Mean: 16 (SD: 6.7)	Mean: 51 (SD: 9.0; range: 33–74)	55% pre, 45% post	100% ER+, 66% PR+, 100% HER2−	96% N0, 4% N1	8% grade 1, 70% grade 2, 19% grade 3, 3% unknown	Median: 1.3 (range: 0.3–6.0)	73% partial, 19% total, 8% NR

Study Risk categories and cut-offs	Patients analyzed, overall and by risk category, n (%)	Risk score	Age, years	Meno-pause status, %	Receptor status, %	Node status, %	Tumour grade, %	Tumour size (cm), %	Mastect-omy type, %
Prosigna									
Hequet et al. (2017)[54] LR (ROR ≤40) IR (ROR 41–60) HR (ROR >60)	n=200 93 (46%) 67 (34%) 40 (20%)	NR	Mean: 62 (99% ≥50)	100% post	100% ER+, 86% PR+, 100% HER2−	100% N0	NR	79% ≤2.0, 21% >2.0–5.0	NR
Wuerstlein et al. 2016[55] LR (ROR ≤40) IR (ROR 41–60) HR (ROR >60)	n=198 85 (43%) 70 (35%) 43 (22%)	NR	Median: 64 (range: 40–81)	100% post	100% ER+, 87% PR+, 100% HER2−	100% N0	NR	77% ≤2.0, 23% >2.0–5.0	NR

[a] Two patients were withdrawn due to a protocol violation after the RS assay was ordered; n=71 for all other variables unless otherwise specified.

cm: centimetres; ER+: estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; HR: high risk; IR: intermediate risk; LR: low risk; n: number; N0: node-negative; N1: node-positive (1–3 nodes); NR: not reported; post: postmenopausal; PR+: progesterone receptor positive; pre: premenopausal; ROR: risk of recurrence; RS: recurrence score; SD: standard deviation

TABLE H.4: Impact of Oncotype DX testing on final treatment recommendation, in node-negative patients

Risk categories and cut-offs	# of patients	No CT pre-test		CT pre-test		Total treatment change, %[a]	Pre-test CT, %	Post-test CT, %	Net change in CT, %[a]	CT administered, %
		Unchanged, %	No CT to CT, %	Unchanged, %	CT to no CT, %					
Albanell et al. (2016)[48]										
Overall	527[b]	45%	10%	23%	22%	32%	45%	34%	↓12% (*p*<0.0001)	--
LR (RS <18)	293	60%	<1%	6%	33%	19%	22%	4%	↓18%	--
IR (RS 18–30)	185	31%	22%	38%	10%	11%	16%	21%	↑5%	--
HR (RS >30)	49	4%	22%	74%	0%	2%	7%	9%	↑2%	--
Dieci et al. (2018)[49]										
Overall	124	57%	4%	31%	8%	12%	39%	35%	↓4% (*p*=NS)	--
LR (RS <18)	NR	--	--	--	--	--	--	--	--	--
IR (RS 18–30)	NR	--	--	--	--	--	--	--	--	--
HR (RS >30)	NR	--	--	--	--	--	--	--	--	--
Ozmen et al. (2016)[50]										
Overall	165	38%	6%	31%	25%	31%	56%	37%	↓19% (*p*<0.001)	--
LR (RS <18)	93	55%	0%	10%	35%	20%	25%	6%	↓20%	--
IR (RS 18–30)	58	21%	12%	53%	14%	9%	24%	23%	↓1%	--
HR (RS >30)	14	0%	21%	79%	0%	2%	7%	8%	↑2%	--
Loncaster et al. (2017)[52]										
Overall	136	0%	0%	40%	60%	60%	100%	40%	↓60%	--
LR (RS <18)	46	0%	0%	2%	98%	33%	100%	1%	↓33%	--
IR (RS 18–30)	70	0%	0%	51%	49%	25%	100%	26%	↓25%	--
HR (RS >30)	20	0%	0%	85%	15%	2%	100%	85%	↓2%	--
Panousis et al. (2017)[53]										
Overall	113[c]	53%	9%	14%	24%	33%	38%	23%	↓15% (*p*=0.009)	--
LR (RS <18)	68	--	--	--	--	20%	--	--	--	--
IR (RS 18–30)	42	--	--	--	--	13%	--	--	--	--
HR (RS >30)	3	--	--	--	--	0%	--	--	--	--

Note: Five studies[72-76] in the 2016 CCO systematic review[25] also found that the proportion of change in treatment recommendations ranged from 24 to 52%.

[a] Calculated using total patient population for the denominator.

[b] Data only available for 527 of 565 patients.

[c] Data only available for 113 of 114 patients.

CT: chemotherapy; HR: high risk; IR: intermediate risk; LR: low risk; NR: not reported; NS: not significant; *p*: *p*-value statistic; RS: recurrence score

TABLE H.5: Impact of Prosigna testing on final treatment recommendation, in node-negative patients

Risk categories and cut-offs	# of patients	No CT pre-test		CT pre-test		Total treatment change, %[a]	Pre-test CT, %	Post-test CT, %	Net change in CT, %[a]	CT administered, %
		Unchanged, %	No CT to CT, %	Unchanged, %	CT to no CT, %					
Hequet et al. (2017)[54]										
Overall	194[b]	57%	13%	26%	5%	18%	30%	39%	↑8% (*p*=0.01)	--
LR (ROR ≤40)	88	--	0%	--	8%	4%	--	--	--	--
IR (ROR 41–60)	66	--	15%	--	3%	6%	--	--	--	--
HR (ROR >60)	40	--	38%	--	0%	8%	--	--	--	--
Wuerstlein et al. (2016)[55]										
Overall	198	66%	11%	20%	3%	14%	23%	31%	↑9% (*p*=0.002)	--
LR (ROR ≤40)	85	91%	0%	6%	3%	1%	4%	2%	↓1%	--
IR (ROR 41–60)	70	73%	10%	14%	3%	5%	6%	9%	↑2%	--
HR (ROR >60)	43	7%	35%	58%	0%	8%	13%	20%	↑8%	--

[a] Calculated using total patient population for the denominator.

[b] Data only available for 194 of the 200 patients included.

CT: chemotherapy; HR: high risk; IR: intermediate risk; LR: low risk; *p*: *p*-value statistic; ROR: risk of recurrence

TABLE H.6: Impact of Oncotype DX testing on final treatment recommendation, in node-positive (N1) patients

Risk categories and cut-offs	# of pts	No CT pre-test			CT pre-test			Unsure pre-test			Total tx change, %[a]	Pre-test CT, %	Post-test CT, %	Net change in CT, %[a]	CT administered, %
		Un-changed, %	No CT to CT, %	No CT to un-sure, %	Un-changed, %	CT to no CT, %	CT to un-sure, %	Un-changed, %	Un-sure to no CT, %	Un-sure to CT, %					
Dieci et al. (2018)[49]															
Overall	126	39%	4%	--	41%	16%	--	--	--	--	20%	57%	45%	↓12% (p=0.003)	--
LR (RS <18)	NR	--	--	--	--	--	--	--	--	--	--	--	--	--	--
IR (RS 18–30)	NR	--	--	--	--	--	--	--	--	--	--	--	--	--	--
HR (RS >30)	NR	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Loncaster et al. (2017)[52]															
Overall	65	0%	0%	--	31%	69%	--	--	--	--	69%	100%	31%	↓69%	--
LR (RS <18)	40	0%	0%	--	8%	92%	--	--	--	--	57%	100%	5%	↓57%	--
IR (RS 18–30)	19	0%	0%	--	63%	37%	--	--	--	--	11%	100%	18%	↓11%	--
HR (RS >30)	6	0%	0%	--	83%	17%	--	--	--	--	1%	100%	8%	↓1%	--
Torres et al. (2018)[51]															
Final treatment recommendation															
Overall	67	16%	4%	--	48%	31%	--	--	--	--	36%	79%	52%	↓27% (p=0.0005)	42%
LR (RS <18)	38	24%	0%	--	29%	47%	--	--	--	--	27%	43%	16%	↓27%	--
IR (RS 18–30)	23	9%	4%	--	74%	13%	--	--	--	--	6%	30%	27%	↓3%	--
HR (RS >30)	6	0%	33%	--	67%	0%	--	--	--	--	3%	6%	9%	↑3%	--
Patient treatment decision															
Overall	66[b]	13%	2%	2%	21%	12%	9%	12%	21%	8%	53%	--	--	↓12% (p<0.001)	--
LR (RS <18)	38	21%	0%	0%	13%	16%	13%	11%	21%	5%	32%	--	--	↓14%	--
IR (RS 18–30)	23	4%	4%	0%	35%	9%	4%	9%	26%	9%	18%	--	--	0%	--
HR (RS >30)	5	0%	0%	20%	20%	0%	0%	40%	0%	20%	3%	--	--	↑2%	--

Note: Two studies[73, 74] in the 2016 CCO systematic review[25] also found that the proportion of change in treatment recommendations ranged from 26 to 41%.

[a] Calculated using total patient population for the denominator.

[b] One patient did not answer the questionnaire after the study.

CT: chemotherapy; HR: high risk; IR: intermediate risk: LR: low risk; N1: 1–3 nodes; NR: not reported; *p*: *p*-value statistic; pts: patients; RS: recurrence score; tx: treatment

TABLE H.7: Clinician perceptions of Oncotype DX testing contribution to treatment decision, in node-negative and node-positive (N1) patients

Node status	Risk categories and cut-offs	# of patients	Outcome	Pre-test, %	Post-test, %	% change	*p*-value
Albanell et al. (2016)[48]							
Node-negative	Overall	527	Confidence in treatment recommendation	--	--	↑33–60%, ↓7–15%, no change 33–52%	*p*<0.01
Ozmen et al. (2016)[50]							
Node-negative	Overall	165	RS contributes to treatment decision	31%	88%	--	--
			RS provides additional information	41%	85%	--	--
Torres et al. (2018)[51]							
Node-positive (N1)	Overall	67	Confidence in treatment recommendation	64%	88%	↑49%, ↓11%, no change 40%	*p*<0.001
	LR (RS <18)	38		--	--	↑56%, ↓10%, no change 34%	*p*=0.002
	IR (RS 18–30)	23		--	--	↑39%, ↓13%, no change 48%	*p*=NS
	HR (RS >30)	6		--	--	↑50%, ↓0%, no change 50%	*p*=NS

Note: Three studies[72, 73, 76] in the 2016 CCO systematic review[25] also found that clinician confidence in treatment recommendations increased after receiving the test results.

HR: high risk; IR: intermediate risk; LR: low risk; N1: 1–3 nodes; NS: not significant; *p*: *p*-value statistic; RS: recurrence score

TABLE H.8. Patient perceptions of Oncotype DX and Prosigna testing contribution to treatment decision, in node-negative and node-positive (N1) patients

Node status	Genetic test	Risk categories and cut-offs	# of patients	Outcome	Pre-test, %	Post-test, %	% change	*p*-value
Hequet et al. (2017)[54]								
Node-negative	Prosigna	Overall	158	Mean decisional conflict score	9.8	6.2	↓37%	*p*<0.001
			171	Mean State Trait Anxiety Inventory (state anxiety component)	43.3	41.5	↓4%	*p*=0.02
			151	Mean functional assessment	79.4	80.2	↑1%	*p*=NS
Wuerstlein et al. (2016)[55]								
Node-negative	Prosigna	Overall	178	Mean decisional conflict score	17.0	12.8	↓25%	*p*<0.001
			187	Mean State Trait Anxiety Inventory (state anxiety component)	40.5	38.5	↓5%	*p*=NS
			184	Mean functional assessment	19.6	20	↑2%	*p*=NS
Torres et al. (2018)[51]								
Node-positive (N1)	Oncotype DX	Overall	66[a]	Confidence in treatment recommendation	38%	74%	↑54%, ↓14%, no change 32%	*p*<0.001
		LR (RS <18)	38		--	--	↑50%, ↓18%, no change 32%	*p*=0.02
		IR (RS 18–30)	23		--	--	↑70%, ↓4%, no change 26%	*p*=0.001
		HR (RS >30)	5		--	--	↑20%, ↓20%, no change 60%	NR

[a] One patient did not answer the questionnaire after the study.

HR: high risk; IR: intermediate risk: LR: low risk; N1: 1–3 nodes; NR: not reported; NS: not significant; *p*: *p*-value statistic; RS: recurrence score

TABLE H.9: Quality improvement data from Alberta for Oncotype DX – study characteristics

Study	Study design	Country # of centres Time period	Patient sample	Pre-test treatment determination	Post-test treatment determination	Source(s) of funding	Conflicts of interest
Urgoiti et al. (n.d.)[78]	Retrospective analysis of prospectively collected data	Canada Two centres Mar 2014–Jun 2015	n=591 Patients aged ≤70 years diagnosed with ER+, HER2−, N0 tumours (one patient was male) Participant losses: RS test not performed (426), RS test performed but no evaluable decision data (15)	Recommendation: Oncologist (clinicopathology results)	Recommendation: Oncologist (clinicopathology results and RS) Decision: Oncologist and patient preference	None	1 of 9 co-authors participated in an advisory board for Genomic Health

ER+: estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; n: number; N0: node-negative; n.d.: no date; RS: recurrence score

TABLE H.10: Quality improvement data from Alberta for Oncotype DX – patient characteristics

Study Risk categories and cut-offs used	Patients analyzed, overall and by risk category, n (%)	Risk score	Age, years	Meno-pause status, %	Receptor status, %	Node status, %	Tumour grade, %	Tumour size (cm), %	Mastect-omy type, %
Urgoiti et al. (n.d.)[78] LR (RS ≤18) IR (RS 19–30) HR (RS >30) Oncologist predicted RR LR IR HR	n=163 113 (69%) 37 (23%) 13 (8%) n=150 15 (10%) 125 (83%) 10 (7%)	NR	Median: 55 (range: 34–70; 72% ≥50)	NR	100% ER+, PR+ NR, 100% HER2−	100% N0	76% grade 2, 24% grade 3	12% ≤1, 62% >1–2, 25% >2–5, 1% >5	NR

cm: centimetres; ER+: estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; HR: high risk; IR: intermediate risk; LR: low risk: n: number; N0: node-negative; n.d.: no date; NR: not reported; PR+: progesterone receptor positive; RR: recurrence risk; RS: recurrence score

TABLE H.11: Quality improvement data from Alberta for Prosigna – impact of testing on final treatment recommendation in node-negative patients

Risk categories and cut-offs	# of pts	No CT pre-test			CT pre-test			Unsure pre-test			Total treatment change, %[a]	Net change in CT, %[a]	CT admin-istered, %
		Un-changed, %	No CT to CT, %	No CT to unsure, %	Un-changed, %	CT to no CT, %	CT to unsure, %	Un-changed, %	Unsure to no CT, %	Unsure to CT, %			
Provincial Quality Assurance Working Group (personal communication, Jan 2019)													
Overall	95	38%	6%	0%	24%	2%	0%	9%	11%	9%	28%	↑14%	--
LR (ROR ≤40)	35	43%	0%	0%	6%	6%	0%	17%	29%	0%	13%	↓2%	--
IR (ROR 41–60)	39	51%	0%	0%	28%	0%	0%	5%	0%	15%	6%	↑6%	--
HR (ROR >60)	21	5%	28%	0%	48%	0%	0%	5%	0%	14%	9%	↑9%	--

[a] Calculated using total patient population for the denominator.

CT: chemotherapy; HR: high risk; IR: intermediate risk; LR: low risk; *p*: *p*-value statistic; pts: patients; ROR: risk of recurrence

TABLE H.12: Potentially relevant ongoing studies identified through clinical trial registers

Principal Investigator Identifier Acronym Country	Study design # of centres Enrolment	Start date Completion date Status	Purpose	Population	Outcomes	Sponsors and collaborators
NR NCT02627703[a] NR Canada	Prospective cohort study Multicentre N=80	May 2010 Dec 2017[b] Unknown	To examine the impact of Oncotype DX on clinician and patient decision-making regarding adjuvant CT	Patients aged 18–79 years with ER+, HER2−, N1 operable primary BC who are eligible for adjuvant CT	1. Change in clinician treatment recommendation 2. Cost differences	British Columbia Cancer Agency; Genomic Health
Vacirca J NCT02625935[c] NR United States	Prospective cohort study Multicentre N=206	Dec 2015 Oct 2017 Completed	To examine the impact of Prosigna on clinician treatment recommendations for adjuvant CT and the actual treatment received	Postmenopausal patients with ER+, HER2−, N0, surgically resected BC, eligible for adjuvant CT	1. Change in clinician adjuvant treatment recommendation 2. Change from initial recommendation to actual treatment received 3. Patient decisional conflict 4. Patient anxiety levels	NanoString Technologies
Rouzier R NCT03080428[d] OPTIGEN France	RCT Multicentre N=0	May 2017 NA Withdrawn due to lack of funding	To compare the impact of four genetic tests (Oncotype DX, Prosigna, Endopredict, Mammaprint) on adjuvant CT decision-making	Patients with ER+, HER2−, N0 or N1 BC, who have completed surgery and are eligible for adjuvant CT	1. Clinical utility 2. Distant disease-free survival 3. Changes in decision based on test result 4. Feasibility of test 5. Change in treatment based on test result 6. Cost-effectiveness	Unicancer

[a] Full study record available at: *https://clinicaltrials.gov/ct2/show/NCT02627703*.

[b] Expected, not actual.

[c] Full study record available at: *https://clinicaltrials.gov/ct2/show/NCT02625935*.

[d] Full study record available at: *https://clinicaltrials.gov/ct2/show/NCT03080428*.

BC: breast cancer; CT: chemotherapy; ER+: estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; N: number; N0: node-negative; N1: node-positive (1–3 nodes); NR: not reported; RCT: randomized controlled trial; RS: recurrence score

Appendix I: Rapid Review 2 – Studies with Combined Data for Node-Negative and Node-Positive (N1) Patients

Although the main focus of rapid review 2 was on clinician and patient treatment choices for adjuvant chemotherapy in the distinct populations of node-negative and node-positive (N1) patients, a number of potentially eligible studies were excluded because they reported combined results that could not be disaggregated by node status. These additional data were extracted and tabulated in this appendix for the purpose of comparing and contrasting them with the outcomes for the node-negative and node-positive (N1) patient groups. In total, six studies with combined node-negative and node-positive (N1) data examined Oncotype DX, and their results were generally consistent with the above-mentioned findings for Oncotype DX.

I.1. Methods

The methods for searching for, identifying, and summarizing the results of the relevant primary studies followed those outlined in section 2.1 and Appendix C of this report. The selection process for studies reporting combined node-negative and node-positive (N1) patient data is summarized in Table I.1.

TABLE I.1: Summary of primary studies with combined data for N0/N1 patients

Rapid review	Records identified through database searching and other sources	Records screened after duplicates removed	Full-text articles assessed for eligibility	Primary studies included	References
2: Clinician and patient treatment decisions	2,967	2,469	27	6[a]	109-114

[a] One systematic review[25] containing one relevant primary study[115] was also included.

N0: node-negative; N1: node-positive (1–3 nodes)

I.2. Results

I.2.1. Description of studies

The 2016 CCO systematic review[25] included one prospective primary study that reported combined data for node-negative and node-positive (N1) patients who underwent Oncotype DX testing.[115] The literature searches identified six additional primary studies published subsequent to the CCO systematic review.[109-114]

All six primary studies evaluated Oncotype DX in both pre- and postmenopausal patients. Five were prospective cohort studies and one was a retrospective analysis of prospectively collected data. The studies were published between 2016 and 2018, and were conducted in Germany, Hong Kong, Spain, Switzerland, the United States, and the United Kingdom (one study each). Two studies only included patients with an intermediate risk of recurrence based on clinicopathologic factors.[112, 114] The total number of patients enrolled in the studies ranged from 50 to 401 (median: 170). The studies generally included patients with similar characteristics (for example, age, ER status, HER2 status, tumour size, and tumour grade) to those included in rapid review 2. In 67% of the studies, one or more of the primary study authors had affiliations with Genomic Health.

See Table I.2 for a summary of outcomes reported across the studies, and Tables I.3 and I.4 for study and patient characteristics.

TABLE I.2: Summary of included studies and outcome data

Study	Study design	# of patients	Total treatment change	Net change in CT	Treatment received	Decisional outcomes[a]
Oncotype DX (primary studies from 2016 CCO systematic review[25])						
Eiermann et al. (2013)[115]	Systematic review's inclusion criteria: Study designs must involve prospectively enrolled patients and prospectively collected tumour samples	366	•			•
Oncotype DX (primary studies)						
Evans et al. (2016)[109]	Prospective cohort study	193			•	•
Kuchel et al. (2016)[110]	Prospective cohort study	135	•	•		•
Leung et al. (2016)[111]	Prospective cohort study	146	•	•		•
Martínez del Prado et al. (2018)[112]	Prospective cohort study	401	•	•	•	
Pestalozzi et al. (2016)[113]	Prospective cohort study	221	•	•	•	
Voelker et al. (2018)[114]	Retrospective analysis of prospectively collected data	50	•	•		

[a] Decisional outcomes may include but are not limited to: patient and clinician confidence, preferences, and satisfaction; patient decisional conflict and psychological effects.

CT: chemotherapy; N0: node-negative; N1: node-positive (1–3 nodes)

TABLE I.3: Primary study characteristics

Study	Study category and design	Country # of centres Time period	Patient sample	Pre-test treatment determination	Post-test treatment determination	Source(s) of funding	Conflicts of interest
Evans et al. (2016)[109]	Prospective cohort study	United States Multicentre 2011–2015	n=352 Patients with early-stage (I–II) BC (ER+) Participant losses: Unavailable (95), ineligible (38), declined to participate (19), declined to participate before receiving RS result (7)	NR	NR	American Cancer Society, National Cancer Institute	None declared
Kuchel et al. (2016)[110]	Prospective cohort study	United Kingdom Multicentre NR	n=147 Patients with early-stage BC (ER+, HER2−), N0 or with micrometastases (aged ≤50 years) or N1 (aged >50 years) Participant losses: Excluded or lost to follow up (3), made a definitive treatment decision regardless of RS score (6), given wrong RS score (1)	Recommendation: Oncologist (clinicopathology results)	Recommendation: Oncologist (clinicopathology results and RS) Decision: Oncologist and patient preference	Genomic Health	3 of 11 co-authors received honoraria and/or provided consulting/advisory services to Genomic Health
Leung et al. (2016)[111]	Prospective cohort study	Hong Kong Multicentre NR	n=150 Consecutive patients aged 18–69 years with early-stage BC (ER+, HER2−) Participant losses: Not evaluable (4), ineligible on further review (3), not recommended any adjuvant therapy (1)	Recommendation: Multidisciplinary team meeting (clinicopathology results)	Recommendation: Multidisciplinary team meeting (clinicopathology results and RS)	NR	2 of 15 co-authors are employed by Genomic Health

Study	Study category and design	Country # of centres Time period	Patient sample	Pre-test treatment determination	Post-test treatment determination	Source(s) of funding	Conflicts of interest
Martínez del Prado et al. (2018)[112]	Prospective cohort study	Spain Multicentre Sep 2012–Sep 2015	n=401 Patients with early-stage BC (ER+, HER2−) and intermediate risk for cancer recurrence according to clinicopathologic criteria Participant losses: None	Recommendation: Oncologist (clinicopathology results)	Recommendation: Oncologist (clinicopathology results and RS) Decision: Oncologist and patient preference	None	1 of 10 co-authors received honoraria from Genomic Health All authors declared no conflicts of interest
Pestalozzi et al. (2016)[113]	Prospective cohort study	Switzerland Multicentre Jul 2013–Jun 2014	n=244 Patients with early-stage BC (ER+, HER2−, N0 or N1) Participant losses: Ineligible (13), withdrew (2), withdrawn (1), did not obtain RS (7)	Decision: Multidisciplinary team meeting (clinicopathology results) and patient preference	Recommendation: Oncologist (clinicopathology results and RS) Decision: Oncologist and patient preference	Genomic Health provided the RS tests free of charge Partly supported by the Swiss State Secretariat for Education, Research and Innovation	1 of 19 co-authors received honoraria from Genomic Health
Voelker et al. (2018)[114]	Retrospective analysis of prospectively collected data	Germany Single centre 2013–2016	n=954 Patients with early-stage BC (ER+, HER2−, N0 or N1) in whom the benefit of CT was uncertain Participant losses: 904 tumours did not require extended analysis to determine CT benefit	Recommendation: Multidisciplinary team meeting (clinicopathology results)	Recommendation: Multidisciplinary team meeting (clinicopathology results and RS) Decision: Multidisciplinary team meeting and patient preference	NR	None declared

BC: breast cancer; CT: chemotherapy; ER+ estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; n: number; N0: node-negative; N1: node-positive (1–3 nodes); NR: not reported; PR+: progesterone receptor positive; RS: recurrence score (calculated using Oncotype DX)

TABLE I.4: Patient characteristics

Study Risk categories and cut-offs used	Patients analyzed, overall and by risk category, n (%)	Risk score	Age, years	Meno-pause status, %	Receptor status, %	Node status, %	Tumour grade, %	Tumour size (cm), %	Mastect-omy type, %
Evans et al. (2016)[109] LR (RS NR) IR (RS NR) HR (RS NR)	n=193 116 (60%) 60 (31%) 17 (9%)	NR	Mean: 57 (SD: 9.9)	NR	100% ER+, PR+ NR, HER2− NR	81% N0, 8% N1, 11% unknown	24% grade 1, 81% grade 2, 16% grade 3, 18% unknown	26% ≤1.0, 46% >1.1–2.0, 10% >2.1–3.0, 7% >3.1–5.0, 11% unknown	NR
Kuchel et al. (2016)[110] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=137 71 (52%) 58 (42%) 8 (6%)	Median: 17 (range: 1–76)	Median: 55 (range: 31–80)	NR	100% ER+, PR+ NR, 100% HER2−	72% N0, 27% N1, 1% unknown[a]	6% grade 1, 66% grade 2, 28% grade 3	57% ≤2.0, 40% 2.1–5.0, 3% >5.0	NR
Leung et al. (2016)[111] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=146 74 (51%) 51 (35%) 21 (14%)	NR	8% <40, 32% 40–49, 35% 50–59, 25% ≥60	47% pre, 53% post	100% ER+, PR+ NR, 49% HER2− (51% equivocal)	84% N0, 16% N1	25% grade 1, 47% grade 2, 25% grade 3, 3% unknown	16% ≤1.0, 53% >1.1–2.0, 30% 2.0–4.0, 1% >4.0	NR
Martínez del Prado et al. (2018)[112] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=401 222 (55%) 153 (38%) 26 (7%)	NR	Mean: 57 24% <50, 76% ≥50	35% pre, 64% post, 1% unknown	100% ER+, 81% PR+, 100% HER2−	77% N0, 23% N1	19% grade 1, 71% grade 2, 10% grade 3, <1% unknown	13% <1.0, 65% 1.1–2.0, 22% >2.1	84% partial, 16% total
Pestalozzi et al. (2016)[113] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=221[b] 134 (61%) 67 (30%) 20 (9%)	NR	Median: 58 (range: 32–82)	28% pre, 4% peri, 68% post	100% ER+, PR+ NR, 100% HER2−	62% N0, 38% N1	13% grade 1, 66% grade 2, 21% grade 3	60% ≤2.0, 35% >2.1–5.0, 5% >5.1	NR
Voelker et al. (2018)[114] LR (RS <18) IR (RS 18–30) HR (RS >30)	n=50 31 (62%) 16 (32%) 3 (6%)	Mean: 27 (SD: 8.5; range: 5–37)	Mean: 53 (SD: 11.0)	NR	100% ER+, 100% PR+, 100% HER2−	66% N0, 34% N1	8% grade 1, 82% grade 2, 10% grade 3	4% <1.0, 50% 1.1–2.0, 44% 2.1–5.0, 2% >5.0	NR

[a] Two patients did not undergo axillary surgery due to previous axillary dissection.

[b] n=229 for all other patient characteristics.

cm: centimetres; ER+: estrogen receptor positive; HER2−: human epidermal growth factor receptor 2 negative; HR: high risk; IR: intermediate risk; LR: low risk; n: number; N0: node-negative; N1: node-positive (1–3 nodes); NR: not reported; peri: perimenopausal; post: postmenopausal; PR+: progesterone receptor positive; pre: premenopausal; RS: recurrence score; SD: standard deviation

I.2.2. Total treatment change and net change in chemotherapy use

In six primary studies,[110-115] treatment decisions changed in a median of 37% of cases (range: 16 to 41%) after Oncotype DX testing. Before testing, a median of 52% of patients were scheduled for chemotherapy (range: 24 to 57%), compared with a median of 28% after testing (range: 20 to 46%). This corresponded to a median net reduction in chemotherapy use of 14% (range: 4 to 31%). The changes were statistically significant in all but one study.[114]

Treatment changes and net changes in chemotherapy use were stratified by Oncotype DX risk score in four[111-114] and three[110, 112, 114] studies, respectively. The total treatment change was highest in the low-risk patients (median: 13%; range: 6 to 28%) and lower in the intermediate-risk patients (median: 5.5%; range: 4 to 6%) and high-risk patients (median: 1.5%; range: 1 to 4%). The net reduction in chemotherapy use was greatest in the low-risk patients (range: 2 to 28%) compared with the intermediate-risk patients (range: 1 to 6%). The high-risk patients contributed a net increase in chemotherapy use of 1 to 4%.

Leung et al.[111] also noted that chemotherapy intensity was changed in 5% of patients: four patients (two low risk) were prescribed a less intense regimen, while three patients (all high risk) had their chemotherapy regimen escalated.

In two of the three studies reporting actual treatment administered, only one patient each changed the final decision prior to treatment.[109, 112] In Pestalozzi et al.,[113] five patients slated for chemotherapy did not receive it. The reasons for these changes were not clearly reported in any of the studies.

For complete outcome data, see Table I.5.

I.2.3. Clinician decisional outcomes

Three studies contributed outcome data. The study included in the CCO systematic review[25] reported an increase in clinician confidence in treatment recommendations after Oncotype DX testing.[115] Similarly, Kuchel et al.[110] found that clinician confidence was substantially improved from 49% to 81% of cases after testing (p-value not reported). Leung et al.[111] reported no change in clinician confidence in treatment recommendations, but pre-test confidence was already very high (96%). Consequently, only 30% of clinicians in this study thought that Oncotype DX testing contributed to their treatment decisions.

I.2.4. Patient decisional outcomes

Two studies contributed outcome data. In Evans et al.,[109] patients were more aware of the pros and cons of chemotherapy after receiving the test results ($p<0.001$), and their perceived risk of recurrence was significantly lower three weeks after receiving the test results ($p=0.004$). The authors speculated that this may be due to patients having accepted chemotherapy as part of their treatment plan. However, the patients did not feel more reassured following testing, as there was no discernible change in cancer-related distress. None of these results differed when stratified by risk level. In Kuchel et al.,[110] mean decisional conflict among 132 patients decreased by 43% after they received the Oncotype DX results, irrespective of risk score category ($p<0.0001$). It was also noted that, in 14 cases (9 intermediate and 4 low risk), the post-test treatment recommendation did not correlate with the final treatment chosen by the patients. Patients who switched to chemotherapy were younger and more likely to have nodal metastases, whereas those who eschewed chemotherapy were older and node-negative.

TABLE I.5: Impact of Oncotype DX testing on final treatment recommendation in combined N0/N1 patients

Risk categories and cut-offs	# of patients	No CT pre-test		CT pre-test		Total treatment change, %[a]	Pre-test CT, %	Post-test CT, %	Net change in CT, %[a]	CT administered, %
		Un-changed, %	No CT to CT, %	Un-changed, %	CT to no CT, %					
Evans et al. (2016)[109]										
Overall	193	--	--	--	--	--	--	24%	--	24%
LR (RS NR)	116	--	--	--	--	--	--	3%	--	3%
IR (RS NR)	60	--	--	--	--	--	--	13%	--	13%
HR (RS NR)	17	--	--	--	--	--	--	8%	--	8%
Kuchel et al. (2016)[110]										
Overall	135[b]	40%	9%	19%	32%	41%	51%	28%	↓23% (p<0.0001)	--
LR (RS <18)	69	--	--	--	--	--	27%	2%	↓24%	--
IR (RS 18–30)	58	--	--	--	--	--	21%	20%	↓1%	--
HR (RS >30)	8	--	--	--	--	--	3%	6%	↑2%	--
Leung et al. (2016)[111]										
Overall	146	46%	2%	36%	16%	19%	52%	38%	↓14% (p<0.001)	--
LR (RS <18)	74	--	0%	--	24%	12%	--	--	--	--
IR (RS 18–30)	51	--	0%	--	12%	4%	--	--	--	--
HR (RS >30)	21	--	14%	--	0%	2%	--	--	--	--
Martínez del Prado et al. (2018)[112]										
Overall	401	42%	2%	23%	33%	35%	56%	25%	↓31% (p<0.0001)	25%
LR (RS <18)	222	47%	0%	2%	51%	28%	29%	1%	↓28%	1%
IR (RS 18–30)	153	42%	3%	42%	13%	6%	21%	17%	↓4%	17%
HR (RS >30)	26	0%	15%	85%	0%	1%	6%	7%	↑1%	7%
Pestalozzi et al. (2016)[113]										
Overall	221	56%	4%	24%	17%	20%	40%	27%	↓13% (p<0.0001)	23%[c]
LR (RS <18)	134	--	--	--	--	14%	--	4%	--	--
IR (RS 18–30)	67	--	--	--	--	5%	--	14%	--	--
HR (RS >30)	20	--	--	--	--	1%	--	9%	--	--

Risk categories and cut-offs	# of patients	No CT pre-test		CT pre-test		Total treatment change, %[a]	Pre-test CT, %	Post-test CT, %	Net change in CT, %[a]	CT administered, %
		Un-changed, %	No CT to CT, %	Un-changed, %	CT to no CT, %					
Voelker et al. (2018)[114]										
Overall	50	70%	6%	14%	10%	16%	24%	20%	↓4% (*p*=NS)	--
LR (RS <18)	31	84%	4%	6%	6%	6%	8%	6%	↓2%	--
IR (RS 18–30)	16	56%	0%	25%	19%	6%	14%	8%	↓6%	--
HR (RS >30)	3	0%	67%	33%	0%	4%	2%	6%	↑4%	--

[a] Calculated using total patient population for the denominator.

[b] Data only available for 135 of 137 patients.

[c] Data were not reported for 3 of 221 patients.

CT: chemotherapy; HR: high risk; IR: intermediate risk; LR: low risk; N0: node-negative; N1: node-positive (1–3 nodes); NS: not significant; *p*: *p*-value statistic; RS: recurrence score

Appendix J: Rapid Review 3 – Evidence Summary Tables

TABLE J.1: Study characteristics

Study	Study design	Country Study period	Population	Intervention(s)	HRQoL tool used	Source of funding Conflicts of interest
Chemotherapy vs. no chemotherapy						
Kim et al. (2015)[56]	Cross-sectional study	Korea 2012	Patients with BC who had surgery as primary treatment (consecutive series)	3% received CT (no details on drug(s) or regimen provided)	EQ-5D-3L	Funding: Bayer Korea Conflicts: None
Lidgren et al. (2007)[57]	Cross-sectional study	Sweden 2005	Patients with previous diagnosis of BC	21% received CT (no details on drug(s) or regimen provided)	EQ-5D	Funding: AstraZeneca Conflicts: NR
Moro-Valdezate et al. (2014)[58] (multiple publication[59])	Prospective cohort study	Spain 2003–2007	Patients with stage 0–IIIB BC who underwent mastectomy or breast-conserving surgery	97% received CT (no details on drug(s) or regimen provided)	EQ-5D-3L	Funding: NR Conflicts: NR
Tiezzi et al. (2017)[60]	Cross-sectional study	Brazil 2013–2014	Patients aged 40–70 years who underwent treatment for BC 1–3 years prior to study	76% of study group received CT (FEC, EC, or EC + taxane), surgery, and RT Comparator group received surgery + RT, with/without ET	SF-36	Funding: None Conflicts: None
Different chemotherapy regimens						
Berger et al. (2009)[61]	RCT	United States 2003–2006	Patients aged ≥19 years, first diagnosis of stage I–IIIA BC, post-modified radical mastectomy or lumpectomy, scheduled to begin 4 treatments of anthracycline-based CT	Patients were randomized to:[a] a) dose-dense (AC for 4 cycles every 2 weeks) with a taxane (docetaxel or paclitaxel); b) dose-standard (AC for 4 cycles every 3 weeks) with a taxane (docetaxel or paclitaxel); or c) dose-standard (AC for 4 cycles every 3 weeks) without a taxane	SF-36 version 2	Funding: National Institutes of Health, National Institute of Nursing Research Conflicts: NR

Study	Study design	Country Study period	Population	Intervention(s)	HRQoL tool used	Source of funding Conflicts of interest
Paskett et al. (2009)[62]	RCT	United States 1999	Patients with stage II BC	Patients were randomized to: a) low-dose CAF (300 mg/m^2, 30 mg/m^2, and 300x2 mg/m^2 over 4 cycles); b) standard-dose CAF (400 mg/m^2, 40 mg/m^2, and 400x2 mg/m^2, over 6 cycles); or c) high-dose CAF (600 mg/m^2, 60 mg/m^2, and 600x2 mg/m^2, over 4 cycles)	SF-36	Funding: National Institutes of Health Conflicts: NR
Shiroiwa et al. (2011)[63]	RCT	Japan 2001–2003	Patients aged 18–70 years with stages I–IIIA BC, with no previous ET or CT, in an Eastern Cooperative Oncology Group performance status of 0–1	Patients were randomized to: a) 4 cycles of an anthracycline + paclitaxel; b) 4 cycles of anthracycline-based regimen + docetaxel; c) 8 cycles of paclitaxel; or d) 8 cycles of docetaxel	EQ-5D	Funding: Comprehensive Support Project for Oncology Research, Health Outcomes Study of Public Health Research Foundation, corporate and individual sponsors Conflicts: NR
Chemotherapy without comparator						
Abu Farha et al. (2017)[64]	Cross-sectional study	Palestine 2016	Patients aged ≥18 years treated for BC >12 months prior to the study	97% received CT (most commonly AC or paclitaxel), with or without RT and/or ET, following surgery	EQ-5D-5L	Funding: None Conflicts: None
Daldoul et al. (2018)[65]	Cross-sectional study	Tunisia 2016–2017	Patients aged 18–70 years with histological evidence of BC	94% received CT (no details on drug(s) or regimen provided)	SF-36	Funding: NR Conflicts: None
Kaur et al. (2018)[66]	Cross-sectional study	India 2014–2017	BC survivors without metastatic, recurrent, or inoperable disease who had completed their primary treatment for BC	96% received CT (most commonly CAF or paclitaxel-based regimen)	SF-36	Funding None Conflicts: None

Study	Study design	Country Study period	Population	Intervention(s)	HRQoL tool used	Source of funding Conflicts of interest
Lee et al. (2012)[67]	Cross-sectional study	Korea 2009–2011	BC survivors who were medically stable, ≥1 year past surgery, and had completed treatment Control group consisted of healthy patients	80% of study group received CT (no details on drug(s) or regimen provided)	SF-36	Funding: NR Conflicts: None
Safarinejad et al. (2013)[68]	Prospective cohort study	Iran 2009–2011	Patients aged 24–45 years with stage I–II BC who had lumpectomy at least 1 year before recruitment Control group consisted of age-matched healthy patients	68% of study group received CT (no details on drug(s) or regimen are provided)	SF-36	NR No conflicts of interest
Tonosaki et al. (2014)[69]	Prospective cohort study	Japan 2011–2012	Patients aged 20–64 years with stage I–IIIA BC whose CT regimen included an anthracycline	Patients received at least one cycle of: a) AC intravenously every 3 weeks for 4 cycles; b) TC intravenously every 3 weeks for 4 cycles; or c) AC + paclitaxel every 3 weeks for 4 cycles	SF-36	Funding: Ministry of Education, Culture, Sports, Science and Technology of Japan Conflicts: None
Turan et al. (2009)[70]	Prospective cohort study	Turkey NR	Patients with stage I–III BC with osteoporosis (study group) who received adjuvant CT Control group consisted of healthy patients without osteoporosis	100% of study group were treated with 6 cycles of adjuvant CT (cyclophosphamide + epirubicin + fluorouracil)	SF-36	Funding: NR Conflicts: NR

Study	Study design	Country Study period	Population	Intervention(s)	HRQoL tool used	Source of funding Conflicts of interest
Wang et al. (2018)[71]	Cross-sectional study	China 2013–2014	Patients aged ≥18 years clinically diagnosed with stage I–IV BC Control group consisted of patients aged ≥18 years clinically diagnosed with precancer	32% of study group received surgery and postoperative CT (no details on drug(s) or regimen provided)	EQ-5D-3L	Funding: National Natural Science Foundation of China, The Cancer Screening Program in Urban China, supported by the National Health and Family Planning Committee (currently National Health Commission) Conflicts: None

[a] Some patients received variations of these chemotherapy regimens.

AC: doxorubicin and cyclophosphamide; BC: breast cancer; CAF: cyclophosphamide, doxorubicin, and fluorouracil; CT: chemotherapy; EC: epirubicin and cyclophosphamide; EQ-5D: EuroQol 5 dimensions (3L: 3-level version; 5L: 5-level version); ET: endocrine therapy; FEC: fluorouracil, epirubicin, and cyclophosphamide; HRQoL: health-related quality of life; NR: not reported; RCT: randomized controlled trial; RT: radiation therapy; SF-36: 36-Item Short Form Health Survey; TC: docetaxel and cyclophosphamide

TABLE J.2: Patient characteristics

Study	Patients enrolled, n Patients analyzed, n	Age, years	Cancer stage, %	Patients who received mastectomy, % (type, %)	Patients who received adjuvant chemotherapy, % (type, %)	Patients who received other treatment, type and %	Node status, %
Chemotherapy vs. no chemotherapy							
Kim et al. (2015)[56]	Enrolled: 1,002 Analyzed: 827	7% <40, 32% 40–49, 47% 50–59, 15% ≥60	0: 16%, I: 44%, II: 31%, III: 8%	100% (63% partial, 37% total)	3%[a] (NR)	7% RT	NR
Lidgren et al. (2007)[57]	Enrolled: 361 Analyzed: 345	Mean: 57 (range: 28–93)	I–III: 81%, IV: 19%[b]	NR	21%[a] (NR)	36% ET	NR
Moro-Valdezate et al. (2014)[58] (multiple publication[59])[c]	Enrolled: 446 Analyzed: 364	Mean: 59 (SD: 13)	I: 48%, IIA: 27%, IIB: 12%, IIIA: 9%, IIIB: 5%	100% (61% partial, 39% total)	97% (NR)	75% RT	NR
Tiezzi et al. (2017)[60]	Enrolled: 136 Analyzed: 112	CT: Median: 48 (range: 26–79) No CT: Median: 54 (range: 38–77)	0: 4%, I: 12%, II: 43%, III: 37%, NR: 5%	100% (51% tumorectomy, 49% total)	76%[a] (40% FEC, 53% EC, 7% EC + taxane [4 cycles])	100% RT, 36% ET	NR
Different chemotherapy regimens							
Berger et al. (2009)[61]	Enrolled: 196 Analyzed: 158	Mean: 52 (SD: 10; range: 29–83)	I: 31%, II: 55%, III: 15%	100% (42% partial, 58% total)	100% (100% taxane)	NR	NR
Paskett et al. (2009)[62]	Enrolled: 314 Analyzed: 245	Mean: 62 (SD: 10)	II: 100%	100% (22% partial, 78% total)	100% (30% low-dose CAF, 38% standard-dose CAF, 32% high-dose CAF)	23% RT, 46% ET	NR
Shiroiwa et al. (2011)[63]	Enrolled: 300 Analyzed: 299	Median: 53 (range: 18–70)	I–IIIA: NR	100% (42% partial, 58% total, 1% other)	100% (25% ACP, 25% ACD, 25% paclitaxel, 25% docetaxel)	NR	55% N1, 27% N2, 18% N3

Study	Patients enrolled, n Patients analyzed, n	Age, years	Cancer stage, %	Patients who received mastectomy, % (type, %)	Patients who received adjuvant chemotherapy, % (type, %)	Patients who received other treatment, type and %	Node status, %
Chemotherapy without comparator							
Abu Farha et al. (2017)[64]	Enrolled: 170 Analyzed: 170	Mean: 52 (SD: 11)	I: 34%, II: 14%, III: 24%, IV: 28%[b]	82% (62% total, 38% unknown)	97% (57% AC,[d] 47% paclitaxel[d])	37% RT, 35% ET	NR
Daldoul et al. (2018)[65]	Enrolled: 70 Analyzed: 70	Mean: 41 (SD: 14)	I: 24%, II: 27%, III: 24%, IV: 24%[b]	89% (NR)	94% (NR)	76% RT, 70% ET, 16% TT	NR
Kaur et al. (2018)[66]	Enrolled: 230 Analyzed: 230	Mean: 50 (SD: 10)	I: 7%, II: 50%, III: 43%	100% (24% partial, 76% total)	96% (NR)	83% RT, 58% ET	NR
Lee et al. (2012)[67]	Enrolled: 97 Analyzed: 96	Mean: 53 (SD: 10)	I: 39%, II: 42%, III: 19%, IV: 1%	100% (28% partial, 72% total)	80% (NR)	32% RT, 90% ET	NR
Safarinejad et al. (2013)[68]	Enrolled: 236[e] Analyzed: 186[e]	Mean: 38 (SD: 6)	I: 62%, II: 38%	100% (100% sentinel lymph node excision)	68% (NR)	46% RT, 80% ET	NR
Tonosaki et al. (2014)[69]	Enrolled: 38 Analyzed: 28	Mean: 50 (range: 27–64)	I–IIIA: NR	NR	100% (43% AC, 29% TC, 29% AC + paclitaxel)	NR	NR
Turan et al. (2009)[70]	Enrolled: 26[e] Analyzed: 26[e]	Median: 49 (range: 26–75)	I: 8%, II: 73%, III: 19%	100% (19% partial, 81% total)	100% (NR)	84% RT, 39% ET	NR
Wang et al. (2018)[71]	Enrolled: NR Analyzed: 2,626	Mean: 49[f]	I: 19%[f], II: 47%, III: 21%, IV: 9%, NR: 4%	59% (NR)	69%[f] (NR)	8% RT,[f] 4% ST, 1% other	NR

[a] HRQoL data presented for both chemotherapy and no chemotherapy groups.

[b] Outcome data reported separately by stage/state of cancer.

[c] Data from most recent publication[34] was extracted, as it provided more outcome data; sample size and patient characteristics varied slightly between publications.

[d] Not mutually exclusive (some patients received both chemotherapy regimens).

[e] Early-stage breast cancer group.

[f] Data was not clearly reported and was calculated by reviewer.

AC: doxorubicin and cyclophosphamide; ACD: anthracycline-based regimen with docetaxel; ACP: anthracycline-based regimen with paclitaxel; CAF: cyclophosphamide, doxorubicin, and fluorouracil; CT: chemotherapy; EC: epirubicin and cyclophosphamide; ET: endocrine therapy; FEC: fluorouracil, epirubicin, and cyclophosphamide; HRQoL: health-related quality of life; n: number; N1: 1–3 positive nodes; N2: 4–9 positive nodes; N3: 10+ positive nodes; NR: not reported; RT: radiation therapy; SD: standard deviation; ST: symptomatic treatment; TC: docetaxel and cyclophosphamide; TT: targeted therapy

TABLE J.3: Impact of chemotherapy versus no chemotherapy on health-related quality of life – EQ-5D

Group	Outcome measure	Chemotherapy		No chemotherapy		Chemotherapy vs. no chemotherapy, *p*-value
		n	Score	n	Score	
Kim et al. (2015)[56]						
All patients	Index score, mean (SD)	26	0.90 (0.081)	793	0.92 (0.088)	Index score: *p*=0.36
	VAS, mean (SD)	26	76.7 (18.9)	793	78.5 (16.6)	VAS: *p*=0.60
Lidgren et al. (2007)[57]						
"State P" (first year after primary)	Index score, mean [95% CI]	23	0.62 [0.51, 0.70]	17	0.74 [0.57, 0.84]	*p*=NR
"State R" (first year after recurrence)	Index score, mean [95% CI]	7	0.77 [0.57, 0.84]	4	0.82 [0.73, 0.96]	
"State S" (second and following years after primary/recurrence)	Index score, mean [95% CI]	NR	NR	79	0.82 [0.79, 0.86]	
Moro-Valdezate et al. (2014)[58]						
All patients	Index score, median	364	0.83	NR	NR	Index score, multivariate analysis of adjuvant chemotherapy status: *p*<0.001, favours chemotherapy
	VAS, median	361	80.0			

CI: confidence interval; EQ-5D: EuroQol 5 dimensions; n: number (sample size); NR: not reported; *p*: *p*-value statistic; SD: standard deviation; VAS: visual analogue scale

TABLE J.4: Impact of chemotherapy versus no chemotherapy on health-related quality of life – SF-36

Group	Outcome measure	Chemotherapy		No chemotherapy		Chemotherapy vs. no chemotherapy, *p*-value
		n	Score	n	Score	
Tiezzi et al. (2017)[60]						
All patients	Physical functioning, mean (SD)	85	60.4 (25.2)	27	77.4 (17.9)	*p*=0.01, favours no chemotherapy
	Role physical, mean (SD)		28.8 (40.9)		60.2 (43.4)	*p*=0.01, favours no chemotherapy
	Bodily pain, mean (SD)		50.0 (26.4)		55.2 (22.9)	*p*=NS
	General health, mean (SD)		70.5 (24.3)		72.5 (21.4)	*p*=NS
	Vitality, mean (SD)		60.5 (25.2)		60.9 (25.5)	*p*=NS
	Social functioning, mean (SD)		64.6 (31.5)		70.4 (32.7)	*p*=NS
	Role emotional, mean (SD)		56.1 (44.9)		69.1 (40.2)	*p*=NS
	Mental health, mean (SD)		65.3 (24.7)		63.0 (19.5)	*p*=NS

n: number (sample size); NS: not significant; *p*: *p*-value statistic; SD: standard deviation; SF-36: 36-Item Short Form Health Survey

TABLE J.5: Impact of different chemotherapy regimens on health-related quality of life – EQ-5D

Chemotherapy regimen	Outcome measure	n	Score	Comparison of chemotherapy regimens, *p*-value
Shiroiwa et al. (2011)[63]				
ACP	Index score, mean [95% CI]	74	0.85 [0.81, 0.89]	ACP vs. docetaxel: p=0.005 ACD vs. docetaxel: p<0.0001 Paclitaxel vs. docetaxel: p=NS Scores significantly higher for ACP and ACD vs. docetaxel
ACD	Index score, mean [95% CI]	75	0.85 [0.81, 0.89]	
Paclitaxel	Index score, mean [95% CI]	75	0.80 [0.77, 0.84]	
Docetaxel	Index score, mean [95% CI]	75	0.79 [0.76, 0.83]	

ACD: anthracycline-based regimen with docetaxel; ACP: anthracycline-based regimen with paclitaxel; CI: confidence interval; EQ-5D: EuroQol 5 dimensions; n: number (sample size); NS: not significant

TABLE J.6: Impact of different chemotherapy regimens on health-related quality of life – SF-36

Chemotherapy regimen	Outcome measure	n	Score	Comparison of chemotherapy regimens, *p*-value
Berger et al. (2009)[61]				
All chemotherapy groups	PCS, mean (SD)	158	45.1 (9.4)	PCS: *p*=0.02, favours standard-dose without a taxane MCS: *p*=NS
	MCS, mean (SD)		49.2 (10.6)	
Dose-dense taxane-based	PCS, mean (SD)	59	44.5 (9.6)	
	MCS, mean (SD)		48.4 (10.3)	
Standard-dose taxane-based	PCS, mean (SD)	37	44.1 (10.0)	
	MCS, mean (SD)		51.2 (10.1)	
Standard-dose without a taxane	PCS, mean (SD)	62	46.7 (8.9)	
	MCS, mean (SD)		48.9 (11.1)	
Paskett et al. (2009)[62]				
Low-dose CAF	Physical functioning, mean (SD)	74	75.1 (30.6)	Role physical: *p*<0.0001, mean score was highest in high-dose arm (84.9) and lowest in standard-dose arm (65.1) All other subscales: *p*=NS
	Role physical, mean (SD)		74.7 (39.4)	
	Bodily pain, mean (SD)		73.7 (24.1)	
	General health, mean (SD)		74.5 (21.5)	
	Vitality, mean (SD)		61.4 (22.7)	
	Social functioning, mean (SD)		87.5 (23.8)	
	Role emotional, mean (SD)		86.9 (31.1)	
	Mental health, mean (SD)		77.7 (16.6)	
Standard-dose CAF	Physical functioning, mean (SD)	93	73.0 (30.7)	
	Role physical, mean (SD)		65.1 (41.6)	
	Bodily pain, mean (SD)		71.4 (24.3)	
	General health, mean (SD)		68.9 (20.6)	
	Vitality, mean (SD)		56.8 (22.1)	
	Social functioning, mean (SD)		82.1 (27.1)	
	Role emotional, mean (SD)		77.8 (36.2)	
	Mental health, mean (SD)		76.6 (17.4)	
High-dose CAF	Physical functioning, mean (SD)	78	82.3 (22.9)	
	Role physical, mean (SD)		84.9 (30.2)	
	Bodily pain, mean (SD)		77.3 (21.2)	
	General health, mean (SD)		75.4 (18.0)	
	Vitality, mean (SD)		64.6 (17.3)	
	Social functioning, mean (SD)		87.2 (21.1)	
	Role emotional, mean (SD)		87.9 (27.0)	
	Mental health, mean (SD)		76.1 (15.9)	

CAF: cyclophosphamide, doxorubicin, and fluorouracil; MCS: Mental Component Summary; n: number (sample size); NS: not significant; *p*: *p*-value statistic; PCS: Physical Component Summary; SD: standard deviation; SF-36: 36-Item Short Form Health Survey

TABLE J.7: Impact of chemotherapy (no comparator) on health-related quality of life – EQ-5D

Group	Outcome measure	n	Score
Abu Farha et al. (2017)[64]			
Breast cancer stage I	Index score, median (IQR)	58	0.72 (0.55-0.85)
Breast cancer stage II	Index score, median (IQR)	24	0.61 (0.52-0.77)
Breast cancer stage III	Index score, median (IQR)	40	0.67 (0.51-0.81)
Wang et al. (2018)[71]			
Breast cancer patients with surgery and postoperative chemotherapy	Index score, mean [95% CI]	849	0.79 [0.78, 0.80]

CI: confidence interval; EQ-5D: EuroQol 5 dimensions; IQR: interquartile range; n: number (sample size)

TABLE J.8: Impact of chemotherapy (no comparator) on health-related quality of life – SF-36

Group	Outcome measure	n	Score
Daldoul et al. (2018)[65]			
Breast cancer stage I	Total score, mean (SD)	17	50.6 (5.0)
Breast cancer stage II	Total score, mean (SD)	19	58.2 (5.4)
Breast cancer stage III	Total score, mean (SD)	17	51.0 (5.3)
Kaur et al. (2018)[66]			
Breast cancer survivors	PCS, mean (SD)	230	39.1 (6.5)
	MCS, mean (SD)		46.8 (6.2)
	Physical Functioning, mean (SD)		51.1 (18.6)
	Role physical, mean (SD)		45.7 (18.1)
	Bodily pain, mean (SD)		54.1 (15.0)
	General health, mean (SD)		51.7 (15.1)
	Vitality, mean (SD)		48.3 (15.9)
	Social functioning, mean (SD)		60.9 (16.3)
	Role emotional, mean (SD)		64.4 (19.8)
	Mental health, mean (SD)		69.1 (10.4)
Lee et al. (2012)[67]			
Breast cancer survivors	Physical functioning, mean (SD)	96	69.7 (25.0)
	Role physical, mean (SD)		48.4 (40.4)
	Bodily pain, mean (SD)		66.4 (22.2)
	General health, mean (SD)		49.7 (18.3)
	Vitality, mean (SD)		52.8 (16.6)
	Social functioning, mean (SD)		71.4 (22.0)
	Role emotional, mean (SD)		54.5 (43.6)
	Mental health, mean (SD)		60.9 (18.6)
Safarinejad et al. (2013)[68]			
All patients	Physical functioning, mean (SD)	186	78.2 (12.4)
	Limitations due to physical health, mean (SD)		78.7 (10.3)
	Pain, mean (SD)		82.8 (12.1)
	General health, mean (SD)		64.7 (14.8)
	Energy/fatigue, mean (SD)		63.8 (11.6)
	Limitations due to emotional problems, mean (SD)		71.5 (12.5)
	Social functioning, mean (SD)		63.7 (11.6)
	Emotional well-being, mean (SD)		57.4 (10.3)

Group	Outcome measure	n	Score
	Health change, mean (SD)		67.4 (11.6)
Tonosaki et al. (2014)[69]			
All patients	Physical functioning, mean (SD)	28	87.0 (14.4)
	Role physical, mean (SD)		71.7 (25.6)
	Bodily pain, mean (SD)		71.7 (24.9)
	General health, mean (SD)		57.1 (13.8)
	Vitality, mean (SD)		62.1 (20.9)
	Social functioning, mean (SD)		68.8 (24.9)
	Role emotional, mean (SD)		75.6 (28.2)
	Mental health, mean (SD)		66.3 (19.1)
Turan et al. (2009)[70]			
Patients with breast cancer	Physical functioning, mean (SD)	26	62.1 (24.2)
	Role physical, mean (SD)		17.3 (37.3)
	Bodily pain, mean (SD)		70.8 (32.7)
	General health, mean (SD)		56.7 (26.5)
	Vitality, mean (SD)		51.2 (25.0)
	Social functioning, mean (SD)		70.2 (29.5)
	Role emotional, mean (SD)		30.8 (45.1)
	Mental health, mean (SD)		54.2 (23.9)

MCS: Mental Component Summary; n: number (sample size); PCS: Physical Component Summary; SD: standard deviation; SF-36: 36-Item Short Form Health Survey

Appendix K: Outcomes, Costs, Effectiveness, and Cost-Effectiveness

TABLE K.1: Outcomes, costs, effectiveness, and cost-effectiveness of Oncotype DX, Prosigna, and no testing, for a population of 1,000 node-negative patients

	Oncotype DX	Prosigna	No testing
Outcomes (number of patients)			
Provided test	1,000	1,000	--
Provided adjuvant chemotherapy	212	334	489
Hospital visit for toxicity	14	23	33
10-year distant recurrence	60	53	75
10-year death	50	44	62
Costs			
Providing test	$3.74 million	$2.87 million	--
Providing adjuvant chemotherapy	$3.10 million	$4.89 million	$7.16 million
Incurred prior to distant recurrence	$14.28 million	$14.31 million	$13.83 million
Incurred following distant recurrence	$3.18 million	$2.80 million	$3.89 million
Incurred last 3 months	$2.67 million	$2.35 million	$3.27 million
Total lifetime costs	$26.98 million	$27.21 million	$28.16 million
Effect			
QALYs	17,066	17,237	16,682
Cost-effectiveness			
ICER	--	$1,377	--
WTP $20,000/QALY	23.8%	76.1%	0.1%
WTP $50,000/QALY	21.1%	78.9%	0.1%
WTP $100,000/QALY	20.0%	79.9%	0.1%

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness-to-pay

TABLE K.2: Outcomes, costs, effectiveness, and cost-effectiveness of Oncotype DX, Prosigna, and no testing, for a population of 1,000 node-positive patients

	No testing	Oncotype DX	Prosigna
Outcomes (number of patients)			
Provided test	--	1,000	1,000
Provided adjuvant chemotherapy	489	348	788
Hospital visit for toxicity	33	24	54
10-year distant recurrence	183	163	85
10-year death	152	136	70
Costs			
Providing test	--	$3.74 million	$2.87 million
Providing adjuvant chemotherapy	$7.16 million	$5.10 million	$11.52 million
Incurred prior to distant recurrence	$12.25 million	$12.65 million	$13.47 million
Incurred following distant recurrence	$8.42 million	$7.61 million	$4.24 million
Incurred last 3 months	$7.10 million	$6.41 million	$3.57 million
Total lifetime costs	$34.93 million	$35.50 million	$35.67 million
Effect			
QALYs	14,263	14,715	16,446
Cost-effectiveness			
ICER	--	Extendedly dominated	$339
WTP $20,000/QALY	0.0%	0.6%	99.4%
WTP $50,000/QALY	0.0%	0.4%	99.6%
WTP $100,000/QALY	0.0%	0.4%	99.6%

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; WTP: willingness-to-pay

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Michelle Pollock wrote the Background, oversaw the conduct of the clinical review, conducted rapid review 1, helped conduct rapid reviews 2 and 3, wrote the Discussion, and approved the final version of the report for publication.

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Andrew Sutton conducted the economic evaluation, wrote the Discussion, and approved the final version of the report for publication.

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Lisa Tjosvold conducted the literature searches for the Background, rapid reviews 2 and 3, and the economic evaluation, and approved the final version of the report for publication.

Bing Guo oversaw the conduct of the report, helped write the Background, reviewed drafts of the clinical review and economic evaluation, and approved the final version of the report for publication.

This Alberta Health Evidence Review report examines the clinical effectiveness and cost-effectiveness of Oncotype DX and Prosigna genetic testing in early-stage, estrogen receptor-positive, human epidermal growth factor 2-negative, node-negative or node-positive (one to three nodes) breast cancer, contextualized to the Alberta setting.

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