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Gene expression profiles to guide adjuvant chemotherapy in luminal, HER2-negative breast cancer

Nilsson Ek A, Linderholm B, Olofsson Bagge R, Kovács A, Stadig I, Svanberg T, Svensson M, Wallerstedt SM, Strandell A

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Gene expression profiles to guide adjuvant chemotherapy in luminal, HER2-negative breast cancer [Genuttrycksprofil för beslut om adjuvant cytostatikabehandling vid hormonkänslig, HER2-negativ bröstcancer]

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1. Abstract

Background Breast cancer is the most common cancer among women in Sweden, 8,000 being diagnosed annually. Both incidence and survival rates have increased over the years. According to clinical routine, patients with hormone sensitive (luminal) breast cancer are treated post-operatively with adjuvant endocrine therapy for 5-10 years. Patients that are hormone-receptor negative are instead most often treated with adjuvant chemotherapy, and patients that are HER2-positive receive both chemotherapy and HER2-directed therapies. There are also a high-risk group of patients with luminal breast cancer either with a higher grade or proliferation (Luminal B) or patients that are node-positive where adjuvant chemotherapy often are recommended. To improve the prediction of clinical outcomes and to identify breast cancer patients in this group for whom chemotherapy can be withheld, and thereby adverse effects associated with such treatment avoided, gene expression assays have been developed.

Questions at issue

1. In breast cancer patients with luminal tumour and intermediate clinical risk of recurrence, how does the use of gene expression assays affect clinical outcomes and decisions to withhold adjuvant chemotherapy, compared with not using such molecular profiling?
2. In breast cancer patients with luminal tumour, intermediate clinical risk of recurrence, and low/intermediate genetic risk of recurrence according to a gene expression assay, will survival, health-related quality of life, and/or recurrence be affected if chemotherapy is withheld?

Methods Two authors performed searches (August 2018, updated January 2019) in Medline, Embase, PubMed, the Cochrane Library, PsycInfo and a number of HTA-databases. They independently assessed the abstracts, and selected, in consensus, full-text articles to be sent to the other authors, who then decided on inclusion/exclusion. The included studies were critically appraised, and data extracted. When possible, data were pooled in a meta-analysis using RevMan 5.2. The certainty of evidence was assessed according to GRADE.

Results Three randomised controlled trials (RCTs) and 21 observational studies were included in this health technology assessment (HTA).

There were no studies comparing the use of gene expression assays, versus no such use, regarding potential effects on overall survival and health-related quality of life, and one inconclusive study on recurrence. Fourteen cross-sectional studies, in various settings, investigated the decision to withhold chemotherapy, with versus without a gene expression assay. Similar number of studies reported a decrease in the use of chemotherapy as the opposite, that is, an increase in the use of chemotherapy.

The evidence for clinical outcomes regarding the comparison withholding versus providing chemotherapy was mainly based on three RCTs, providing data on overall survival and recurrence, but not health-related quality of life.

Overall survival (OS) was reported in one RCT including 6,711 breast cancer patients with intermediate clinical and low/intermediate genetic risk (according to gene expression assay) of recurrence. Similar OS rates of 94% at nine years were found in both groups; HR 0.99 (95% CI 0.79 to 1.22). Three cohort studies, reporting point estimates favouring chemotherapy, did not contribute further to the conclusion.
Conclusion: Withholding adjuvant chemotherapy in breast cancer patients with intermediate clinical risk of recurrence and low/intermediate risk according to a gene expression assay, compared with providing chemotherapy, probably results in little or no difference in overall survival within nine years (GRADE⊕⊕⊕◯).

Recurrence was reported in three RCTs and in five cohort studies. In the largest RCT, the HR for recurrence was 1.11 (95% CI 0.90 to 1.37). Recurrence occurred in 5.4% vs 4.6% in the ITT analysis. The absolute difference was a 0.76 percentage point increase (95% CI -0.3 to 1.8), for patients in whom chemotherapy was withheld. Regarding distal recurrence, data from the largest RCT were combined with data from subgroups in two other RCTs fulfilling the PICO of this HTA. The pooled HR comparing withholding versus providing chemotherapy was 1.13 (95% CI 0.90 to 1.41). The five cohort studies did not contribute further to the conclusion.
Conclusion: Withholding adjuvant chemotherapy in breast cancer patients with intermediate clinical risk of recurrence and low/intermediate risk according to a gene expression assay, compared with providing chemotherapy, can probably not exclude a small increased risk of recurrence. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

The costs for introducing gene expression testing in Region Västra Götaland depend on the price of the test and the proportion of patients that will be withheld chemotherapy based on the test result. In a base case scenario without any change in chemotherapy use, the total health care costs per year would increase by 4.5 million SEK, corresponding to an increased cost per patient of 18,000 SEK (current assay price). If the proportion of patients withheld chemotherapy increases by more than 22.5% by the use of gene expressions assays, the costs will decrease for the health care sector. Potential cost savings because of reduced sick leave in patients withheld chemotherapy are not included in these calculations.

Concluding remarks This HTA on gene expression testing in patients with luminal breast cancer at intermediate clinical risk of recurrence reveals a lack of studies, comparing test versus no test, evaluating overall survival, health-related quality of life, and recurrence. The studies on chemotherapy decision making were performed in various settings where chemotherapeutic traditions may vary, and no general conclusions can be drawn whether the use of chemotherapy would decrease or increase by the use of such tests. After gene expression testing, withholding adjuvant chemotherapy, versus providing such treatment, probably results in similar overall survival rates over nine years, while a slightly increased risk of recurrence can probably not be excluded. The effects of avoiding adverse reactions from chemotherapy by withholding such treatment, has not been studied in the patient group at issue.

2. Populärvetenskaplig sammanfattning – Swedish summary

I denna HTA-rapport har vi utvärderat två frågeställningar som båda har att göra med test av brösttumörers gener:

1. *Hos kvinnor med bröstcancer och måttligt hög risk för att tumören ska komma tillbaka enligt etablerade riskfaktorer:*
   Påverkas överlevnad, livskvalitet eller återfall om man gjort gentest på tumören eller inte, och skiljer sig användningen av cellgifter?
2. *Hos kvinnor med bröstcancer, måttligt hög risk för att tumören ska komma tillbaka enligt etablerade riskfaktorer och låg/måttligt hög risk enligt gentest:*
   Påverkas överlevnad, livskvalitet eller återfall om man avstår från cellgiftsbehandling?

Den typ av test som rapporten avser har utvecklats för att identifiera patienter där man kan avstå från cellgifter utan att öka risken för återfall. Syftet är alltså inte att öka överlevnaden eller att minska risken för att cancern ska återkomma. Istället vill man kunna identifiera patienter som kan slippa en behandling som ger mycket biverkningar, utan att samtidigt öka risken att dö i förtid eller att tumören kommer tillbaka.

Sammanfattningsvis visar vår genomgång av den vetenskapliga litteraturen inom området att det inte finns några studier som har undersökt om testning av brösttumörers genprofiler i förlängningen påverkar överlevnad eller livskvalitet. När det gäller återfall fanns det bara en studie, för liten för att dra kunna dra slutsatser av. I studier som undersökt om gentest påverkar användningen av cellgifter har man sett både ökning och minskning av användningen. Detta kan bero på att användningen av cellgifter varierar stort i just denna patientgrupp. Avseende den andra frågeställningen skiljer sig överlevnaden efter nio år troligen inte hos dem som avstått från cellgiftsbehandling jämfört med dem som fått sådan behandling. I båda grupperna lever 94% av patienterna efter denna tid. Risken för återfall är låg, men det kan troligen inte uteslutas att risken för att tumören kommer tillbaka är något högre för dem som utifrån gentest avstått från cellgiftsbehandling. Ingen studie har i just denna patientgrupp jämfört livskvaliteten hos dem som fått respektive inte fått cellgifter.

Bakgrund Bröstcancer är den vanligaste sortens cancer hos kvinnor. Sjukdomen drabbar 8000 kvinnor i Sverige varje år. Efter att tumören opererats bort, bestäms behandlingen utifrån hur hög risken är för att tumören ska komma tillbaka (återfall). Om risken är hög, behandlas kvinnan i allmänhet med cellgifter, och om risken är låg avstår man ofta från sådan behandling. Om risken är måttligt hög behandlas kvinnan oftast med cellgifter. I denna grupp av patienter är man dock mer osäker på nytta/risk-balansen av cellgiftsbehandling, inte minst för att cellgifter kan ge besvärliga biverkningar. Behandlingen varierar därför avsevärt mellan olika delar av Sverige. Med målsättningen att bättre kunna identifiera patienter där man kan avstå från cellgiftsbehandling och därmed undvika dessa biverkningar, har företag utvecklat tester för att undersöka generna i brösttumören. Denna typ av gentest används i vissa andra länder, men inte i svensk sjukvård.

Metod Med hjälp av etablerade metoder identifierade vi vetenskapliga artiklar som kunde bidra till att få svar på de aktuella frågeställningarna. Resultaten i rapporten baserades på dessa studier. För att veta hur stor tillförlitligheten var till resultaten, bedömde vi även den vetenskapliga kvaliteten på studierna var för sig och sammantaget.

Resultat När det gäller den första frågeställningen, avseende värdet av gentest för bröstcancerpatienter med måttligt hög risk för återfall, saknades i princip studier som utvärderade hur det gick för kvinnor som gjort respektive inte gjort ett sådant test. I 14 studier undersöktes hur stor andel av patienterna som fick avstå från cellgiftsbehandling med respektive utan gentest.

Det var lika många studier som visade att en större andel fick avstå cellgifter som tvärtom, det vill säga att en ökad andel fick cellgiftsbehandling med gentest som beslutsunderlag. Detta kan bero på att användningen av cellgifter varierar stort i just denna patientgrupp. Studierna kan därför inte bidra till en generell slutsats om hur användningen av cellgifter skulle påverkas om gentest infördes.

Avseende den andra frågeställningen identifierade vi totalt tre studier där kvinnor, som enligt test av brösttumörens gener hade låg/måttligt hög risk för att tumören skulle komma tillbaka, slumpmässigt (randomiserat) hade fått respektive inte fått cellgifter, och där man sedan följt upp hur det gått. Denna typ av vetenskaplig design ger bäst information om effekter av olika behandlingsalternativ. Det beror på att det annars inte är en slump vem som får vad, eftersom både läkare och patienter gör aktiva behandlingsval. Valet för en enskild patient baseras dels på hur stor risk man bedömer att det är att tumören ska komma tillbaka, dels på hur man ser på denna risk. I den största av dessa tre studier, omfattande 6711 patienter, visades att överlevnaden efter nio år troligen inte skilde sig mellan grupperna.

När resultat från alla tre randomiserade studier som redovisade återfall lades ihop, visade det sig att det troligen inte kan uteslutas att risken för återfall är något högre för de patienter som inte fått cellgifter jämfört med dem som fått cellgifter. Risken för återfall är dock låg i båda grupperna. Dessa resultatet har en måttlig tillförlitlighet. De ytterligare sju studier som undersökt frågeställningen utan slumpmässig tilldelning av behandling tillförde inget ytterligare till slutsatsen. Ingen studie utvärderade livskvalitet. Ett gentest kostar idag 18000 kronor. Om användningen av cellgifter inte förändras medför införande av gentest i Region Västra Götaland att sjukvårdskostnaderna ökar med 4,5 miljoner kronor. Om gentestning innebär att fler patienter skulle avstå från cellgiftsbehandling minskar denna kostnadsökning, och om andelen som avstår från sådan behandling ökar med >22,5% leder gentestning inte till ökade sjukvårdskostnader. Kostnadsbesparingar om man kan minska sjukskrivningar relaterade till cellgiftsbehandling är inte inräknade i dessa siffror.

The above summaries were written by representatives from HTA-centrum. The HTA was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a summary in lay language intended for decision makers and those who are not familiar with challenges associated with breast cancer treatment.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, April 24 2019

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DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of Findings

Outcomes	Study design Number of studies	Relative effect Hazard ratio (95% CI)	Absolute effect	Certainty of evidence GRADE[1]
PICO 1 (Use vs no use of gene expression assay)				
Overall survival	0 studies	-		-
Health-related quality of life	0 studies			
Recurrence	1 cohort study		2 vs 0 events	
Decision to withhold chemotherapy	14 cross-sectional studies	-	Range 26-85% (11 studies) vs 0-83% (14 studies)	
PICO 2 (Chemotherapy vs no chemotherapy after gene expression assay)				
Overall survival	1 RCT 3 cohort studies	9 years: HR_{death} 0.99 (95% CI 0.79 to 1.22)	9 years: ITT: 93.9% vs 93.8%	⊕⊕⊕◯[2]
Health-related quality of life	0 studies			
Recurrence	3 RCT 5 cohort studies	*Distant recurrence* 3 RCT; 5-10 years: HR_{DR} 1.13 (0.90 to 1.41) *Any recurrence* 1 RCT; 9 years: HR_{recurr} 1.11 (0.90 to 1.37)	*Distant recurrence* 2 RCT; 9-10 years: 3.52% vs 3.03% Diff: 0.49% (-0.32 to 1.30) *Any recurrence* 1 RCT; 9 years: 5.41% vs 4.65% Diff: 0.76% (-0.28 to 1.80)	⊕⊕⊕◯[3]

DR = distant recurrence

[1] Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes:
[2]Downgraded one level due to a skewed distribution regarding loss to follow-up in the comparison groups, being large in relation to the number of events, and directness (uncertain screening procedure in an American health care setting).
[3]Downgraded one level due to a skewed distribution regarding loss to follow-up in the comparison groups.

4. Abbreviations/Acronyms

ASCO = American Society of Oncology
BC = Breast cancer
ER = Oestrogen Receptor
EP = EndoPredict
FFPE = Formalin-Fixed Paraffin-Embedded
GRADE = Grading of Recommendations Assessment, Development and Evaluation
HER2 = Human Epidermal growth factor Receptor 2
HRQL = Health Related Quality of Life
HTA = Health Technology Assessment

N0 = No regional lymph metastases
N1 = Metastasis in 1-3 axillary lymph nodes ipsilateral
N2 = Metastasis in 4-9 axillary lymph nodes ipsilateral
N3 = Metastasis in 10 or more axillary lymph nodes or in supra- and/or infra clavicular lymph nodes

NICE = National Institute for Health and Care Excellence
PgR = Progesterone receptor
qRT-PCR = quantitative real-time reverse transcription polymerase chain reaction
RCT = Randomised Controlled Trial
ROR = Risk of recurrence score
RS = Recurrence Score
RT-PCR = Reverse transcriptase polymerase chain reaction
SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Services
SVF = standardised care course [Standardiserat Vårdförlopp]
SweBCG = Swedish Breast Cancer Group

T1 = <20 mm
T2 = >20 <50 mm
T3 = >50 mm
T4 = Any size, but growth in wall of the thorax and/or the skin

5. Background

Breast cancer

Breast cancer is the most common cancer among women in Sweden. Annually, about 8,000 women are diagnosed (Socialstyrelsen, 2018). The incidence has increased over the years, and so has the survival rate (Socialstyrelsen, 2014b). Screening efforts and adjuvant treatment have contributed to these developments (Blok et al., 2018; Socialstyrelsen, 2014b).

Today, treatment decisions are guided by the following prognostic and predictive characteristics of the tumour (besides size and extension): expression of oestrogen and progesterone receptors (so called luminal breast cancer that is sensitive to endocrine treatment), histological grade of the tumour, expression of the human epidermal growth factor receptor 2 (HER2), proliferative rate (Ki67), and presence of lymph node metastasis (node status) (Regionala cancercentrum, 2019). According to clinical routine, patients with luminal breast cancer are treated with adjuvant endocrine therapy for 5-10 years. If they are also HER2 negative and have 0-3 lymph node metastases, some are considered at intermediate risk of recurrence and receive adjuvant chemotherapy in addition to endocrine treatment. However, the benefit of this treatment with 2-3% absolute reduced risk of recurrence is considered quite small (Harris et al., 2016), and the risks associated with this treatment are not negligible. The challenge is to determine who will benefit from chemotherapy and who will not. To improve the prediction of clinical outcomes and to identify breast cancer patients in whom chemotherapy can be withheld, gene expression profiling has been developed. None is used in clinical practice in Sweden today.

Prevalence and incidence

In Region Västra Götaland, about 1,400 patients were diagnosed with breast cancer in 2016. In breast cancer patients who had undergone surgery (without distant metastases, age 19-71, irrespective of tumour size and local expansion (T0-T4), irrespective of HER2 status) and were oestrogen receptor (ER) positive and without lymph node metastasis (N0), 22.2% were treated with chemotherapy. For those with lymph node metastasis (N1-N3), 60% were treated with chemotherapy. Summarised, 26% of those with N0-N3 status were treated with chemotherapy (Regionala cancercentrum, 2017). Approximately 6-10% of the luminal breast cancers are HER2 positive and shall according to international guidelines receive chemotherapy combined with HER2 blocking antibody treatment (Socialstyrelsen, 2014a).

Present treatment and the normal pathway through the healthcare system

The majority of breast cancer patients are diagnosed within the standardised care course (Standardiserat Vårdförlopp, SVF). This is an established system where patients with certain symptoms and clinical findings are referred, identified through the breast cancer screening program or through other imaging diagnostic procedures. The first step in SVF is triple diagnostics with palpation, diagnostic imaging of the breast and the axilla, as well as morphological diagnostics with cytology or biopsy (middle or large needle biopsy if pre-operative treatment is considered). The next step is the analysis of earlier described prognostic, predictive, and treatment guiding characteristics: ER and progesterone receptor (PgR)-expression, HER2-expression and Ki67 performed at the Department of Pathology. The patient is then discussed at a multidisciplinary conference where breast surgeons, pathologists, oncologists, contact nurses and other administrative personnel participate. The conference proposes a treatment plan based on stage (extent of breast cancer) and biological markers. The decision to provide or withhold chemotherapy is based on the patient's risk category. The treatment plan for patients in the intermediate risk group usually include surgery and subsequent referral to an oncologist for the start of chemotherapy (Regionala cancercentrum, 2015). After chemotherapy, radiation therapy will usually follow, as will treatment with oral endocrine therapy: tamoxifen or an aromatase inhibitor.

According to clinical routine, adjuvant chemotherapy is provided in a scheduled regimen where cytostatic drugs are combined. The chemotherapy schedule lasts for approximately 16 weeks. The treatment is administered by nurses at a day care ward. Every visit includes pre-chemotherapy arrangements, and the actual chemotherapy infusion takes 2-3 hours. A central vein catheter is inserted by either anaesthetic personnel or a specialized nurse, after which the position is confirmed by x-ray. Acute/early adverse effects, including nausea and fatigue, are frequent. Patients in employment often require sick-leave, both because of the chemotherapy administration *per se* and side effects. Late and chronic adverse reactions may also occur, including neuropathies, potentially affecting the patients for the rest of their lives. According to the American Society of Oncology (ASCO) guidelines, studies have shown that the risk of fatal, life-threatening, or permanent life-changing toxicities are at least 2-3% in women who participated in prospective trials receiving adjuvant chemotherapy (Harris et al., 2016). Persistent chemotherapy-induced peripheral neuropathy one to three years after therapy is reported in 11-80% of patients at high risk for such reactions, e.g. those>66 years of age. Persistent cognitive dysfunction remaining for years after treatment affects approximately 15-25% of breast cancer patients provided chemotherapy compared with 10% of those who do not receive such treatment (O'Shaughnessy, 2002). If we, on a more solid basis, can identify patients who can be withheld chemotherapy without increasing the risk of recurrence, we could avoid side-effects and associated health care and societal costs.

Present recommendations from medical societies or health authorities

According to ASCO guidelines, gene expression tests may be used in early breast cancer to inform decision making regarding adjuvant systemic chemotherapy (Harris et al., 2016; Krop et al., 2017). The guidelines emphasize that patients shall be informed that a benefit from chemotherapy cannot be excluded (Krop et al., 2017). According to the guidelines by the European Society for Medical Oncology (ESMO) from 2015, gene expression profiles may be used to gain prognostic and/or predictive information and to predict the benefit of adjuvant chemotherapy (Senkus et al., 2015). Based on a review by the National Institute for Health and Care Excellence (NICE), United Kingdom guidelines from 2018 conclude that Oncotype DX, EndoPredict and Prosigna/PAM50 are recommended as options for guiding adjuvant chemotherapy decisions in ER positive, HER2 negative, and lymph node negative early breast cancer at intermediate risk of distant recurrence using a validated tool, e.g. PREDICT (NICE, 2018). According to the experience of the clinical experts involved in this report, genetic testing of breast cancer tumour is used for patients with luminal, HER2 negative breast cancer in several countries including France, Spain, Germany, the Netherlands, Belgium, Denmark, and Norway.

To date, no gene expression profile has been introduced in clinical routine in Sweden. The Swedish Breast Cancer Group (SweBCG) has decided to recommend implementation of gene expression assays in the coming update of the national guidelines.

6. Health Technology at issue: Gene expression assays

Today there are four commercial gene expression assays available in Europe for use in health care: Oncotype DX, PAM50/Prosigna, MammaPrint, and EndoPredict. ASCO has determined that they all have sufficient evidence regarding clinical utility in women with early stage invasive, luminal, HER2-negative and node-negative breast cancer. For MammaPrint, the use is restricted to those with high clinical risk (Harris et al., 2016; Krop et al., 2017), some of whom corresponding to the patients in focus in this HTA. Prosigna/PAM50 and EndoPredict can be analysed by local pathology laboratories, while the other two tests have to be sent to central laboratories (Blok et al., 2018).

Oncotype DX Recurrence Score (Genomic Health Inc., Redwood City, CA) uses the reverse transcriptase-polymerase chain reaction (RT-PCR) for expression of 21 genes, 16 of which being cancer-related. The relative expression of these genes gives a score (Recurrence Score) from 0-100 for prediction of distant recurrence within ten years for those with tamoxifen treatment. The original scores 0-17 indicated low risk, 18-30 intermediate risk, and 31-100 high risk. The category cut-offs were changed after the most recent validation trial to 0-10, 11-25, and 26-100. The RT-PCR is performed on Formalin-Fixed Paraffin-Embedded (FFPE) cancer tissue (Blok et al., 2018; UpToDate, 2018; NICE, 2017).

PAM50/Prosigna, The Predictor Analysis of Microarray by Prosigna (NanoString Technologies, Seattle, WA) is a test using quantitative real-time reverse transcription PCR (qRT-PCR) evaluating expression of 46 genes, distinguishing between the different intrinsic subtypes of breast cancer: luminal A or B, HER2-enriched, normal-like and basal-like. This test provides a risk of recurrence score (ROR) and a corresponding risk category. The test is performed on FFPE cancer tissue (Blok et al., 2018; UpToDate, 2018).

MammaPrint (Agendia BV, Amsterdam, The Netherlands), also called the 70-gene Signature, is an assay using mRNA expression of 70 different genes in a microarray technology. This provides a prognosis profile with categorisation in low or high risk. It was first approved for use with unfixated frozen tissue but is now adjusted for use on FFPE cancer tissue (Blok et al., 2018; Cardoso et al., 2016; UpToDate, 2018).

EndoPredict (Myriad Genetics Inc., Salt Lake City, UT) evaluates the expression of eight cancer related genes (three proliferation associated and five hormone-receptor associated), three reference genes, and one control gene, by analysing expression of mRNA using RT-qPCR. The test provides a prognostic risk score for recurrence over ten years ranging from zero to 15 and categorised into low or high risk. The EndoPredict score (EP) can also be combined with the clinical characteristics, tumour size and nodal status which gives a more extensive risk score; EPclin. The RT-qPCR is performed on FFPE cancer tissue from either the diagnostic core biopsy or the tissue from the surgery (Blok et al., 2018; UpToDate, 2018; NICE, 2017).

7. Objective

In breast cancer patients with luminal tumour and intermediate clinical risk of recurrence, how does the use of gene expression assays affect clinical outcomes and chemotherapy decisions, compared with not using such molecular profiling?

In breast cancer patients with luminal tumour, intermediate clinical risk, and low/intermediate risk after a gene expression assay, will survival, health-related quality of life (HRQL), and/or recurrence be affected if chemotherapy is withheld?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

PICO 1

P - Breast cancer patients after surgery (±radiotherapy) with intermediate clinical risk for recurrence, either according to the study's criteria or according to the following criteria:

1. Oestrogen- and/or Progesterone receptor positive (Luminal)
2. Negative for Human epidermal growth factor 2 expression (HER2-negative)
3. No axillary lymph node metastases (N0) or 1-3 axillary lymph node metastases (N1)
4. Plus at least one of the following criteria:
   - Tumour size >20 mm
   - Ductal histology grade 2 or 3
   - N1

I – Gene expression assay (to identify those at low risk for recurrence of cancer)

C – No gene expression assay

O – Overall survival, HRQL, recurrence, decision to withhold adjuvant chemotherapy

PICO 2

P – Breast cancer patients after surgery (±radiotherapy) with intermediate clinical risk for recurrence according to clinical standard:

- Oestrogen- and/or Progesterone receptor positive (Luminal)
- Negative for Human epidermal growth factor 2 expression (HER2-negative)
- No axillary lymph node metastases (N0) or 1-3 axillary lymph node metastases (N1)

and low/intermediate genetic risk according to a gene expression assay

I – No chemotherapy (only endocrine therapy)

C – Chemotherapy (in addition to endocrine therapy; standard treatment)

O – Overall survival, HRQL, recurrence

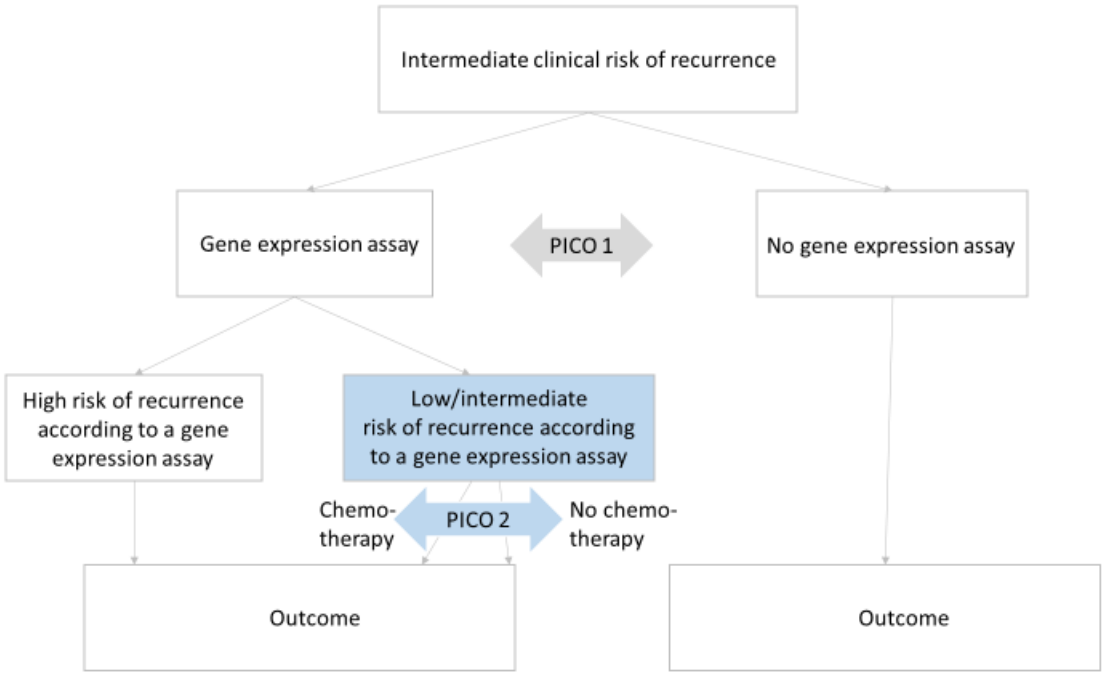

Figure 1. Illustration of populations in the two PICOs.

8. Methods

Systematic literature search (Appendix 1)

During August 2018, with an update in January 2019, two authors (IS, TS) performed systematic searches in Medline, Embase, PubMed, the Cochrane Library, PsycInfo and a number of HTA-databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria, and a graphic presentation of the selection process are presented in Appendix 1. The authors independently assessed the abstracts according to the PICO, and full-text articles when necessary. During a consensus discussion, they made a selection of full-text articles to be considered for inclusion or exclusion by the other authors. Finally, the latter authors independently read the articles and decided, during consensus discussions, which articles to include in the HTA.

Critical appraisal and certainty of evidence

The included studies and their design as well as patient characteristics are presented in Appendix 2. The excluded studies, including reasons for exclusions, are presented in Appendix 3. Included studies reporting patient relevant outcomes were critically appraised using the checklists for assessment of randomised controlled trials (RCT) and cohort studies provided by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). As chemotherapy decisions primarily reflect the physicians'/patients' belief in the test and not the value of the test *per se*, we refrained from assessing studies merely reporting this outcome. In Appendix 4, the results and the quality of each study are summarised per outcome. Data were extracted by at least two authors. When possible, RCT data were pooled in a meta-analysis using RevMan 5.2 and presented as a forest plot. Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 8). The certainty of evidence was assessed according to GRADE (Atkins et al., 2004).

Ongoing research

A search in Clinicaltrials.gov (Dec 21, 2018) using the search terms *(multigene OR nanostring OR pam50 OR prosigna OR endopredict OR oncotype OR oncotypedx OR mammaprint OR 70-gene OR "seventy gene" OR 21-Gene OR "twenty-one gene" OR 12-gene OR 50-gene OR earlyR OR agendia OR "breast cancer index") AND ((breast OR mammary OR mamma OR ductal) AND (neoplasm OR tumor OR tumour OR carcinoma OR cancer OR malignant OR sarcoma OR sarcomas OR adenocarcinoma OR adeno carcinoma)) [DISEASE]* identified 88 trials.

9. Results

Systematic literature search (Appendix 1)

After removal of duplicates, the literature search identified 2,283 articles. After reading the abstracts 2,133 articles were excluded. Another 53 articles were excluded by two authors after reading the articles in full text. The remaining 97 articles were sent to all participants of the project group, and 24 articles (3 RCTs, 21 observational studies) were finally included in the assessment (Appendix 2). The 73 excluded articles are reported with reason for exclusion in Appendix 3.

Results per outcome

PICO 1

Overall survival

No studies were identified.

Conclusion: No evidence provides guidance regarding potential effects of the use of gene expression tests on overall survival in breast cancer patients with intermediate clinical risk of recurrence.

Health-related quality of life

No studies were identified.

Conclusion: No evidence provides guidance regarding potential effects of the use of gene expression tests on health-related quality of life in breast cancer patients with intermediate clinical risk of recurrence.

Recurrence (Appendix 4.1.1)

Recurrence was reported in one cohort study but had insufficient data for any analysis.

Conclusion: Available evidence does not provide any guidance regarding potential effects of the use of gene expression tests on recurrence in breast cancer patients with intermediate clinical risk.

Decision to withhold adjuvant chemotherapy (Appendix 4.1.2)

Decision to withhold adjuvant chemotherapy in the adjuvant setting was investigated in 14 cross-sectional studies. Chemotherapy was withheld in 0% to 83% of those without a genetic profile, based solely on clinical parameters. In the 11 studies where choice of treatment was not predetermined based on the gene test results, the decision to withhold chemotherapy ranged from 26% to 85%. Among the 10 studies providing numbers on proportion of patients for whom chemotherapy was withheld, with and without a gene expression assay, five studies reported a decrease in the use of chemotherapy whereas the other five reported the opposite, that is, an increase in the use of chemotherapy.

Conclusion: In patients with breast cancer at intermediate clinical risk of recurrence, conflicting evidence does not allow conclusions regarding whether gene expression assays decrease or increase the use of chemotherapy.

PICO 2

A total of three RCTs and seven cohort studies fulfilled criteria for PICO 2. The main RCT reported both overall survival and recurrence in a composite outcome (invasive-disease recurrence, second primary cancer, or death). This study had a non-inferiority approach with the significance level set at 0.1, in which the as-treated analysis can be regarded as more relevant than the intention-to-treat (ITT) analysis. Reported hazard ratios for the composite outcome at nine years, comparing withholding versus providing adjuvant chemotherapy, were 1.08 (95% CI 0.94 to 1.24) in the ITT analysis and 1.14 (0.99 to 1.31) in the as-treated analysis. The p-values were 0.26 and 0.06, respectively.

The composite outcome occurred in 12.8% vs 12.1% in the ITT analysis, and in 12.8% vs 12.0% in the as-treated analysis. The absolute difference was a 0.75 percentage point increase (95% CI -0.3 to 1.9) and 0.84% (-0.8 to 2.3), respectively, for patients in whom chemotherapy was withheld.

Overall survival (Appendix 4.2.1)

Overall survival was reported in one RCT and in three cohort studies. In the RCT, including 6,711 breast cancer patients with intermediate clinical risk of recurrence and low/intermediate risk according to a gene expression assay, similar overall survival rates were found at 9 years: 93.9% vs 93.8%, HR 0.99 (95% CI 0.79 to 1.22). The study had some remarks regarding study limitations and directness. In the three cohort studies, the point estimates all favoured chemotherapy, reaching statistical significance in one study.

Conclusion: Withholding adjuvant chemotherapy in breast cancer patients with intermediate clinical risk of recurrence and low/intermediate risk according to a gene expression assay, compared with providing chemotherapy, probably results in little or no difference in overall survival within nine years.
Moderate certainty of evidence based on the RCT (GRADE⊕⊕⊕◯)

Health-related quality of life

No studies were identified.

Conclusion: No evidence provides guidance regarding potential effects of withholding adjuvant chemotherapy on health-related quality of life in breast cancer patients with intermediate clinical risk of recurrence and low/intermediate risk according to a gene expression assay.

Recurrence (Appendix 4.2.2)

Recurrence was reported in three RCTs and in five cohort studies. In the largest RCT, the HR for recurrence was 1.11 (95% CI 0.90 to 1.37). Recurrence occurred, as first event, in 5.4% vs 4.6% in the ITT analysis, and in 5.2% vs 4.9% in the as-treated analysis. The absolute difference was a 0.76 percentage point increase (95% CI -0.3 to 1.8) and 0.27% (95% CI -0.8 to 1.3), respectively, for patients in whom chemotherapy was withheld.

Regarding distal recurrence, data from the largest RCT were combined with data from subgroups in two other RCTs fulfilling the PICO of this HTA. The reported hazard ratios were pooled in a meta-analysis, resulting in a summarized HR of 1.13 (95% CI 0.90 to 1.41) (Figure 2). Absolute risk difference was not possible to estimate from data in the pooled analysis. The five cohort studies did not contribute further to the conclusion.

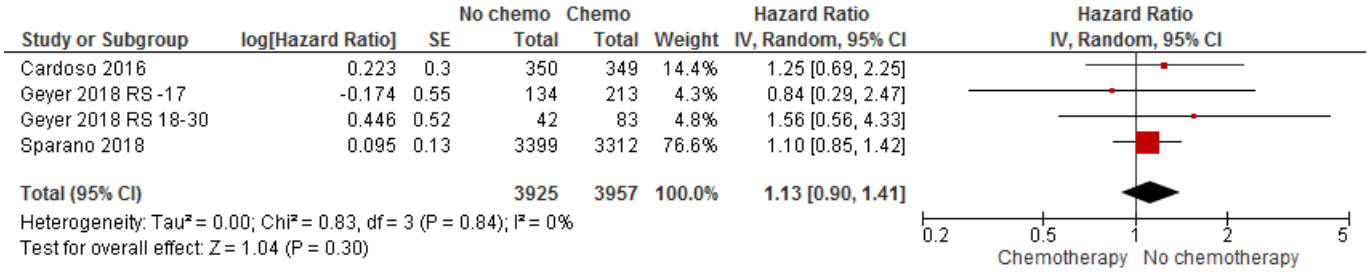

Figure 2. Meta-analysis of RCTs, comparing withholding versus providing adjuvant chemotherapy, regarding distant recurrence in breast cancer patients with intermediate clinical risk of recurrence and low/intermediate risk according to a gene expression assay.

Conclusion: Withholding adjuvant chemotherapy in breast cancer patients with intermediate clinical risk of recurrence and low/intermediate risk according to a gene expression assay, compared with providing chemotherapy, can probably not exclude a small increased risk of recurrence. Moderate certainty of evidence (GRADE⊕⊕⊕◯)

10. Ethical aspects

If a gene expression assay can identify breast cancer patients in whom chemotherapy can safely be withheld, acute or long-term adverse effects of chemotherapy, including death, could be prevented. In addition to patient benefit, successful identification of such patients could also reduce health care costs as well as societal costs due to sick leave.

As is often the case with diagnostic tools, studies evaluating patient-relevant effects are largely lacking regarding gene expression tests. Further, although the absolute increased risk is small (<1%), it cannot be ruled out that withholding chemotherapy based on a gene expression test may imply an increased relative risk of recurrence. Given this evidence, it may be suggested that the benefit-risk balance of using gene expression tests is negative. However, the absence of studies evaluating potential HRQL effects when chemotherapy was withheld based on a gene expressions test, does not exclude positive effects on HRQL. Indeed, chemotherapy is known to cause adverse effects and decreased HRQL during and after the course of treatment with some irreversible side-effects (Au et al., 2013). Taking this into account, the benefit-risk balance of using gene expression tests may also be positive.

Using a gene expression assay to guide chemotherapy decision making in breast cancer patients with intermediate clinical risk implies no major ethical problems regarding equality and justice, autonomy, and privacy. However, as the evidence suggests that a slightly increased risk of recurrence cannot be excluded, benefits have not been clearly shown and testing implies a cost, there may be issues regarding cost-effectiveness. Indeed, the evidence diverges regarding decisions to withhold chemotherapy based on molecular profiling, including both a decreased and an increased proportion with such treatment, making evidence-based cost saving calculations difficult.

The gene expression assay itself is performed on tissue taken from standard surgery. Therefore, the use of such tests will not put patients at risk of additional physical harm or pain. Nevertheless, given the evidence compiled in this HTA, there may be a risk of a false sense of security when relying on genetic tests. On the other hand, physicians and patients may be more comfortable with chemotherapy decisions when faced with an internationally used “objective” test result. However, comfort aspects were not evaluated in the present review. Further, we did not evaluate the added value of a gene expression test to predict recurrence, when performed in addition to the standard care procedure in which clinical risk of recurrence is assessed with established methods.

11. Organisational aspects

Time frame for the putative introduction of the new health technology

The equipment for gene expression assays in breast cancer is already available at the Department of Clinical Molecular Pathology, Sahlgrenska University Hospital and responsible personal are ready to start if the technology is approved. In accordance with the decision in the SweBCG, it is recommended that gene expression analyses are performed at large laboratories in university hospitals, to which patient samples could be sent from other hospitals. As the test preferred by SweBCG representatives, Prosigna/PAM50, is based on paraffin-embedded material, transport costs are not extensive.

Present use of the technology in other hospitals in Region Västra Götaland

Currently, gene expression tests are not used in any hospital in Region Västra Götaland. The Prosigna/PAM50 test has been used in research at Uppsala Akademiska University Hospital. So far, no results have been published, but work is ongoing to implement PAM50 in clinical routine in Uppsala and Stockholm.

Consequences of the new health technology for personnel

Before gene expression tests can be introduced, relevant personnel has to be educated, ranging from personnel at the surgery ward where the tissue samples are collected, to personnel working in the laboratory, and the oncologists interpreting the results in their decision making. As paraffin embedded material can be used, we do not consider the handling of specimen more complicated than today.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

If fewer breast cancer patients are provided chemotherapy, resources in the Oncology Department can be saved, particularly regarding treatment administration.

12. Economic aspects

Present costs of currently used technologies

Breast cancer is estimated to account for approximately 13% of the total cancer costs in Sweden. In 2013, the breast cancer costs were estimated to 5 billion Swedish kronor (SEK), an estimate which includes both health care costs and societal costs due to production loss.

We estimate that the average health care cost for adjuvant chemotherapy in breast cancer patients is 80,000 Swedish kronor (SEK). Societal costs caused by production loss due to absence from work is not included in this amount. Patients with adjuvant chemotherapy are often absent from work for six months.

Expected costs of the new health technology

The current health care costs for the gene expression assay is 18,000 SEK. Annually, we estimate that the test would be performed in 250 breast cancer patients in Region Västra Götaland. At 18,000 SEK/test, the total costs per year would amount to 4.5 million SEK.

Estimated change in health care costs

Figure 1 illustrates the relationship between (i) the proportion of patients for whom the chemotherapy decision would be changed, and (ii) the change in total health care costs. In five studies in our systematic review, the proportion of patients treated with chemotherapy decreased with the use of gene expression assays, whereas the other five studies reported an increased proportion (Appendix 4.1.2).

As a similar number of studies reported a decrease and an increase, respectively, in the proportion of patients withheld chemotherapy, we chose a base case scenario without any change. Using this approximation, the total health care costs per year would increase by 4.5 million SEK, corresponding to an increased cost per patient of 18,000 SEK. These costs do not include societal costs due to absence from work. If the proportion of patients, in whom chemotherapy is withheld, increases by more than 22.5% by the use of gene expressions assays, the costs will decrease for the health care sector. In Region Västra Götaland, the use of chemotherapy is expected to decrease but the magnitude is unknown.

The costs also depend on the price of the test. Substantially reduced prices have been seen over the years, and further reductions can be anticipated. In Figure 3, we illustrate the impact of 25% and 50% reduced assay costs on the change in total health care costs.

Possibility to adopt and use the new technology within the present budget

As explained above and shown in Figure 3 the budget impact depends on if, and to what extent, the test leads to changes in chemotherapy decisions. If fewer than an additional 22.5% of the tested patients are withheld adjuvant chemotherapy, the gene assays would not be possible to adopt within in the present budget and will therefore displace other care.

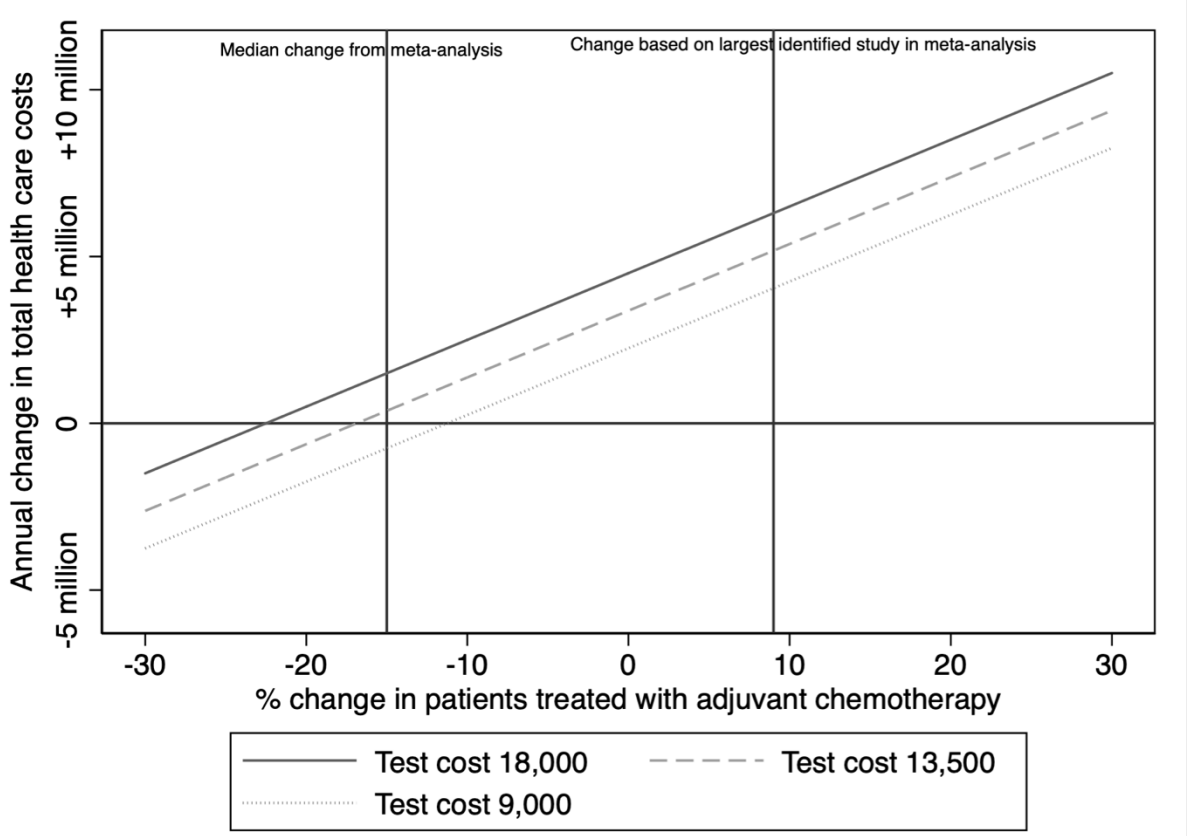

Figure 3 Relationship between the proportion of patients for whom the chemotherapy decision would be changed by the use of a gene expression test and the change in total annual health care costs (250 patients)

Available economic evaluations or cost advantages/disadvantages

There is a substantial literature studying the cost-consequences and cost-effectiveness of tumor profiling tests to guide treatment decisions regarding adjuvant chemotherapy for patients with breast cancer. In our literature search, we identified 48 studies published between 2005 and 2018, set in different countries and using various types of tests. None of the studies were based on the Swedish health care setting.

The cost-effectiveness results varied largely, as did comparator used, health care setting, and patient risk profiles; the results spanning from reasonably cost-effective to very cost-ineffective. An important uncertainty in the health economics analyses concerns the impact of the test result on decision making regarding chemotherapy. Further, as shown in this review, there are insufficient data to draw conclusions on health outcomes with and without genetic testing.

13. Discussion

Summary of main results

The overall aim of this HTA was to assess the evidence for using gene expression assays to guide chemotherapy decisions in breast cancer patients when the clinical risk of recurrence does not suffice for clear-cut decisions. These patients constitute about 30% of breast cancer patients with oestrogen/progesterone-sensitive and HER2-negative tumours with up to three positive lymph nodes, corresponding to about 200-300 patients annually in Region Västra Götaland.

We found that studies regarding the potential effects of gene expression tests on overall survival, health-related quality of life, and recurrence are largely lacking. This is often the case for new diagnostic or prognostic tools. Available evidence does not allow conclusions regarding whether gene expression tests would decrease or increase the use of chemotherapy. Local guidelines and therapeutic traditions may explain the diverging results. We expect that in our region, where chemotherapy is common in the patients at issue, the use of tumour gene tests primarily would guide decisions towards withholding chemotherapy.

Withholding chemotherapy in those with low risk according to a gene expression assay does probably not affect survival rates over nine years. These results are based on the follow-up time in the major RCT (Sparano et al., 2018). As 94% were still alive at this point, the data are immature and further follow-up is essential to gain evidence on long-term effects, in particular as our evidence synthesis also shows that a slightly increased risk of recurrence cannot be excluded. Therefore, as highlighted in the ASCO guidelines (Krop et al., 2017), it is important that patients are informed that a benefit from chemotherapy cannot be excluded, also when the gene expression assay indicates a low/intermediate risk of recurrence. Indeed, even though non-inferiority was claimed in the major RCT, the lower confidence limit in the as-treated analysis was 0.99, with a p-value below the predefined level of significance, indicating that chemotherapy was superior to no chemotherapy regarding recurrence. Nevertheless, low numbers on recurrence were reported in both comparison groups. The trial had some study limitations and some problems when it came to directness. However, relevant patients were randomised, and the nine-year follow-up is a long enough time for the majority of recurrences in luminal breast cancers. The other two RCTs contributing to the recurrence results recruited a broader patient group, and a subset fulfilling our PICO could be included in the meta-analysis. All but one cohort study had major problems regarding study limitations and/or precision. The one with minor problems evaluated overall survival and reported better outcomes, in matched comparisons, for those treated with chemotherapy (Ibraheem et al., 2019).

When interpreting the results, one need to bear in mind that health care systems differ between countries. Many studies were performed in the United States where the reimbursement system differs from that in Sweden. The results may therefore not be readily translated to Swedish conditions.

In this HTA, all but one RCT and all cohort studies, evaluating overall survival and recurrence with and without chemotherapy, used Oncotype DX to determine genetic risk in the tumour. The Recurrence Score obtained by this test, defining high/intermediate/low risk, has varied over the years, and the intervals therefore differed between the studies. Oncotype DX would probably not be selected in Sweden, should an implementation decision be made, because of the restricted amount of information obtained with this test. In countries with similar health care system, Prosigna/PAM50 or MammaPrint has been the test of choice. For Prosigna/PAM50, additional biological markers are obtained simultaneously with potential advantages in the future. On the other hand, Oncotype DX, Prosigna/PAM50, and EndoPredict are all recommended in NICE guidelines, given that certain conditions are fulfilled (NICE, 2017). MammaPrint was omitted in these guidelines because it was not considered cost-effective.

Gene expression assays would complement rather than replace established clinical standards. If implemented in Region Västra Götaland, one may consider well-thought-out follow-up, planned beforehand. Indeed, as illustrated in this report, simplistic comparisons regarding patient outcomes, with the use of routinely recorded register data, may be biased. Patients with and without chemotherapy often differ from start, the ones receiving chemotherapy being younger and having more advanced cancer. Indeed, treatment is not random, as both physicians and patients make informed decisions.

14. Future perspectives

Scientific knowledge gaps

Studies examining the effects of using gene expression assays on patient outcomes is largely lacking. Regarding withholding adjuvant chemotherapy in breast cancer patients based on genetic tumour risk, we are moderately confident that such an approach results in little or no difference in overall survival over nine years but does not exclude a slightly increased risk of recurrence. No studies have been performed evaluating the effects on HRQL when chemotherapy is withheld based on the results of a gene expression assay. As the results are based on other assays than Prosigna/PAM50 which would probably be chosen in Region Västra Götaland, important evidence is still lacking.

Ongoing research

In all, 88 ongoing clinical trials were identified in clinicaltrials.gov, 15 of which fulfilling one of our two PICOs, none of which with a randomised design (Appendix 6). One of 14 trials fulfilling PICO 1 had recurrence as outcome (NCT00904566, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan), the remaining evaluating decision making. One study fulfilled PICO 2, evaluating overall survival and recurrence with an observational design and using EndoPredict to determine genetic risk (NCT03503799, Frauenklinik der Technischen Universität München, München, Bayern, Germany).

15. Participants in the project

The question was nominated by
Erik Johnsson, MD, PhD, Head of department, Consultant Surgeon, Surgical department, Sahlgrenska University Hospital, Gothenburg, Sweden

Participating health care professionals
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Declaration of interests
R Olofsson Bagge has received research grants from Astra Zeneca, speaker honorarium from Roche and Pfizer, and has served on advisory boards for Amgen, Bristol-Myer Squibb and MSD.
B Linderholm is a member of the Swedish Breast Cancer Group (SweBCG) which has initiated a working group with the aim to use the same gene expression profile in several regions of Sweden. She is a member of advisory boards for Pfizer and Astra Zeneca.
A Kovács has a consulting or advisory role for Pfizer and Roche and has received honoraria from these companies.
None of the above-mentioned pharmaceutical companies provides gene expression assays in breast cancer, but economic interests within the field cannot be ruled out.
A Nilsson Ek, I Stadig, T Svanberg, A Strandell, SM Wallerstedt declare no conflict of interest.
Both external reviewers declare no conflict of interest.

Project time
This HTA was accomplished during the period of 2018-06-15 – 2019-06-11.
Literature searches were made in August 2018 and updated January 30, 2019.

Appendix 1: Search strategy, study selection and references

Question(s) at issue:

In breast cancer patients with luminal tumour and intermediate clinical risk, how does the use of gene expression assays affect clinical outcomes and chemotherapy decisions, compared with not using such molecular profiling?

In breast cancer patients with luminal tumour, intermediate clinical risk, and low/intermediate risk after a gene expression assay, will survival, health-related quality of life (HRQL), and/or recurrence be affected if chemotherapy is withheld?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

PICO 1

P - Breast cancer patients after surgery (±radiotherapy) with intermediate clinical risk for recurrence, either according to the study's criteria or according to the following criteria:

1. Oestrogen- and/or Progesterone receptor positive (Luminal)
2. Negative for Human epidermal growth factor 2 expression (HER2-negative)
3. No axillary lymph node metastases (N0) or 1-3 axillary lymph node metastases (N1)
4. Plus at least one of the following criteria:
   - Tumour size >20 mm
   - Ductal histology grade 2 or 3
   - N1

I – Gene expression assay (to identify those at low risk for recurrence of cancer)

C – No gene expression assay

O – Overall survival, HRQL, recurrence, decision to withhold adjuvant chemotherapy

PICO 2

P – Breast cancer patients after surgery (±radiotherapy) with intermediate clinical risk for recurrence according to clinical standard:

- Oestrogen- and/or Progesterone receptor positive (Luminal)
- Negative for Human epidermal growth factor 2 expression (HER2-negative)
- No axillary lymph node metastases (N0) or 1-3 axillary lymph node metastases (N1)

and low/intermediate genetic risk according to a gene expression assay

I – No chemotherapy (only endocrine therapy)

C – Chemotherapy (in addition to endocrine therapy; standard treatment)

O – Overall survival, HRQL, recurrence

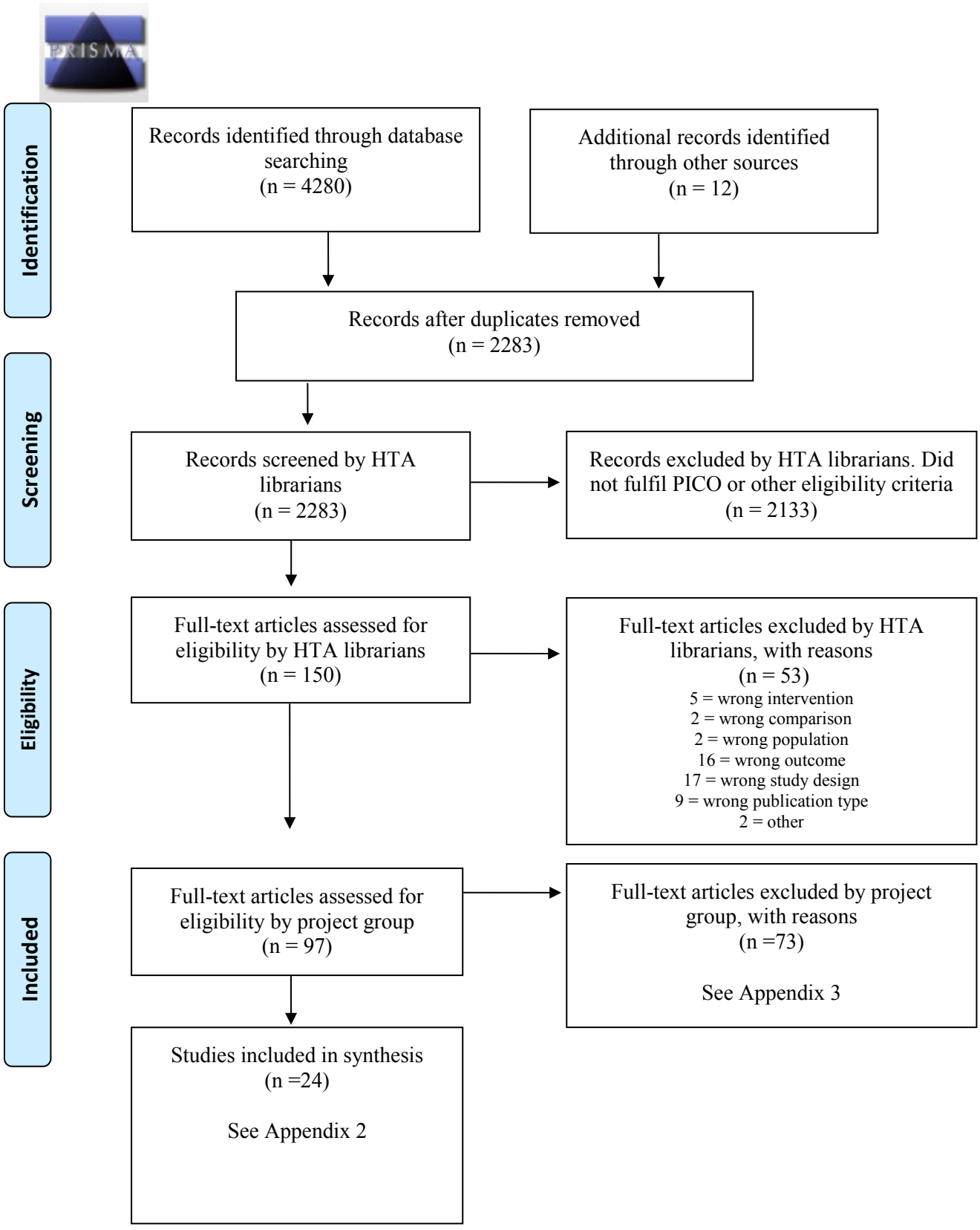
Eligibility criteria

Study design:
Randomised controlled trials
Non-randomised controlled studies
Systematic reviews published 2016-
Case series, before-after gene expression profile if ≥ 100 patients

Language:
English, Swedish, Norwegian, Danish

Publication date: 2002-

Selection process – flow diagram



Search strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to August 15, 2018
Date: Aug 16, 2018
No of results: 1435
Search updated: Jan 30 2019, 156 results

#	Searches	Results
1	((breast or breasts or mammary or mamma or ductal) adj3 (neoplasm* or tumor* or tumour* or carcinoma* or cancer* or malignan* or sarcoma* or adenocarcinoma* or adeno carcinoma*)).ab,ti.	319955
2	exp Breast Neoplasms/	266379
3	1 or 2	376056
4	(multigene or multi-gene or nanostring or pam50 or prosigna or endopredict or oncotype* or mammaprint or mamma-print or 70-gene or seventy gene or 21-Gene or twenty-one gene or 12-gene or 50-gene or earlyR or agendia or genomic health or myriad genetics or breast cancer index or biotheranostics).ab,ti.	11580
5	3 and 4	1529
6	(animals not (animals and humans)).sh.	4455124
7	(animal or animals or rat or rats or mouse or mice or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or swine or sheep or cattle).ti.	1776136
8	6 or 7	4755449
9	5 not 8	1502
10	**limit 9 to (yr="2002 -Current" and (danish or english or norwegian or swedish))**	**1435**

Database: Embase 1974 to 2018 August 15 (OvidSP)
Date: Aug 16, 2018
No of results: 1412
Search updated: Jan 30 2019, 362 results

#	Searches	Results
1	((breast or breasts or mammary or mamma or ductal) adj3 (neoplasm* or tumor* or tumour* or carcinoma* or cancer* or malignan* or sarcoma* or adenocarcinoma* or adeno carcinoma*)).ab,ti.	416742
2	breast tumor/ or exp breast cancer/	442831
3	1 or 2	517659
4	(multigene or multi-gene or nanostring or pam50 or prosigna or endopredict or oncotype* or mammaprint or mamma-print or 70-gene or seventy gene or 21-Gene or twenty-one gene or 12-gene or 50-gene or earlyR or agendia or genomic health or myriad genetics or breast cancer index or biotheranostics).dm,dv,mv,my.	432
5	(multigene or multi-gene or nanostring or pam50 or prosigna or endopredict or oncotype* or mammaprint or mamma-print or 70-gene or seventy gene or 21-Gene or twenty-one gene or 12-gene or 50-gene or earlyR or agendia or genomic health or myriad genetics or breast cancer index or biotheranostics).ab,kw,ti.	16157
6	4 or 5	16331
7	3 and 6	3723
8	(animal not (animal and human)).sh.	1003652
9	(animal or animals or rat or rats or mouse or mice or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or swine or sheep or cattle).ti.	1784440
10	8 or 9	2542957
11	7 not 10	3703
12	limit 11 to ((danish or english or norwegian or swedish) and yr="2002 -Current")	3594
13	limit 12 to (embase or medline)	1473
14	**limit 13 to (article or article in press or chapter or conference paper or note or "review" or short survey)**	**1412**

Database: The Cochrane Library
Date: Aug 16, 2018
No of results: 316
Ttrials 316
Search updated: Jan 30 2019, 24 results

ID	Search	Hits
#1	((breast or breasts or mammary or mamma or ductal) NEAR/3 (neoplasm* or tumor* or tumour* or carcinoma* or cancer* or malignan* or sarcoma* or adenocarcinoma* or adeno carcinoma*)):ti,ab,kw	28294
#2	MeSH descriptor: [Breast Neoplasms] explode all trees	11079
#3	#1 OR #2	28294
#4	(multigene OR "multi gene" OR nanostring OR pam50 OR prosigna OR endopredict OR oncotype* OR mammaprint OR "mamma print" OR "70 gene" OR "seventy gene" OR "21 Gene" OR "twenty one gene" OR "12 gene" OR "50 gene" OR earlyR OR agendia OR "genomic health" OR "myriad genetics" OR "breast cancer index" OR biotheranostics):ti,ab,kw	535
#5	**#3 AND #4**	**316**

Database: PsycINFO (EBSCOhost)
Date: Aug 16, 2018
No of results: 21
Search updated: Jan 30 2019, 2 results

#	Undran	Resultat
S5	**S1 AND S4**	**21**
S4	S2 OR S3	13,267
S3	DE "Breast Neoplasms"	10,388
S2	TI (((breast or breasts or mammary or mamma or ductal) N3 (neoplasm* or tumor* or tumour* or carcinoma* or cancer* or malignan* or sarcoma* or adenocarcinoma* or adeno carcinoma*))) OR AB (((breast or breasts or mammary or mamma or ductal) N3 (neoplasm* or tumor* or tumour* or carcinoma* or cancer* or malignan* or sarcoma* or adenocarcinoma* or adeno carcinoma*)))	12,285
S1	TI (multigene OR multi-gene OR nanostring OR pam50 OR prosigna OR endopredict OR oncotype* OR mammaprint OR mamma-print OR 70-gene OR "seventy gene" OR 21-Gene OR "twenty-one gene" OR 12-gene OR 50-gene OR earlyR OR agendia OR "genomic health" OR "myriad genetics" OR "breast cancer index" OR biotheranostics) OR AB (multigene OR multi-gene OR nanostring OR pam50 OR prosigna OR endopredict OR oncotype* OR mammaprint OR mamma-print OR 70-gene OR "seventy gene" OR 21-Gene OR "twenty-one gene" OR 12-gene OR 50-gene OR earlyR OR agendia OR "genomic health" OR "myriad genetics" OR "breast cancer index" OR biotheranostics)	129

Database: PubMed
Date: Aug 16, 2018
No of results: 347
Search updated: Jan 30 2019, 142 results

Search	Query	Items found
#18	**Search #7 NOT #10 Filters: Publication date from 2002/01/01; Swedish; Norwegian; English; Danish**	**347**
#12	Search #7 NOT #10 Filters: Publication date from 2002/01/01	355
#11	Search #7 NOT #10	360
#10	Search #8 OR #9	4775685
#9	Search (animal[Title] OR animals[Title] OR rat[Title] OR rats[Title] OR mouse[Title] OR mice[Title] OR dog[Title] OR dogs[Title] OR cat[Title] OR cats[Title] OR hamster[Title] OR hamsters[Title] OR rabbit[Title] OR rabbits[Title] OR swine[Title] OR sheep[Title] OR cattle[Title])	1770577
#8	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4485487
#7	Search #6 AND #1	362
#6	Search #4 AND #5	1730
#5	Search (multigene[Title/Abstract] OR multi-gene[Title/Abstract] OR nanostring[Title/Abstract] OR pam50[Title/Abstract] OR prosigna[Title/Abstract] OR endopredict[Title/Abstract] OR oncotype*[Title/Abstract] OR mammaprint[Title/Abstract] OR mamma-print[Title/Abstract] OR 70-gene[Title/Abstract] OR seventy gene[Title/Abstract] OR 21-Gene[Title/Abstract] OR twenty-one gene[Title/Abstract] OR 12-gene[Title/Abstract] OR 50-gene[Title/Abstract] OR earlyR[Title/Abstract] OR agendia[Title/Abstract] OR genomic health[Title/Abstract] OR myriad genetics[Title/Abstract] OR breast cancer index[Title/Abstract] OR biotheranostics[Title/Abstract])	15019
#4	Search #2 OR #3	397421
#3	Search "Breast Neoplasms"[Mesh]	266130
#2	Search ((breast[Title/Abstract] OR breasts[Title/Abstract] OR mammary[Title/Abstract] OR mamma[Title/Abstract] OR ductal[Title/Abstract])) AND (neoplasm*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR carcinoma*[Title/Abstract] OR cancer*[Title/Abstract] OR malignan*[Title/Abstract] OR sarcoma*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR adeno carcinoma*[Title/Abstract])	352539
#1	Search pubmednotmedline[sb] OR inprocess[sb] OR publisher[sb]	3611486

Database: CRD
Date: Aug 16, 2018
No of results: 63

Line	Search	Hits
1	(((breast or breasts or mammary or mamma or ductal) AND (neoplasm* or tumor* or tumour* or carcinoma* or cancer* or malignan* or sarcoma* or adenocarcinoma* or adeno carcinoma*)))	2511
2	MeSH DESCRIPTOR breast neoplasms EXPLODE ALL TREES	1798
3	#1 OR #2	2511
4	(multigene OR multi-gene OR nanostring OR pam50 OR prosigna OR endopredict OR oncotype* OR mammaprint OR mamma-print OR 70-gene OR seventy gene OR 21-Gene OR twenty-one gene OR 12-gene OR 50-gene OR earlyR OR agendia OR genomic health OR myriad genetics OR breast cancer index OR biotheranostics)	74
5	**#3 AND #4**	**63**

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
2018-08-16
Two references relevant to the question at issue were found at SBU, nothing relevant was found at Folkehelseinstituttet.

Reference lists
A comprehensive review of reference lists brought 10 new records

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Appendix 2 Characteristics of included studies

Author Year Country	Study Design	Years of inclusion	Follow up time	Patients (n)	Age (years)	Test	Outcome variables
PICO 1 Test vs no test							
Dieci 2018 Italy	Cross-sectional, intra-individual	2014- 2016	N/A	n=250	Median: 55	Oncotype DX	Chemotherapy decision
Fallowfield 2018 UK	Cross-sectional, intra-individual	2015-2016	N/A	n=149	Mean: 56	EndoPredict	Chemotherapy decision
Friese 2017 USA	Cross-sectional inter-individual	2013-2014	N/A	n=1,527	Mean: 61	Oncotype DX	Chemotherapy decision
Kuchel 2016 United Kingdom	Cross-sectional, intra-individual	Not available	N/A	n=137	Median: 55	Oncotype DX	Chemotherapy decision
Kuijer 2016a The Netherlands	Cross-sectional inter-individual	2011-2013	N/A	n=2,043	Mean: 56	MammaPrint	Chemotherapy decision
Loncaster 2017 United Kingdom	Cross-sectional, intra-individual	2012-2015	N/A	n=201	Mean: 55	Oncotype DX	Chemotherapy decision
Martín 2015 Spain	Cross-sectional, intra-individual	2013-2014	N/A	n=200	99% (n=198) over 50 years old	PAM50/Prosigma	Chemotherapy decision
Martínez Del Prado 2018 Spain	Cross-sectional, intra-individual	2012-2015	N/A	n=401	76% (n=303) over 50 years old	Oncotype DX	Chemotherapy decision
Panousis 2017 Greece	Cross-sectional, intra-individual	2009-2012	N/A	n=114	Mean: 51	Oncotype DX	Chemotherapy decision
Rath 2018 Germany	Cohort	2011-2014	Mean: 25 months	n=88	Median: 58	Oncotype DX	Recurrence Chemotherapy decision
Schreuder 2018 The Netherlands	Cross-sectional, inter-individual	2014-2016	N/A	n=2,506	85% between 50-70 years old	Oncotype DX	Chemotherapy decision
Wuerstlein 2016 Germany	Cross-sectional, intra-individual	2013-2014	N/A	n=198	Median: 64	PAM50/Prosigma	Chemotherapy decision
Zeng 2017 China	Cross-sectional, intra-individual	2013-2016	N/A	n=227	Mean: 49	Oncotype DX	Chemotherapy decision
Zhang 2015 China	Cross-sectional, intra-individual	2011-2012	N/A	n=134	Median: 48	Oncotype DX	Chemotherapy decision

Project: Molecular profile in breast cancer

Appendix 2 Characteristics of included studies

Author Year Country	Study Design	Years of inclusion	Follow up time	Patients (n)	Age (years)	Test	Outcome variables
PICO 2 No chemotherapy vs chemotherapy							
Cardoso 2016 Europe	RCT	2007-2011	Median: 5 years	n=699	Median: 55	MammaPrint	Recurrence
Barcenas 2017 USA	Cohort	2005-2011	Median: 58 months	Matched n=178 Unmatched n=549	Median in unmatched groups: 57 (intervention), 50 (control)	Oncotype DX	OS Recurrence
Chen 2018 USA	Cohort	2006-2012	Median: 46 months	n=21,991	31.9% (n=7,014) between 50-59	Oncotype DX	OS
Geyer 2018 USA	RCT	1988-1993	Not available	n=569	Median: 51	Oncotype DX	Recurrence
Ibraheem 2019 USA	Cohort	2010-2014	Median: 41 months	Unmatched n=73,185 Matched n=27,470	Mean in unmatched groups: 58.86 (intervention), 53.98 (control) Mean in matched groups: 55.63 (intervention), 55.50 (control)	Oncotype DX	OS
Le Du 2015 USA	Cohort	2004-2013	Median: 38.4 months	n=341	Median: 54	Oncotype DX	Recurrence
Sparano 2018 USA	RCT	2006-2010	Median: 90 months (recurrence), 96 months (OS)	n=6,711	Median: 55	Oncotype DX	OS Recurrence
Stemmer 2017a (node-) Israel	Cohort	2006-2010	Median: 74 months	n=1,801	Median: 60	Oncotype DX	Recurrence
Stemmer 2017b (node+) Israel	Cohort	2006-2011	Median: 70.8 months	n=637	Median: 62	Oncotype DX	Recurrence
Wen 2016 USA	Cohort	2008-2013	Median: 46 months	n=1,406	Median: 56	Oncotype DX	Recurrence

N/A = Not applicable; OS = overall survival

Project: Molecular profile in breast cancer
Appendix 3 Excluded articles

Author, year	Reason for exclusion
Aalders 2017	Wrong population, includes multifocal breast cancer
Added value of… (EUnetHTA) 2018	Wrong population, includes HER2-positive
Ademuyiwa 2011	Wrong population, includes both clinical low- and high risk breast cancer
Albanell 2012	Wrong population, includes clinical low risk breast cancer
Altman 2018	Wrong population, include HER2-positive
Bear 2017	Wrong population, not suitable for surgery
Blok 2018	SR, poorly defined population
Buechler 2018	Wrong population, not gone through surgery
Bueno-de-Mesquita 2007	Wrong population, HER2-status missing
Chang 2017	SR, studies with high clinical risk included
Chinn-Lenn 2018	Wrong population, includes both clinical low- and high risk breast cancer
Curtit 2019	Wrong population, not clinical intermediate breast cancer
Cusumano 2014	Wrong population, includes both clinical low- and high risk breast cancer
Davidson 2013	Wrong population, includes too many clinical low risk breast cancer
De Boer 2013	Wrong population, includes too many clinical low risk breast cancer
Dinan 2015	HER2-status unavailable, including up to N, includes clinical high risk breast cancer
Drukker 2013	Wrong population, includes HER2-positive and ER-negative
Drukker 2014	Wrong population
Dzimitrowicz 2017	Wrong population, includes too many clinical low risk breast cancer, wrong comparison group – controls also receive RS-test.
Eichler 2019	Wrong population, not clinical intermediate breast cancer
Eiermann 2013	Wrong population, includes too many clinical low risk breast cancer
Ellis 2016	Wrong comparison group
Evans 2016	Wrong population, ER- and/or HER2-status missing. Wrong outcome
Fried 2014	Wrong population, HER2-status not available
Geffen 2011	Wrong population, includes too many clinical low risk breast cancer, HER2-status poorly described
Gluz 2016	Wrong population and wrong comparison
Green 2018	Wrong comparison
Harris 2016	Population poorly defined
Hassett 2012	Wrong population, including HER2-positive and N2
Holt 2013	Wrong population, includes too many clinical low risk breast cancer, include HER2-positive
Hochheiser 2019	Cost-effectiveness study
Jasem 2016	Wrong population, includes too many clinical high risk breast cancer
Jasem 2017	Wrong comparison
Joh 2011	Wrong population, HER2-positive included
King 2016	Wrong comparison
Kizy 2017	Wrong population, includes only lobular carcinoma
Klang 2010	Wrong population, HER2-status missing

Project: Molecular profile in breast cancer
Appendix 3 Excluded articles

Author, year	Reason for exclusion
Kuijer 2016b	Reports two different time periods.
Kuijer 2017	Wrong population, includes too many clinical low risk breast cancer
Lee 2015	Wrong population, includes too many clinical low risk breast cancer
Leung 2016	Wrong population, includes too many clinical low risk breast cancer
Levine 2016	Wrong population, includes too many both clinical low- and high risk breast cancer
Lo 2010	Wrong population, HER2-positive included
Lyman 2007	Economic analysis. Unclear description of population
Marcinkowski 2017	Wrong comparison
McVeigh 2014	Wrong population, includes too many clinical low risk breast cancer
Muller 2013	Wrong population, includes both clinical low- and high risk breast cancer
Narain 2017	Wrong design. The report investigates the gene expressions tests as a prediction tool for adjunct chemotherapy and recurrence.
Nitz 2017	Wrong population, includes N2-N3. Wrong comparison
Ohnstad 2017	Wrong comparison
Ozmen 2016	Wrong population, includes too many both clinical low- and high risk breast cancer
Park 2018	Wrong comparison
Parsons 2016	Wrong comparison
Peethambaram 2017	Wrong population, includes too many clinical high risk breast cancer
Pestalozzi 2017	Wrong population, includes too many both clinical low- and high risk breast cancer
Petkov 2016	Wrong comparison
Pohl 2016	Wrong population, intermediate clinical risk not defined
Prat 2019	Wrong population, includes metastatic disease
Ray 2016	Wrong population, includes too many clinical low risk breast cancer
Retel 2013	Wrong comparison
Roberts 2017	Wrong population. Wrong comparison
Schreuder 2017	Wrong population, includes too many both clinical low- and high risk breast cancer
Scope 2017	SR, studies with high clinical risk included
Sestak 2018	Wrong comparison and outcome
Smyth 2015	Wrong population, HER2-status missing
Sparano 2015	Wrong comparison
Stemmer 2013	HER2-status missing in control group
Tang 2011	HER2-status missing
Torrisi 2013	Wrong population, includes too many both clinical low- and high risk breast cancer
Turashvili 2018	Comparison missing
Tzeng 2010	Comparison missing
Xiao 2017	Wrong comparison
Yamauchi 2014	Wrong population, includes too many clinical low risk breast cancer

Project: Molecular profile in breast cancer

* + No or minor problems
? Some problems
- Major problems

Appendix 4.1.1 PICO 1: Gene expression assay vs. no gene expression assay in low-intermediate breast cancer
Outcome variable: Recurrence

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (Gene expression assay)	Control (No gene expression assay)				
Rath 2018 Germany	Cohort	88 I=44 C=44	0	2 cases with recurrence. One patient rejected recommended chemotherapy and one patient withdrew from endocrine therapy because of side effects	0 cases with recurrence		+	-	-

Project: Molecular profile in breast cancer
Appendix 4.1.2 PICO 1
Outcome variable: Decision to refrain from chemotherapy

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Type of test	Number of patients	With-drawals - dropouts	Results		Comments
				Intervention Gene expression assay	Control No gene expression assay	
Dieci 2018 Italy	Cross-sectional, intra-individual Oncotype DX	250		150 (60%) Changed recommendation in total: 40 (16%)	130 (52%)	Physician recommendation recorded Distribution RS: <11: n=53 (21%) 11-25: n=155 (62%) >25: n=42 (17%)
Fallowfield 2018 United Kingdom	Cross-sectional, intra-individual Endopredict	149		87 (58%) Changed decision in total: 55 (37%)	88 (59%)	Patient decision recorded Distribution high vs low risk: Low: n=75 (50%) High: n=74 (50%)
Friese 2017 USA	Cross-sectional, inter-individual Oncotype DX	Reported: 1,527 I: 778 C: 749 In results figure: 1,615 I: 784 C: 831		≈202 (26%)	≈308 (37%)	Chemotherapy receipt recorded
Kuchel 2016 United Kingdom	Cross-sectional, intra-individual Oncotype DX	Physician recommendation: 67 Patient decision: 65 (relevant subgroup out of 137 patients)		Physician recommendation: 40 (60%) Changed recommendation in total: 33 (49%) Patient decision: 38 (58%) Changed decision in total: 19 (29%)	Physician recommendation: 27 (70%) Patient decision: 43 (66%)	Physician recommendation and patient decision recorded RS distribution in relevant subgroup not reported
Kuijer 2016 The Netherlands	Cross-sectional, inter-individual 70-gene signature, MammaPrint	2,043 I: 1,745 C: 298		9.5% (-15,7% to 3,3%) absolute reduction in administration of CT		Chemotherapy receipt recorded Distribution high vs low risk: Low: n=169 (57%) High: n=95 (32%) Unknown: n=34 (11%)

Project: Molecular profile in breast cancer
Appendix 4.1.2 PICO 1
Outcome variable: Decision to refrain from chemotherapy

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Type of test	Number of patients	With-drawals - dropouts	Results		Comments
				Intervention Gene expression assay	Control No gene expression assay	
Loncaster 2017 United Kingdom	Cross-sectional, intra-individual Oncotype DX	201		127 (63%) Changed recommendation in total: 127 (63%)	0 (0%)	Physician recommendation recorded Predetermined recommendation according to test results All included patient had recommendation for adjuvant chemotherapy based on clinicopathological factors and PREDICT (prognostic tool for adjuvant treatment in BC patients). Distribution RS: <18: n=86 (43%) 18-30: n=89 (44%) >31: n=26 (13%)
Martín 2015 Spain	Cross-sectional, intra-individual Prosigna, PAM50	67	3	Absolute counts not reported, 12 additional patients were recommended to refrain chemotherapy Changed recommendation in total: 14 (20.9%)	Not reported	Physician recommendation recorded. Distribution Prosigma test risk: Low risk: 38.8% Intermediate risk: 40.3% High risk: 20.0%
Martínez del Prado 2018 Spain	Cross-sectional, intra-individual Oncotype DX	401		301 (75%) Changed recommendation in total: 142 (35%)	177 (44%)	Physician recommendation recorded Predetermined recommendation according to test results Distribution RS: <18: n=86 (43%) 18-30: n=89 (44%) >31: n=26 (139%)
Panousis 2016 Greece	Cross-sectional, intra-individual Oncotype DX	114		88 (77%) Changed recommendation in total: 37 (33%)	70 (61%)	Physician recommendation recorded Distribution RS: <18: n=68 (60%) 18-30: n=43 (38%) >31: n=3 (3%)

Project: Molecular profile in breast cancer
Appendix 4.1.2 PICO 1
Outcome variable: Decision to refrain from chemotherapy

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design Type of test	Number of patients	With-drawals - dropouts	Results		Comments
				Intervention Gene expression assay	Control No gene expression assay	
Rath 2018 Germany	Cross-sectional, intra-individual	69	5	39 (61%) Changed recommendation in total: 39 (61%)	0 (0%)	Physician recommendation recorded Predetermined recommendation according to test results
Schreuder 2018 The Netherlands	Cross-sectional, inter-individual Oncotype DX	2,506 I=137 C=2,369		117 (85%)	1,858 (78%)	Chemotherapy receipt recorded
Wuerstlein 2016 Germany	Cross-sectional, intra-individual Prosigna, PAM50	76	6	53 (76%) Changed recommendation in total: 9 (13%)	58 (83%)	Physician recommendation recorded Distribution ROR: Low risk: n=20 (26%) Intermediate risk: n=28 (37%) High risk: n=28 (37%)
Zeng 2017 China	Cross-sectional, intra-individual Oncotype DX	227		100 (44%) Changed recommendation in total: 78 (34%)	40 (18%)	Physician recommendation recorded Distribution RS: <18: n=139 (61%) 18-30: n=68 (30%) >31: n=20 (9%)
Zhang 2015 China	Cross-sectional, intra-individual Oncotype DX	134		104 (78%) Changed decision in total: 39 (29%)	81 (60%)	Patient decision recorded Inter-individual comparisons also reported in the study using a control group with more advanced disease; not reported here Distribution RS: <18: n=97 (72%) 18-30: n=29 (22%) >31: n=8 (6%)

E=Endocrine, CT=Chemo therapy, RS=Recurrence Score, OR=Odds Ratio, 70-GS=70-gene signature, BC=Breast Cancer

* + No or minor problems
? Some problems
- Major problems

Project: Molecular profile in breast cancer
Appendix 4.2.1 PICO 2: No chemotherapy vs. chemotherapy in with intermediate clinical risk and low/intermediate genomic risk
Outcome variable: Overall Survival (OS)

Author year country	Study design Type of test	Number of patients	With-drawls - drop-outs	Results Intervention No chemotherapy HR (95% CI) intervention vs control	Results Control Chemotherapy	Comments	Directness *	Study limitations *	Precision *
Sparano 2018 USA	RCT Oncotype DX	6,711 I=3,458 C=3,449	I=59 C=137	<u>RS 11-25</u> *ITT-analysis* OS at 5 years 98.0% ±SE 0.2 OS at 9 years 93.9% ± SE 0.5 HR_{death} 0.99 (0.79 to 1.22) *As-treated analysis* OS at 9 years 98.1% HR_{death} 0.97 (0.78 to 1.21)	<u>RS 11-25</u> *ITT-analysis* OS at 5 years 98.1% ± SE 0.2 OS at 9 years 93.8% ± SE 0.5 *As-treated analysis* OS at 9 years 98.5%	Non-inferiority design. Margin set at 32.2% higher risk of a the composite outcome invasive disease recurrence, second primary cancer or death when calculating HR. Accepting 87% invasive disease-free survival without chemotherapy compared with 90% with chemotherapy.	?	?	+?
Barcenas 2017 USA	Cohort Oncotype DX	549 (unmatched) I=457 C=92 n=178 (matched) I=89 C=89		<u>Unmatched cohort RS 11-25</u> 5 years: 98% (96% to 99%) HR_{death} 0.46 (0.09 to 2.72) <u>Matched cohort RS 18-30</u> HR_{death} 1.16 (0.20 to 6.67)	<u>Unmatched cohort RS 11-25</u> 5 years: 98% (91% to 99%)	In unmatched analyses: patients with chemotherapy were younger and had more advanced cancer. In the publication chemo vs no chemo: HR_{death} 2.19 (0.44 to 11.0), unmatched RS 11-25 HR_{death} 0.86 (0.15 to 4.91), matched RS 18-30	+	?	-
Chen 2018 USA	Cohort Oncotype DX	21,991 I=17,345 C=4,646		<u>RS 11-25</u> 5 years: 97.6% (96.9% to 98.2%) HR_{death} 1.20 (0.80 to 1.81)	<u>RS 11-25</u> 5 years: 97.4% (95.3% to 98.5%)	In the publication chemo vs no chemo: HR_{OS} 0.83 (0.55 to 1.25)	?	-	?
Ibraheem 2019 USA	Cohort Oncotype DX	73,185 (unmatched) I=55,327 C=17,858 27,740 (matched) I=13,735 C=13,735		<u>Unmatched cohort RS 11-30</u> Node-, HR_{death} 1.18 (0.99 to 1.41) Node+, HR_{death} 1.72 (1.35 to 2.22) <u>Matched cohort, RS 11-30</u> Node-, HR_{death} 1.33 (1.09 to 1.67) Node+, HR_{death} 1.92 (1.43 to 2.56)		In unmatched cohort: patients with chemotherapy were younger and had more advanced cancer. In the publication chemo vs no chemo: <u>Unmatched cohort RS 11-30</u> Node-, HR_{death} 0.85 (0.71 to 1.01) Node+, HR_{death} 0.58 (0.45 to 0.74) <u>Matched cohort, RS 11-30</u> Node-, HR_{death} 0.75 (0.60 to 0.92) Node+, HR_{death} 0.52 (0.39 to 0.70)	?	+	+

ITT = intention to treat; HR = hazard ratio; OS = overall survival; RFS = recurrence-free survival; RS=Recurrence score, SE=standard error

* + No or minor problems
? Some problems
- Major problems

Project: Molecular profile in breast cancer
Appendix 4.2.2 PICO 2: No chemotherapy vs. chemotherapy in breast cancer with intermediate clinical risk and low/intermediate genomic risk
Outcome variable: Recurrence

Author year country	Study design Type of test	Number of patients	With-drawals - drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention **No chemotherapy** HR (95% CI); intervention vs control	**Control** **Chemotherapy**				
Cardoso 2016 Europe	RCT, subset MammaPrint	699 I=350 C=349		DRFS at 5 years: 93.9% (95% CI 90.6 to 96.1) HR_{DR} 1.25 (0.69 to 2.25)	DRFS at 5 years 95.5% (95% CI 92.5 to 97.3)	Non-inferiority design in the main study. Subset with high clinical /low genetic risk In the publication chemo vs no chemo: aHR_{DR} 0.80 (0.44 to 1.45)	+	+	-
Geyer 2018 USA	RCT, subset Oncotype DX	569 I=204 C=365	1,794	Distant recurrence at 10 years: RS<18 5/134 (3.7%) aHR_{DR} 0.84 (0.29 to 2.47) RS 18-30 7/42 (16.7%) aHR_{DR} 1.56 (0.56 to 4.33) RS 11-25 9/103 (8.7%) 10yr distant recurrence free: 95% (90 to 99), p=0.43 aHR_{DR} 1.64 (0.74 to 3.85)	Distant recurrence at 10 years: RS<18 DR at 5yrs: 10/213 (4.7%) RS 18-30 DR at 5yrs: 9/83 (10.8%) RS 11-25 Recurrence 10/168 (6.0%) 10yr distant recurrence free: 94% (90 to 98)	Analysis of a subset of an RCT with 2,363 patients 1988-1993 to treatment with or without chemotherapy, including patients with an RS score available and excluding HER2+ individuals. In the publication chemo vs no chemo: aHR_{DR} 1.19 (0.40 to 3.49), RS<18 aHR_{DR} 0.64 (0.23 to 1.75), RS 18-30 aHR_{DR} 0.61 (0.26 to 1.35), RS 11-25	?	-	?
Sparano 2018 USA	RCT Oncotype DX	6,711 I=3,458 C=3,449	I=59 C=137	RS 11-25 Distant recurrence: *ITT-analysis* DRFS at 5 years 98.0% ±SE 0.3 DRFS at 9 years 94.5% ±SE 0.5 HR_{DR} 1.10 (0.85 to 1.41) *As-treated analysis* HR_{DR} 1.11 (0.90 to 1.37) Loco-regional or distant recurr: *ITT-analysis* RFS at 5 years 96.9% ±SE 0.3 RFS at 9 years 92.2% ±SE 0.6 HR_{recurr} 1.11 (0.90 to 1.37) *As-treated analysis* RFS at 9 years 94.8% HR_{recurr} 1.12 (0.91 to 1.38)	RS 11-25 Distant recurrence: *ITT-analysis* DRFS at 5 years 98.2% ±SE 0.2 DRFS at 9 years 95.9% ±SE 0.5 Loco-regional or distant recurr: *ITT-analysis* RFS at 5 years 97.0% ±SE 0.3 RFS at 9 years 92.9% ±SE 0.6 *As-treated analysis* RFS at 9 years 95.1%	Non-inferiority design. Margin set at 32.2% higher risk of the composite outcome invasive disease recurrence, second primary cancer or death when calculating HR. Accepting 87% invasive disease-free survival without chemotherapy compared with 90% with chemotherapy.	?	?	+?

* + No or minor problems
? Some problems
- Major problems

Project: Molecular profile in breast cancer
Appendix 4.2.2 PICO 2: No chemotherapy vs. chemotherapy in breast cancer with intermediate clinical risk and low/intermediate genomic risk
Outcome variable: Recurrence

Author year country	Study design Type of test	Number of patients	With-drawals - drop-outs	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention **No chemotherapy** HR (95% CI); intervention vs control	**Control** **Chemotherapy**				
Barcenas 2017 USA	Cohort Oncotype DX	549 I=457 C=92 178 I=89 C=89		Unmatched cohort RS 11-25 RFS at 5 years: 96% (94% to 98%) HR_{recurr} 0.68 (0.19 to 2.44) Matched cohort RS 18-30 HR_{recurr} 1.02 (0.33 to 3.13)	Unmatched cohort RS 11-25 RFS at 5 years: 95% (86% to 98%)	In unmatched analyses: patients with chemotherapy were younger and had more advanced cancer. In the publication chemo vs no chemo: HR_{recurr} 1.46 (0.41 to 5.23), unmatched RS 11-25 HR_{recurr} 0.98 (0.32 to 3.06), matched RS 18-30	+	?	-
Le Du 2015 USA	Cohort Oncotype DX	341 I=189 C=152		RS 18-30 Recurrence 10/189 (5.3%)	RS 18-30 Recurrence 16/152 (10.5%)	The control group was younger, had higher histologic grade, higher nuclear grade and higher Ki67 expression	+	-	-
Stemmer 2017a Israel	Cohort Oncotype DX	562 I=473 C=89		RS 18-25 Recurrence 17/473 (3.6%)	RS 18-25 Recurrence 5/89 (5.6%)	Node-. Patients with chemotherapy were younger and had more advanced cancer	?	-	?
Stemmer 2017b Israel	Cohort Oncotype DX	637 I=508 C=129		Recurrence RS<18: 10/352 (2.9%) RS 18-30: 15/156 (9.7%) RS 11-25: 17/379 (4.6%) RS<25: 21/488 (4.4%)	Recurrence RS<18: 2/27 (7.7%) RS 18-30: 1/102 (1.0%) RS 11-25: 1/83 (1.2%) RS<25: 2/89 (2.3%)	Node+. Characteristics not reported in the compared groups	+	-	-
Wen 2016 USA	Cohort Oncotype DX	1,406 I=1,236 C=170		RS<18 Recurrence 5/1,236 (0.4%)	RS<18 Recurrence 1/170 (0.6%)	Characteristics not reported in the compared groups	+	-	-

aHR = adjusted hazard ratio; DM = distant metastases; DRFS = distant recurrence free survival; ITT = intention to treat; RCT = randomised controlled trial; RFS = recurrence-free survival; RS = recurrence score, SE = standard error

Project: Molecular profile in breast cancer
Appendix 5 Ethical aspects

The effect of the intervention on health	
Q1: Health: How does the intervention affect patients' health in terms of quality of life and life-length (including adverse effects)?	If a gene expression assay can identify intermediate risk breast cancer patients who safely can refrain from chemotherapy, acute or long-term adverse effects of chemotherapy, including death, could be prevented. This HTA shows that life-length would probably not be affected when refraining from chemotherapy in these patients, based on genetic testing of the tumour. However, it can probably not be ruled out that refraining from chemotherapy, based on such test results, implies an increased risk of recurrence. As overall survival data are available up to 9 years when 94% of the patients are still alive, no conclusions regarding potential effects of recurrence on life-length beyond this time period can be drawn. If a gene expression assay can identify breast cancer patients in whom chemotherapy can safely be withheld, acute or long-term adverse effects of chemotherapy, including death, could be prevented. In addition to patient benefit, successful identification of such patients could also reduce health care costs as well as societal costs due to sick leave. However, this HTA illustrates that knowledge about potential patient-relevant effects of gene expression tests is largely lacking. Further, it cannot be ruled out that withholding chemotherapy based on a gene expression test may imply an increased risk of recurrence. As we found no evidence of benefits of using gene expression assays in luminal, HER2-negative breast cancer, and a potential risk concerning recurrence, the benefit-risk balance may be negative. However, the absence of studies evaluating potential HRQL effects when chemotherapy was withheld based on a gene expressions test, does not exclude such effects. Indeed, chemotherapy is known to cause adverse effects and decreased HRQL during the course of treatment. The gene expression assay itself is performed on tissue taken from standard surgery. Therefore, the use of such tests will not put patients at risk of additional physical harm or pain.
Q2: Knowledge gaps: If there is lack of scientific evidence for the effect of the intervention, are there ethical and/or methodological problems with future research in order to strengthen this evidence.	This HTA reveals a lack of evidence regarding patient outcomes with versus without genetic testing of the tumour. As the results suggest that there may be an increased risk of recurrence, when deciding to omit chemotherapy based on the results of such tests, there may be ethical implications in performing randomised controlled studies where patients are allocated to test or no test. However, as overall survival is probably not affected, the risk may be acceptable. Further, gene expression assays are already implemented in some other countries, epidemiological follow-up would be possible, minimising the potential ethical problem of exposing patients to potential harms.
Q3: Degree of severity: What degree of severity has the condition the intervention is supposed to treat?	Breast cancer implies a high severity of disease. The condition *per se* may shorten the life-length, and the treatment may affect health-related quality of life.
Q4: Third parties: How does the intervention affect the health of third parties?	If gene expression assays are introduced in clinical practice, and the proportion of patients refraining from chemotherapy increases by less than 22.5%, the costs will increase for the health care sector. In that case, the use of such tests will displace other care, thereby potentially affecting the health of third parties.
Summary: How can the benefit-risk ratio of the intervention be described? (given the answers of Q1-Q4)?	In this HTA, we found similar overall survival rates with and without chemotherapy when a gene expression test was used to select patients in whom chemotherapy could be omitted. However, we could not find any evidence regarding potential effects on health-related quality of life, an outcome which may be affected by chemotherapy as adverse effects are common. In addition, available evidence does probably not exclude an increased risk of recurrence. Summarised, we found no clear benefits of using gene expression assays in luminal, HER2-negative breast cancer, and a potential risk concerning recurrence. Given available evidence, the benefit-risk balance may therefore be negative.

Project: Molecular profile in breast cancer
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The compatibility of the intervention with ethical values	
Q5: Equality and justice: Is there a risk that access to the intervention violates the Human Dignity principle or the Swedish Discrimination Act?	No major ethical dilemma can be identified within this principle. If implemented, the access could be expected to depend primarily on other aspects than sex, ethnicity, and socio-economic status.
Q6: Autonomy: Can the intervention affect patient's participation in decisions and their ability to make informed decisions?	No major ethical dilemma can be identified concerning this principle. However, it cannot be excluded that the results of gene expression tests, in some cases, may override the patient's voluntary decision making regarding chemotherapy. As this HTA shows no clear benefit of using gene expressions assays to guide adjuvant chemotherapy decisions, it is important, if implemented, that the treating physician is well informed about the scientific evidence, to facilitate informed decision making of the patient. Indeed, there may be a risk of a false sense of security when relying on genetic tests. On the other hand, it may be speculated that such a sense may also add value. This HTA, however, does not provide any information about this aspect.
Q7: Privacy: How does the intervention affect patient's and significant others' physical and personal privacy?	No major ethical dilemma can be identified concerning integrity. However, genetic testing may be perceived more intrusive than other types of testing.
Q8: Cost-effectiveness: Is the balance between the cost and effects of the intervention reasonable?	As (i) no clear benefits of using gene expression assays have been identified in this HTA, (ii) harms may be associated as there may be an increased recurrence rate if chemotherapy is omitted based on test results, and (iii) the assays *per se* imply a cost, the cost-effectiveness ratio may not be favourable. However, if the proportion of patients refraining from chemotherapy increases by more than 22.5% by the use of gene expressions assays, there may be cost savings for the health care, making the cost-effectiveness ratio less unfavourable. Potential savings from decreased costs for sick-leave have not been in included in the cost-effectiveness analysis
Summary: Is the use of the intervention compatible with ethical values (given the answers of Q5-Q8)?	Using gene expression assays to guide chemotherapy decision making in intermediate breast cancer implies no major ethical problems regarding equality and justice, autonomy, and privacy. However, as the evidence suggests harms rather than benefits and testing implies a cost, there may be issues regarding cost-effectiveness.
Structural factors that can affect the use and consequences of the intervention	
Q9: Resources and organisation: Are there resource- or organizational limitations that can affect who will get access to the intervention or that can lead to less access to other care if the intervention is used?	Depending on type of gene expression assay, the analytic procedure may affect the access. For example, Prosigna/PAM50 and EndoPredict can be analysed at local pathological laboratories while the other two tests, Oncotype DX and MammaPrint, have to be sent to central laboratories. In Region Västra Götaland, Prosigna/PAM50 would be the assay of choice. Equal access to genetic profiling will thereby depend on available resources at the departments of pathology and surgery. In addition, before potential implementation, relevant personnel has to be educated, ranging from personnel at the surgery ward where the tissue samples are collected, to personnel working in the laboratory, and the oncologists interpreting the results in their decision making. Available resources may differ between sites and departments, with potential consequences for the educational efforts and thereby access to the intervention.

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Q10: Professional values: Can values of involved professionals influence the use of the intervention and thereby lead to unequal access?	Given the results of this HTA, with greatly varying results regarding chemotherapy decision making based on genetic testing, influence of the values of involved professionals can be expected. First, a gene expression assay will be used or not, at the discretion of the physician or laboratory routine. Second, the inclination to be guided by the test results may vary, regarding the decision to refrain from chemotherapy. Both factors may contribute to unequal breast cancer treatment.
Q11: Stake holder interests: Are there stake holder interests that can influence the use of the intervention and thereby lead to unequal access?	The company behind a gene expression assay may be allowed to promote the product to various extents at different sites. This may be of importance for the access to such tests. Incentives may also vary between pathology departments, with potential implications for access.
Summary: Are there reason to believe that an equal access to the intervention (or other care interventions) can be affected (given the answers to Q9-Q11)?	There may be structural factors affecting the use of, as well as the consequences of, gene expression assays in luminal, HER2-negative breast cancer. Given these factors, including resources and organisation, professional values, and stake holder interests, unequal access to the issue at question cannot be excluded.
Long-term ethical consequences	
Q12: Long-term consequences: Can the use of the intervention result in more long-term consequences?	Survival in luminal HER2-negative breast cancer is relatively long. Therefore, survival data in studies are often immature. In the major RCT contributing data to this HTA, 94% of the patients were still alive at the nine year follow-up. Therefore, the median overall survival had not been reached. Further, no conclusions can be drawn beyond this point of time, regarding potential effects on survival of the potentially increased recurrence rate by refraining from chemotherapy based on genetic testing. Nevertheless, most recurrences in this breast cancer population can be expected to have happened within this time span.
Overall summary	
How can the ethical aspects regarding the intervention be summarised? Does this summary indicate that the intervention should be modified or that there should be special requirements associated with offering the intervention?	There are ethical dilemmas regarding gene expression assays in luminal HER2-negative breast cancer to guide chemotherapy decision making, including the benefit-risk ratio, the compatibility with ethical values, equality in access related to structural factors, as well as long-term consequences. These need to be considered if implemented.

Appendix 6

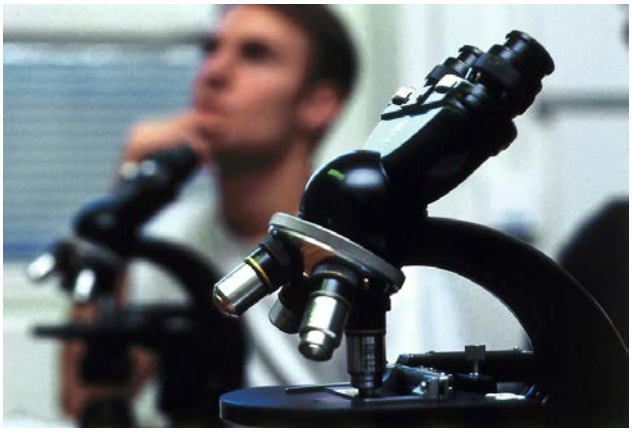
Registered studies in Clinical Trials
Molecular profile in breast cancer

NCT Number	Main scope	Status	Test	Study design	URL
NCT 02347449	Treatment decision making Aux PICO	Unknown status	Oncotype DX	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT02347449
NCT 01423890	Treatment decision making Aux PICO	Completed, no results available	Oncotype DX	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT01423890
NCT 01446185	Treatment decision making Aux PICO	Completed, no results available	Oncotype DX	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT01446185
NCT 02627703	Treatment decision making Aux PICO	Unknown status	Oncotype DX	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT02627703
NCT 02269813	Treatment decision making Aux PICO	Unknown status	MammaPrint	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT02269813
NCT 03080428	Treatment decision making Aux PICO	Withdrawn	EndoPredict, MammaPrint, PAM50/Prosigna, Oncotype DX	Cross-sectional, inter-individual	https://clinicaltrials.gov/ct2/show/NCT03080428
NCT 02625935	Treatment decision making Aux PICO	Completed, no results available	PAM50/Prosigna	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT02625935
NCT 01899079	Treatment decision making Aux PICO	Completed, no results available	PAM50/Prosigna	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT01899079

NCT 02395575	Treatment decision making Aux PICO	Completed, no results available	PAM50/Prosigna	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT02395575
NCT 03503799	Recurrence, OS Main PICO	Recruiting	EndoPredict	Cohort	https://clinicaltrials.gov/ct2/show/NCT03503799
NCT 01974856	Treatment decision making Aux PICO	Completed, no results available	PAM50/Prosigna	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT01974856
NCT 02773004	Treatment decision making Aux PICO	Completed, no results available	EndoPredict	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT02773004
NCT 01926964	Treatment decision making Aux PICO	Completed, no results available	Oncotype DX	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT01926964
NCT 00904566	Recurrence Aux PICO	Completed, no results available	MammaPrint	Cohort	https://clinicaltrials.gov/ct2/show/NCT00904566
NCT 02209857	Treatment decision making Aux PICO	Completed, no results available	MammaPrint	Cross-sectional, intra-individual	https://clinicaltrials.gov/ct2/show/NCT02209857

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

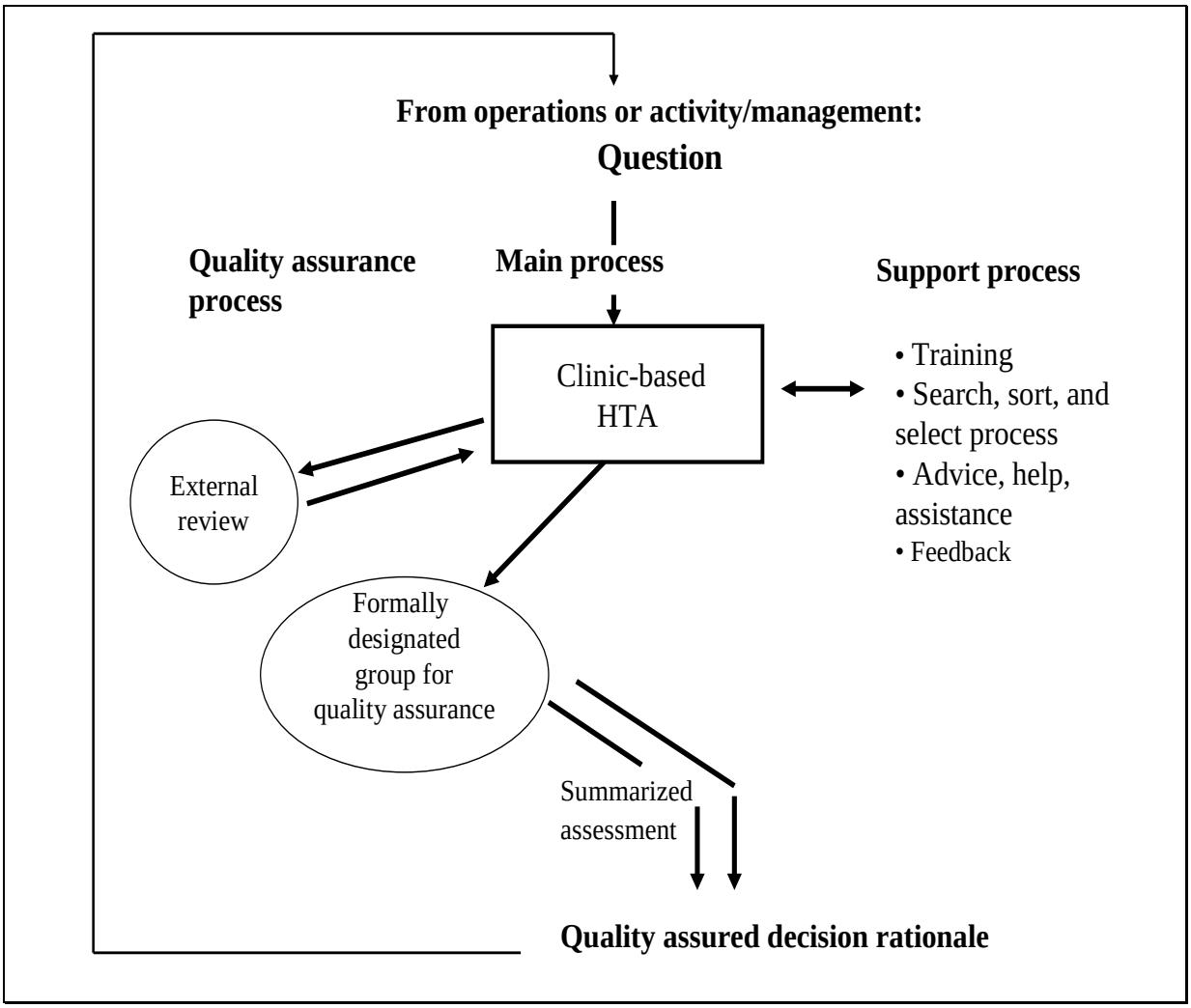
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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