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Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

MAMMAPRINT® TEST FOR PERSONALISED MANAGEMENT OF ADJUVANT CHEMOTHERAPY DECISIONS IN EARLY BREAST CANCER

A RAPID ASSESSMENT

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COLOPHON

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
BCFI – CBIP	Belgian Centre for Pharmacotherapeutical Interventions
CE	Cost Effectiveness
CU	Cost Utility
ER	Estrogen Receptor
EUnetHTA	European Network Health Technology Assessment
GEP	Gene Expression Profiling
HTA	Health Technology Assessment
HER2	Human Epidermal Growth Factor Receptor 2
ICER	Incremental Cost Effectiveness Ratio
IHC	Immunohistochemistry
INAHTA	International Network of Agencies for Health Technology Assessment
IQWIG	German Institute for Quality and Efficiency in Health Care
ITT	Intent To Treat
LN	Lymph node
LYG	Life Years Gained
NICE	National Institute for Health and Care Excellence
NPI	Nottingham Prognosis Index
PP	Per Protocol
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
SR	Systematic Review
ZiN	The National Health Care Institute Netherlands

SCIENTIFIC REPORT

1 INTRODUCTION AND SCOPE

Gene expression profiling (GEP) tests aim to improve decision-making related to adjuvant chemotherapy treatment for women with early breast cancer. In 2014, KCE performed a rapid HTA on this topic[1] and concluded that there were no data on the clinical utility of such tests and that an update of the review should be performed as soon as RCT results on such aspect became available. Following the publication of the results from the MINDACT RCT on MammaPrint®[2] in August 2016, RIZIV/INAMI asked KCE to perform an update of their HTA report.

An assessment of the clinical utility of MammaPrint® has recently been completed by the Zorginstituut Nederland (ZiN), as part of a EUnetHTA[a] joint production collaboration, in which KCE acted as dedicated reviewers[3]. The aim of this report is to complete the clinical assessment, with an assessment of cost effectiveness considerations for MammaPrint® in the Belgian setting.

[a] http://www.eunethta.eu/

2 BREAST CANCER

2.1 Epidemiology

Breast cancer remains the most commonly diagnosed cancer in women in Belgium and worldwide, while the incidence in men is very low. In 2014 the Belgian Cancer Registry reported 10 466 cases of incident breast cancers in women. The European age standardized rate of incident breast cancer in 2014 was 145/100 000 person years in women. Incidence increases markedly with age with a peak in the 70-75 year age category. Mean age at diagnosis is 63 years in women.[b]

2.2 Prognosis and treatment

Although breast cancer has overall a relatively good prognosis in Belgium, with a five-year relative survival rate of 88.0% in women and 78.2% in men and a ten-year relative survival (Flemish region only) of 78.9% and 61.9% respectively, mortality remains considerable, accounting for approximately 20% of all cancer deaths in Belgian women.[4]

Relative survival is dependent on the stage of the tumour at the time of diagnosis. Five-year breast cancer survival in Belgium is 100% for TNM Clinical Stage 0, 99.4% for stage I and falls to 28.0% for Stage IV.[4]

More sophisticated tools to assess the likely prognosis of breast cancer, based on several classifications and patient characteristics have been developed in the recent years, some of them computerized, such as the Adjuvant!Online[c], PREDICT[d] or the Nottingham Prognostic Index (NPI)[e]. Although different, most of these tools consider similar parameters:

NPI: estimations based on tumour size, lymph node involvement (LN) and histologic grade;

Adjuvant! Online: estimations based on tumour size, LN involvement, grade, age and ER status, (as well as HER2 status in its modified version).

PREDICT: estimations based on tumour size, LN involvement, grade, age and ER, HER2 and KI67 status.

Such tools have become more popular in the last years, but the extent to which they are (or have been) used in Belgium in routine practice remains unknown.

Treatment for breast cancer patients usually involves primary surgery, (in some cases preceded by neoadjuvant therapy to reduce the size of the tumour) to remove the primary tumour and any involved lymph nodes. This might be followed by adjuvant therapy such as radiation therapy, endocrine therapy and/or chemotherapy with or without targeted biological therapy, depending on both tumour and patient characteristics.

In Belgium the most recent guidelines were published by KCE in collaboration with the Belgian college of Oncology in 2013.[5] These guidelines recommend that the choice of the adjuvant systemic treatment for invasive breast cancer (including chemotherapy, hormonal therapy, antibody therapy or a combination of them), should be driven by the hormonal sensitivity, risk profile of the tumour, age, menopausal status and comorbidities of the patient.

However, decisions on when the use of adjuvant chemotherapy is appropriate and necessary to minimise the risk of recurrence and improve the prognosis of ER+, HER2- early breast cancer patients with up to 3 affected lymph nodes (i.e. the subject of interest of this review), remain in some cases challenging.

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b http://www.kankerregister.org/

c https://www.adjuvantonline.com/ - Currently unavailable due to an update

d http://www.predict.nhs.uk/

e http://www.pmidcalc.org

3 MAMMAPRINT® IN EARLY BREAST CANCER

3.1 MammaPrint®

It is in this context that tests such as MammaPrint® (Agendia, the Netherlands – http://www.agendia.com), a GEP test based on microarray technology using a 70-gene expression profile, have gained interest as additional decision making tools which could facilitate a more targeted and better informed chemotherapy approach in early breast cancer. It is intended to be used in women of all ages, suffering from invasive early breast cancer with up to 3 involved lymph nodes, and a tumour size ≤ 5.0 cm.

3.2 Methods for assessment of clinical utility

This section offers a brief overview of the main findings of the EUnetHTA clinical assessment[3], to allow for a better comprehension of the economic discussion and the transferability of the results to the Belgian context.

Detailed aspects of the clinical assessment such as the PICO or the evaluation on the quality of the evidence can be found in the full EUnetHTA report.

The aim of the assessment was to study the clinical utility of MammaPrint® by evaluating whether the addition of this GEP test to standard prognostic tools, could help to better identify those early breast cancer patients more at risk of distant recurrence and thus, more likely to benefit from adjuvant chemotherapy, thereby limiting its use (and related AEs), without negatively affecting overall survival.

The study types included in the clinical effectiveness/safety domains of the assessment were limited to randomised controlled trials (RCT). Risk of bias at study level was based on the Cochrane risk of bias tool[f], while the quality of the evidence for each outcome was evaluated using GRADE (Grading of Recommendations, Assessment, Development and Evaluation)[g].

A systematic search of the literature (see EUnetHTA report[3] for details) concluded that the MINDACT trial[2] remains to this date the only prospective RCT investigating the clinical utility of GEP tests (MammaPrint®). This was further confirmed by discussions with Belgian and Dutch experts in the field during two project scoping meetings (held in early 2017).

Only two ongoing RCTs, one of which had already been identified in the previous report,[1] were mentioned as forthcoming RCT evidence (i.e.the TAILORx and the RxPonder, both focusing on the 21-gene expression test Oncotype DX®). The results of the most advanced of these studies, the TAILORx, are planned to be published by the end of 2017.

3.3 Results on the clinical utility of MammaPrint®

The MINDACT study (**M**icroarray **I**n **N**ode-negative and 1 to 3 positive lymph node **D**isease may **A**void **C**hemo**T**herapy)[2] is an open-label, multicentre, randomized controlled trial, carried out on 6,693 female early breast cancer patients enrolled from 2007 to 2011 in 112 centres from nine European countries[h] , followed up for a median of 5 years. Women were aged 18-70, with histologically confirmed primary invasive breast cancer tumours (stage T1, T2 or operable 3) and up to three positive axillary nodes (LN 0-3). It aimed at providing evidence of the clinical utility of the addition of the 70-gene signature (i.e. MammaPrint®) to standard clinical-pathological criteria (captured by means of the modified A!O[i]) in selecting patients for adjuvant chemotherapy. In particular, the study's primary objective was to assess whether distant metastasis free survival (DMFS) at 5 years, in the discordant patient risk groups (i.e. clinical high-risk/ genomic low-risk, and clinical low-risk/genomic high risk) was different for patients exposed to adjuvant

f http://methods.cochrane.org/bias/assessing-risk-bias-included-studies

g http://www.gradeworkinggroup.org/

h Netherlands, France, Germany, Belgium, Spain, Italy, UK, Slovenia, and Switzerland

i The modified A!O, is a version of A!O in which HER2 status is included.

chemotherapy versus patients not receiving it. A non-inferiority threshold of 92% was selected based on 10-year breast cancer probabilities derived from Adjuvant! Online for the clinical high-risk patients.

Two secondary endpoints: Overall survival and progression free survival at 5 years were studied.

During the trial, patients were grouped in 4 risk-categories:

Patients classified as clinical low risk (according to A!O)/ genomic low risk (according to MammaPrint®) did not receive chemotherapy (n=2745).

Patients classified as clinical high risk (according to A!O)/ genomic high risk (according to MammaPrint®) received chemotherapy (n=1806)

Patients on the two discordant groups (i.e. "clinical low risk (according to A!O)/ genomic high risk (according to MammaPrint®)" (n=592) and "clinical high risk (according to A!O)/ genomic low risk (according to MammaPrint®)" (n=1550) were randomised to receiving or not chemotherapy.

In their analysis the investigators focussed on the two discordant risk groups (the randomisation part of the MINDACT study[2]).

For patients in the "clinical low risk/genomic high risk" group, the MINDACT study[2] showed no statistically significant differences in DMFS at 5 years between patients receiving chemotherapy and those who did not. Therefore, no significant advantage could be derived from adding MammaPrint® to standard clinical practice in these patient group.

For patients in the "clinical high risk/genomic low risk" group, both the per protocol (PPS[j]) and the intention to treat (ITT) analyses of the MINDACT[2] did not show any statistically significant differences between patients receiving chemotherapy and those who did not for the primary endpoint of DMFS at 5 years (hazard ratio PPS analysis: 0.60 (95% CI 0.34-1.06); HR ITT analysis: 0.78 (95% CI 0.50-1.21). Therefore, this group was identified as the potential target population for MammaPrint®, (i.e. less chemotherapy use without statistically significant differences in clinical outcomes).

Nevertheless, for the same patient group (i.e. "clinical high risk/genomic low risk") the absolute numbers for DMFS for non-chemotherapy treated patients were 94.0% (95%CI: 91.4-95.8) in the PPS analysis and 94.4% (95%CI: 92.3-95.9) in the ITT analysis, versus 96.5% (95%CI: 94.1-97.9) in the PPS analysis and 95.9%(95%CI: 94-97.2) in chemotherapy treated patients.

In fact, point estimates for all outcomes measured at 5 years (i.e. DMFS, OS and DFS) were slightly higher for patients who received chemotherapy compared with those not receiving chemotherapy (2,5%% in DMFS, 2.5% in OS and 4,5% in DFS in the PPS analysis and 1.4% in DMFS, 1.5% in OS and 1.9% in DFS for the ITT analysis).

Table 1 summarises the main findings from the study (all analyses included). Statistically non-significant differences were found between the chemotherapy treated versus the non-treated clinical high-risk/genomic low-risk population, in the primary outcome of DMFS, as well as in the secondary outcome of OS at 5 years. However, this finding should not be interpreted as evidence of absence of a difference in this specific endpoint, because the study was not powered to find statistical differences between these two groups. Next to that, the wide confidence intervals surrounding the estimates obtained for all outcomes, as well as the indirectness of the evidence (DMFS at 5-years used as a surrogate for 10 year OS), call for a cautious interpretation of the results.

j Analysis carried out after a risk calculation correction due to a non-communicated change in the RNA-extraction solution

Table 1 – Five year HR (95% CI) from the MINDACT trial - clinical high/genomic low risk group

Analysis	DMFS	OS	PFS
Per protocol (n=1228)	0.65 (0.38-1.10)	0.63 (0.29-1.37)	0.64 (0.43-0.95)
Intention to treat (n=1497)	0.78 (0.50-1.21)	0.69 (0.35-1.35)	0.71 (0.50-1.01)
Per protocol sensitivity* (n=1045)	0.60 (0.34-1.06)	0.54 (0.23-1.26)	0.57 (0.37-0.87)

DMFS: Distant metastasis free survival; OS: Overall survival; PFS: Progression free survival.
**Analysis carried out after a risk calculation correction due to a non-communicated change in the RNA-extraction solution*

During the MINDACT study[2], health related quality of life (QoL) was not systematically measured. Short and long term side effects of chemotherapy were captured, but have not yet been published. It is well documented that patients who receive chemotherapy have lower QoL during the chemotherapy courses than those who do not receive chemotherapy.[6-9]. However, improvements of QoL in the long term may depend on the balance between avoiding rare but severe long term AEs (such as acute myeloid leukemia or chronic heart failure) linked to chemotherapy use, and the potential loss of QoL due to higher recurrences after the omission of the chemotherapy, due to the use of the MammaPrint® test.

Taking everything into consideration, it has not yet been demonstrated that patient outcomes (ten-year OS and QoL) are improved by withholding adjuvant chemotherapy based on MammaPrint® testing in the clinical high/genomic low- risk group.

This conclusion is based on the absence of evidence on added value in terms QoL and on the fact that non-inferiority in terms of OS (surrogates five-year DMFS, five-year DFS and five-year OS) is not shown. Next to that there are concerns about the certainty of DMFS because of the imprecision (very wide 95% CI's). Therefore the results do not rule out the possibility of a small, but possibly clinically relevant increase in distant metastasis and hence, risk of death.

Therefore, the statistically non-significant increase in risk for distant metastases (and associated loss in QoL) needs to be weighed against the immediate gain in QoL from avoiding chemotherapy and its side-effects. The patient preference is likely to vary from case to case.

The risk of bias was considered high for the clinical high-risk/genomic low-risk, not just because of the open label nature of the study which impeded the blinding of patients and personnel, but also because of a number of changes in the population analysed (see Table 2) and full EUnetHTA report[3] for more information.

Table 2 – Risk of Bias Assessment at study level (RCTs)

MINDACT risk groups	Adequate random sequence generation	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	Other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Personnel			
Clinical high/Genomic low	Yes	Yes	No*	No*	Yes	Yes**	High
Clinical low/Genomic high	Yes	Yes	No*	No*	Yes	Yes	Low

** Open label study*
*** Of all patients randomized to chemotherapy (n=749), 23% are not included in the PP analysis (of whom 128 did not receive chemotherapy and 26 had a change in risk). Of all patients randomized to no chemotherapy (n=748), 16% are not included in PP analysis (of whom 85 received chemotherapy and 21 had a change in risk). No data on lost to follow up.*

Conclusions

- **Only one RCT, the MINDACT study[2], has so far evaluated the clinical utility of GEP tests (i.e. MammaPrint®) in adjuvant chemotherapy decisions for early breast cancer patients.**
- **For patients classified as *"clinical low risk (by A!O) /genomic high risk (by MammaPrint®)"*, the study showed *no benefit* on the primary outcome of DMFS at 5 years of adding MammaPrint® to standard clinical practice (i.e. no statistically significant differences in DMFS at 5 years between patients receiving chemotherapy and those who did not).**
- **For patients in the "*clinical high risk/genomic low risk*" group, the studyshowed statistically non-significant differences in the primary endpoint of DMFS at 5 years between patients receiving chemotherapy and those who did not. Uncertainties however remain, as indicated by the large CIs that surround the outcomes and their point estimates which tend to favor the use of chemotherapy following standard clinical practice (Adjuvant! Online).**
- **Further limitations include the fact that the data on adverse events were not yet made public and that the quality of life of the patients in the MINDACT trial[2] was not assessed.**

4 SYSTEMATIC LITERATURE REVIEW OF ECONOMIC STUDIES

4.1 Introduction

This chapter provides an overview of published studies evaluating the use of the MammaPrint® test in chemotherapy treatment decisions for early breast cancer patients from an economic perspective. It builds on the KCE report 237 published in 2015[1], focusing on the only GEP test for which there was evidence of clinical utility from RCTs at the time of the publication of this report (i.e. MammaPrint®). The aim is to update the search strategy performed in 2014 with any new economic studies that may have been published since then, and adapt the critical assessment. This would not only facilitate an assessment on the transferability of the results to the Belgian situation but it should also help to better inform future cost effectiveness studies in this field.

4.2 Methods

4.2.1 Search strategy

The systematic literature search carried out originally in mid-September 2014 was replicated for the period September 2014 to March the 6th 2017 in order to update the original review with any economic evaluations published after it on MammaPrint®.

The following databases were consulted: Medline (through OVID), EMBASE, Econlit (through OVID), NHSEED (CRD) and NHSHTA (CRD) in order to retrieve recent primary full economic evaluations (studies comparing both costs and outcomes) and reviews of economic evaluations (i.e. secondary economic evaluations). An overview of the update to the original search strategy is provided as an Appendix 1.1.

Furthermore, the websites of Health Technology Assessment (HTA) institutes listed on the INAHTA website (International Network of Agencies for Health Technology Assessment) and NICE (National Institute for Health and Care Excellence) were consulted to capture any recent reports (published after Sept 2014) on the use of MammaPrint® in early breast cancer patients. No restrictions were imposed for language.

4.2.2 Selection procedure

To identify potentially relevant studies for our analysis we first went through all titles and abstracts in order to exclude any studies that obviously did not match our research subject. All articles that appeared to be interesting, or for which there were some doubts, were read in full in order to select those relevant for inclusion in our review.

Reference lists of the selected primary and secondary economic evaluations found via our search were checked for additional references worth adding to our analysis.

Study selection was completed by one researcher but any doubts that came up during the exercise were discussed and solved in collaboration with a second reviewer.

All studies finally included in our review were critically appraised by using an in-house structured data extraction sheet based on the check list originally developed by Drummond et al.[10]. See Appendix 1.2 for a copy of the template used.

4.2.3 Selection criteria

All full economic evaluations looking at MammaPrint® as a prognostic tool for identifying patients most likely to benefit from chemotherapy treatment in early breast cancer published between September 2014 and March 2017 were included in our review and added to the original list of studies on MammaPrint® already identified in our 2014 report[1].

Cost descriptive analyses or cost comparisons not taking into consideration clinical effectiveness were discarded. Similarly, publications in the form of letters, editorials or notes and abstracts were excluded, since these would not offer enough information to include them in our analysis and critically appraise their findings. An overview of the inclusion/exclusion criteria is given in Table 3.

Table 3 – Selection criteria for full primary economic evaluations

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Early invasive breast cancer patients	Regionally and distantly disseminated cancer
Intervention	MP test	Any other prognostic test/tool
Comparator	Standard clinical assessment tools or other GEP/IHC tests	No prognostic tool excluded
Design	Full economic evaluations (primary or secondary)	Cost descriptive analysis, cost comparisons
Type of publication	Articles or reviews	Letters, editorials, notes, abstracts

MP – MammaPrint®; GEP – Gene Expression Profiling; IHC – immunohistochemistry

Our search returned 88 citations, after eliminating duplicates. Of those, 81 did not meet our inclusion criteria based on a review of their title and/or abstract. Of the 7 citations left, 4 were excluded after reading their full text because of publication type (3)[11-13] and intervention (1)[14]. A further study was excluded since its cost analysis was not described and only the overall results were presented in the published article[15]. Further details on the methodology used for their cost-utility analysis were requested directly from the corresponding author, but no response was obtained by the date of the publication of this report. This left us with 2 relevant studies[16, 17] to be added to the 8 studies on MammaPrint® identified via our 2014 report. An exploration of the references of identified articles resulted in no further relevant studies.

Our literature selection process is illustrated in Figure 1 (see Figure 1 in Appendix). Out of the 10 economic evaluations identified overall, one[18] consisted of a HTA report which included the development of an original cost model for MammaPrint® and thus, was included in our analysis. Two systematic reviews covering MammaPrint® or gene expression profiling in general, which did not include modelling[19, 20] were excluded from our review, but their references were checked, in order to ensure no primary economic evaluations had been missed from our review. Table 4 offers an overview of the 10 studies on MammaPrint® included in our review.

4.3 Overview of economic evaluations

As shown in Table 4, six studies were undertaken in Western Europe, with one of them performed in France,[16] three, by the same author, in the Netherlands[21-23], one in Spain[17] and one in the UK[18]. No Belgian-specific studies were found.

Three more studies were carried out in the USA[24-26] and one in Japan[27].

Seven out of the 10 studies date from 2012 or later, reflecting the importance that the topic has gained in the last years. All studies selected were model-based (decision-tree and/or Markov models).

Table 4 – Main characteristics of economic evaluations on MammaPrint® for chemotherapy decisions in early breast cancer

Author	Year	Country	Type of evaluation	Perspective	Discount rate; both costs and outcomes (%)
Bonastre[16]	2014	France	CUA/CEA	Societal	4%
Chen[24]	2010	USA	CUA/CEA	Healthcare payer	3%
Kondo[27]	2012	Japan	CUA/CEA	Healthcare system although presented as societal	3%
Oestreicher[25]	2005	USA	CUA	Societal	3%
Retel[23]	2013	Netherlands	CUA/CEA	Healthcare system	4% costs and 1,5% outcomes
Retel[22]	2012	Netherlands	CUA/CEA	Healthcare system	4% costs and 1,5% outcomes
Retel[21]	2010	Netherlands	CUA/CEA	Healthcare payer	4% costs and 1,5% outcomes
Segui[17]	2014	Spain	CUA/CEA	Healthcare payer	3%
Ward[18]	2013	UK	CUA	Healthcare system	3,50%
Yang[26]	2012	USA	CUA	Healthcare payer	3%

CEA: Cost effectiveness analysis, CUA: Cost utility analysis

4.3.1 Type of economic evaluation

Three of the studies performed cost-utility analyses[18, 25, 26] and expressed their outcomes in quality-adjusted-life-years (QALYs), while the remaining completed both cost-effectiveness and cost-utility evaluations, presenting their clinical outcomes both in terms of QALYs and life-years-gained (LYG).

4.3.2 Time frame of analyses and discounting

Three studies included in this analysis looked at costs and outcomes over a patient's lifetime[18, 24, 25], a further three, all by the same author, used a time horizon of 20 years[21-23] and two studies looked at a timeframe of 10 years[16, 26]. Finally, the remaining two looked at different time horizons, with Kondo et al. using shorter timeframes of 1, 5, 6 and 10 years[27] and Segui et al. using 5, 10 years and lifetime[17].

Although a lifetime framework is considered the gold standard in economic evaluations, the relatively high age range at which breast cancer tends to be diagnosed, coupled with the fact that most recurrences in these patients take place within the first years after treatment and specially within the first 5 years [28, 29], may justify more limited time horizons of 10-20 years.

All 10 studies discounted costs and outcomes and gave details on the rates used, which reflected different national recommendations.

Five studies used a discount of 3% for both costs and outcomes[17, 24-27], and based their choice, in the case of the US and Japanese studies, on USA guidelines for cost effectiveness analysis. Similarly, Segui et al.[17] referred to Spanish guidelines to support their discounting rate.

The three studies undertaken by Retel in the Netherlands[21-23] used 4% for costs and 1,5% for outcomes as advised by the Health Care Insurance

Board (CVZ) in this country. The UK study by Ward et al.[18] used a rate of 3,5%, following the recommendations of NICE while the French study by Bonastre et al.[16] used 4% in accordance by the recommendations of the Haute Autorité de Santé (HAS).

4.3.3 Perspective

Four studies were performed from a third party payer perspective,[17, 21, 24, 26], while a further four presented their results from a healthcare system perspective.[18, 22, 23, 27], although one of them presented the perspective of their study as societal[27]. Only two study used a societal perspective[16Oestreicher N, 2005 #210] taking into consideration productivity costs (lost wages).

4.3.4 Population

The majority of the studies identified via our review modelled populations of women with early breast cancer with estrogen receptor positive (ER+) and lymph node negative (LN-) disease. However, one study[16] did not give any information on the number of LN involved for the modelled population, while a further study included in their modelling exercise LN+ patients (51%)[25]. Out of the studies that mentioned the HER2 status of the hypothetical patient population, most included only HER2- patients, with only one explicitly mentioning the inclusion of both HER2+/- patients[21], although the other two studies by the same author based their model and population on the same source and thus, must have included also a small proportion of HER2+ patients. The mean age of the population varied, but most used a mean age between 50 and 60.

4.3.5 Comparators

Although there was some variation in the comparators used to describe standard practice depending on the study, most used Adjuvant! Online (A!O),[16, 17, 21, 23, 24] either exclusively or as one of their comparators. These studies would be the most informative for our research purposes, since A!O was the comparator used in the MINDACT trial. [2] However, none of the studies reflected the MINDACT[2] approach, comparing A!O alone versus A!O+ MammaPrint®. Instead, studies focused on comparing A!O alone versus MammaPrint® alone.

For completeness of this review, studies using other comparators were also considered. These included the Nottingham Prognosis Index (NPI)[18] or international clinical guidelines such as St Gallen[21, 27] and the US National Institutes of Health (NIH) guidelines[25], or an approach where all patients received chemotherapy.[16]. The study by Ward et al.[18] referred to “clinical” practice as their main comparator, which combined the use of NPI, A!O and other prognostic information.

The three studies comparing MammaPrint® to other gene profiling tests, used in all cases Oncotype DX as the comparator[17, 22, 26].

4.3.6 Cost and outcome inputs

Different sources were consulted to derive costs. In addition to the published literature, hospital records, national administrative data and medical reimbursement fees/tariffs were also used. For the cost of tests, most studies mentioned direct communication with the manufacturers as their source[16-18, 21-24, 27] and in the case of MammaPrint®, most often quoted a public price of €2 675. The price for Oncotype mentioned in the three studies comparing MammaPrint® to this other GEP test, varied more, from a low of €3 200[17] to a high of US$4 075 (approximately €3 640)[22].

Costs of chemotherapy, appeared to differ greatly from one study to another, even when focusing only on European studies. These costs went from a low of €2825[17] to a high of €8597 in the Dutch studies by Retel[21-23]. However, it is important to note that aside from possible standard practice and price variations between countries, the description of “chemotherapy costs” was in most cases not detailed enough to assess the appropriateness of direct

comparisons between the included studies (see Table 16 in Appendix for a description of costs as reported in the individual studies as well as their sources).

Other frequently considered costs were those linked to AEs, although some studies grouped such costs under their chemotherapy costs[17, 24], others counted them separately. Differences existed in particular regarding long term severe AEs considered, with the three studies performed in the Netherlands by the same author[21-23] focusing on the costs of chronic congestive heart failure, and the UK study[18] focusing on acute myeloid leukemia. The authors of the later, justified their focus on acute myeloid leukemia by the higher costs linked to its management when compared to that of other AEs, even if less frequent. The remaining of the studies included in this review did not specify which AEs they focused on, but one of them[26] differentiated between the costs of minor, major and fatal AEs. These costs were derived from the published literature.

All studies considered the cost of recurrence, while in some cases, end of life costs were presented separately[18, 21-24, 26, 27].

Only two studies included absenteeism and transportation costs in their evaluation[16, 25]. In addition to such costs, Bonastre et al.[16] included also the cost of a hair wig.

Most studies focused purely on incremental costs and as a consequence they did not include for example the cost of oral endocrine therapy, which should not vary greatly from one study arm to another. From the European studies, only those authored by Retel et al. and Ward et al.[18, 21-23] included endocrine therapy in their analyses.

With regard to outcomes, all studies used for their models data from the published literature, and no study used data from the MINDACT RCT[2], due to the fact that publication of those results took place after the publication of the economic evaluations included in this review. The three most common sources used for clinical input linked to MammaPrint® were Buyse et al.[30] Bueno de Mesquita et al.[31] and Van de Vijver[32]. For the studies using Oncotype DX® as a comparator, different studies were used for risk classification and probabilities. (See Table 17 in Appendix for more details).

Quality of life (QoL) is an important factor to bear in mind when studying a condition such as breast cancer, in which QoL can be affected by the illness per se and its evolution, but also by other factors such as the potential adverse events (AEs) linked to chemotherapy. QoL values for all studies were derived from the literature, with Lidgren et al.,[33] being the most commonly reported source, despite the fact that it dates from 2007 and has a relatively small sample size (n=361). The study made use of both EQ-5D questionnaire and the TTO questions, although all evaluations using this study as a source, used the EQ-5D results. (See

Table 19 in Appendix for more detail on the reported utilities). It is important to note that utility inputs varied greatly between studies. As an example, the detrimental effect on patients' utilities of chemotherapy ranged from a high of -0,315 on the Dutch studies[21, 23] to a low of -0,038 on the study by Ward et al.[18]. This is a consequence of the need, due to limited data, to mix utilities from different small studies with different populations. Given that the main advantage of MammaPrint® is to reduce chemotherapy by saving it to those who would benefit the most, the detrimental effect on the utility of receiving chemotherapy is likely to have an important weight on QALY gains and ultimately, on the ICERs.

4.3.7 Modelling

All studies consisted of modelling exercises. Four of which used a similar structure consisting of three health states: free of recurrence, recurrence/distant recurrence and death.[17, 24-26]. Other studies added additional states such as local relapse or long-term adverse events, but overall, the structure remained simple.

None of the studies included a step-wise structure, reflecting the results from the MINDACT trial[2], by which treatment decisions based on standard risk classification approaches (A!O) were compared to a step wise approach in which first, standard risk classification approaches were used, and following that, testing was performed only in those found to be at "high clinical risk" of recurrence.

Instead, the economic evaluations published up to the date of this review, compared the alternative of testing all patients with MammaPrint® and basing treatment decisions on the test results, with that of using "standard" prognostic tools only.

4.3.8 Results

4.3.8.1 Incremental costs

Table 5 shows the mean costs reported in the 10 studies included in our review. Comparisons between studies are difficult primarily because of the different costs borne in mind, differences in cost definitions, in standard practice and in prices.

Four of the five studies specifically comparing MammaPrint® with AO! found that there was a mean incremental cost when using the former,[16, 17, 21, 24] which ranged from €1085[17] to €1759[16]. Only one study[23] found MammaPrint® to be less costly than A!O by a difference of €2401.[23]

The remaining comparisons with other risk assessment tools such as St Gallen or the NIH guidelines as well as the study by Ward et al.[18] using "standard practice" including a mix of approaches, showed different results with two showing MammaPrint® to be cost saving[21, 25] and the two others showing it to be cost additive[18, 27]. Only one study[16] compared MammaPrint® testing to offering chemotherapy for all patients and found MammaPrint® to be cost saving (-€216) in the ER+ population.

When looking at the comparisons made between MammaPrint® and other gene expression profiling tests, the three studies included in this review showed MammaPrint® to be cost saving compared to Oncotype. The potential savings ranged from €880[17] to US$6284, (approximately €5358)[26].

Table 5 – Costs of MammaPrint® (MP) in early breast cancer

Author	Costing yr	Time horizon	Test/Comparator	Population	Costs included	Cost source	Mean incremental cost**
Versus standard practice							
Bonastre* 2014 France	2012	10	MP/A!O MP/chemo for all	<61 yrs, tumour size<5cm, ER+; grade 2-3	Test, chemo, chemo administration, AEs, blood tests, distant recurrence and sick leave	Admin reimbursement tariffs and trial data	€1759 -€216
Chen 2010 USA	2007	Lifetime	MP/A!O	ER+, T1 or T2, LN-, HER2-	Test, chemo, recurrence, palliative care	Lit., vademecum and manufacturers	US$1332 (€1136)
Kondo 2012 Japan	NA	1-5, 6-10	MP/St Gallen	LN–, ER+, HER2-	Test, chemo, AEs, recurrence; palliative care	National medical care fee schedule	US$2571 (€2193)
Oestreicher 2005 USA, Netherlands	2003	Lifetime	MP/NIH guidelines	Pre-menop, TI-II, LN+51%, ER+77%	Test, chemo, recurrence	Lit.	-US$2882 (€2457)

Retel 2013 Netherlands	2005	20	MP/A!O	Grade II, ER+, LN-	Test, chemo, hormonal therapy, disease free survival, relapse, distant metastasis costs, death	Lit. (Lidgren et al. 2008)	-€2401
Retel 2010 Netherlands	2005	20	MP/St Gallen MP/A!O	LN-, ER+, HER2+/-	Test, chemo, hormonal therapy, trastuzumab, cost per health state, distant metastasis, death	Lidgren et al. 2008 and Dutch sources (Health Care Insurance Board 2006)	-€7430 €1130
Segui 2014 Spain	2013	5, 10 years and lifetime	MP/A!O	60-yr old women, LN-, ER+, HER2-	Test, chemo, AEs, diagnostic procedures and medical visits	Questionnaire and consensus sessions with a experts	€1085
Ward 2013 UK	2010	Lifetime	MP (all)/standard practice MP (NPI>3,4)/standard practice	ER+, LN-, HER2-	Test, chemo, hormonal therapy, AEs, distant recurrence, local recurrence, palliative care	BNF, experts and NHS reference costs	GBP3609 to GBP4119 (€4072 to €4648) GBP3997 to GBP5142 (€4510 to € 5,803)
Comparisons between tests							
Retel 2012 Netherlands	2010	20	MP/OT	ER+, LN-	Test, other direct costs	Lidgren et al. 2008 + Dutch sources (Health Care Insurance Board 2006)	-€1475 to -€3941
Segui 2014 Spain	2013	5, 10 years and lifetime	MP/OT	60-yr old women, LN-, ER+, HER2-	Test, chemo, AEs, diagnostic procedures and medical visits	Questionnaire and consensus sessions with a experts	-€880
Yang 2012 USA	2009	10	MP/OT	ER+, LN-	Tests, chemo, AEs, recurrence, palliative care	Lit.	-US$6284 (€5,359)

AEs: Adverse events, A!O: Adjuvant Online!, BNF: British National Formulary, ER: Estrogen receptor, HER2: Human Epidermal growth factor Receptor 2, *LN: Lymph node, MP: MammaPrint®, NPI: Nottingham Prognosis Index, OT: OncotypeDx*
** Results for the ER+ subgroup*
***If more than one time horizon was explored in the study, the lifetime horizon was presented in the table.*
Exchange rates: 1 USD = 0.852823 EUR; 1 GBP = 1.12816 EUR

4.3.8.2 Incremental outcomes

Table 6 shows the outcomes reported in the studies included in this review. From the five studies that compared MammaPrint® with A!O, four measured life years gained (LYG) and consistently reported incremental gains from 0.01[16] to a high of 0.86 LYG[17]. These results appear to be in contrast with the small (statistically non-significant) decreases in the DMFS point estimates found in the MINDACT trial[2] and thus, appear to be too optimistic.

All five evaluations estimated QALYs and once more, all showed gains with MammaPrint® versus A!O. These ranged from 0.02 QALYs[16] to 0.75 QALYs[17]. From the three studies comparing MammaPrint® with other tools such as St Gallen, the NIH guidelines or "standard practice", defined as a mix of approaches, only the oldest study, published in 2005, found a decrease in QALYs. Although this study quoted a loss of 0.22 QALYs when using MammaPrint® compared to NIH guidelines, it is important to highlight that the target population was slightly different (and more at risk of recurrence) than the population used in the other evaluations. Thus, the focus was on a premenopausal, mixed population (LN+51%; ER+77%). The difference found in this population appeared to be due to the lower sensitivity assumed for MammaPrint® to predict risk of recurrence (84%). The authors concluded that a sensitivity of 95% would be needed for MammaPrint® to offer more QALYs than NIH guidelines.

The only study which compared MammaPrint® with chemotherapy for all[16], found a loss of -0.02LYG for MammaPrint® in the ER+ population analysis. However, when QALYs were measured and given the loss of utility linked to chemotherapy, there was an incremental gain of 0.04 QALYs for the MammaPrint® option versus chemotherapy for all in that same ER+ population.

With regard to the comparisons between tests, all three evaluations included in this review reported QALY gains with MammaPrint® versus Oncotype DX®, ranging from 0.14 to 0.40 LYG and from 0.08 to 0.31 QALYs (see Table 6 for more information).

4.3.8.3 Incremental cost-effectiveness ratios (ICERs)

Table 7 gives an overview of the ICERs reported in the evaluations included in this review. The results of the comparisons MammaPrint® versus A!O appear to favour MammaPrint®, with the only exception being a French study by Bonastre et al.[16] which gives an ICER of €87 950/QALY. This appears to be due to the practically equivalent QALYs obtained in the different arms of this French economic evaluation, while the MammaPrint® option appeared to be significantly more costly than the A!O alternative. The remaining studies focusing on that same comparison give relatively low ICERs ranging from €1 557/QALY[17] to US$5 908/QALY (approximately €5 037/QALY)[24], while one study found MammaPrint® to dominate (both more effective and cheaper than A!O)[23].

The remaining studies comparing MammaPrint® with other prognostic tools showed inconsistent results, with one study giving ICERs for MammaPrint® versus St Gallen of US$43 044/QALYs (approximately €36 696/QALY) and a further one concluding that MammaPrint® dominates when compared to the same St Gallen rules. One older study reported the GEP test to be less efficacious but cheaper than standard practice (NIHCC) in a mixed (LN- and LN+) pre-menopausal women.[25]

The study by Ward et al.[18] which compared MammaPrint® with standard practice (a mixed approach including A!O), displayed higher ICERs which varied depending on the testing strategy (testing all with MammaPrint® versus testing only those NPI>3,4) and the clinical inputs used (see Table 7 for more details). Their findings appear particularly uncertain for MammaPrint®, compared with the other evaluations here included.

The only study comparing MammaPrint® with chemotherapy for all patients showed MammaPrint® to dominate.[16]

The three studies comparing MammaPrint® with Oncotype DX showed MammaPrint® to dominate.[17, 22, 26].

Table 6 – Outcomes of MammaPrint® (MP) in early breast cancer

Author	Test/Comparator	Population	Outcomes	Incremental LYG**	Incremental QALYS**
Versus Standard Practice					
Bonastre 2014* France	MP/A!O	<61 yrs, tumour size<5cm, ER+; grade 2-3	LYG & QALYs	0.01	0.02
	MP/Chemo for all			-0.02	0.04
Chen 2010 USA	MP/A!O	ER+/-, T1 or T2, LN-, HER2-	LYG & QALYs	0.143	0.153
Kondo 2012 Japan	MP/St Gallen	LN–, ER+, HER2-	LYG & QALYs	0.05	0.06
Oestreicher 2005 USA, Netherlands	MP/NIH guidelines	Pre-menop, TI-II, LN+51%, ER+77%	QALYs	NA	-0.22
Retel 2013 Netherlands	MP/A!O	Grade II, ER+, LN-	QALYs	NA	0.61
Retel 2010 Netherlands	MP/St Gallen	LN-, ER+, HER2+/-	LYG & QALYs	-0.26	1.2
	MP/A!O			0.2	0.24
Segui 2014 Spain	MP/A!O	60-yr old women, LN-, ER+, HER2-	LYG & QALYs	0.863	0.745
Ward 2013 UK	MP (all)/Standard practice MP (NPI>3,4)/Standard practice	ER+, LN-, HER2-	QALYs	NA NA	0.29-0.08 0.66-0.18
Comparisons between tests					
Retel 2012 Netherlands	MP/OT	ER+, LN-	LYG & QALYs	0.14-0.40 depending on clinical source	0.08-0.31 depending on clinical source
Segui 2014 Spain	MP/OT	60-yr old women, LN-, ER+, HER2-	LYG & QALYs	0.265	0.226
Yang 2012 USA	MP/OT	ER+, LN-	QALYs	NA	0.097

A!O: Adjuvant! Online, ER: Estrogen receptor, HER2: Human Epidermal growth factor Receptor 2, *LN: Lymph node, LYG: life years gained, MP: MammaPrint®, NPI: Nottingham Prognosis Index, OT: Oncotype Dx, QALYs: Quality Adjusted Life Years*

**Results for the ER+ subgroup*

***If more than one time horizon was explored in the study, the lifetime horizon was presented in the table.*

Table 7 – ICERs for MammaPrint® in early breast cancer

Author	Test/Comparator	Population	ICER**	Prob. Of test being cost-effective
Versus standard practice				
Bonastre 2014* France	MP/A!O	<61 yrs, tumour size<5cm, ER+; grade 2-3	€87950/QALY	20% at WTP €50000
	MP/Chemo for all		Dominant	NA
Chen 2010 USA	MP/A!O	ER+, T1 or T2, LN-, HER2-	US$5908 (€5040)/QALY	NA
Kondo 2012 Japan	MP/St Gallen	LN–, ER+, HER2-	US$43 044 (€36 716)/QALY	NA
Oestreicher 2005 USA, Netherlands	MP/NIH guidelines	Pre-menop, TI-II, LN+51%, ER+77%	MP cheaper but less effective	95% for MP to be cheaper but less effective
Retel 2013 Netherlands	MP/A!O	Grade II, ER+, LN-	MP dominates	97% for MP to dominate
Retel 2010 Netherlands	MP/St Gallen	LN-, ER+, HER2+/-	MP dominates	NA
	MP/A!O		€4614/QALY	NA
Segui 2014 Spain	MP/A!O	60-yr old women, LN-, ER+, HER2-	€1257/LY €1457/QALY	Above 95% at WTP €4000
Ward 2013 UK	MP (all)/standard practice	ER+, LN-, HER2-	GBP12 240-GBP53 058 (€13 821-€59 902)/QALY	NA
	MP (NPI>3,4)/standard practice		GBP6 053-GBP29 569 (€6 834-€ 33 369)/QALY	NA
Comparisons between tests				
Retel 2012 Netherlands	MP/OT	ER+, LN-	MP dominates	NA
Segui 2014 Spain	MP/OT	60-yr old women, LN-, ER+, HER2-	MP dominates	NA
Yang 2012 USA	MP/OT	ER+, LN-	MP dominates	82% for MP to dominate

A!O: Adjuvant! Online, ER: Estrogen receptor, HER2: Human Epidermal growth factor Receptor 2, *LN: Lymph node, LYG: life years gained, MP: MammaPrint®, NPI: Nottingham Prognosis Index, OT: Oncotype Dx, QALYs: Quality Adjusted Life Years, WTP: willingness to pay*
**Results for the ER+ subgroup*
Exchange rates: 1 USD = 0.852823 EUR; 1 GBP = 1.12816 EUR

4.3.9 Sensitivity analysis

Uncertainty is intrinsic to any economic evaluations and should therefore always be accounted for. All evaluations performed some kind of sensitivity analysis to assess the robustness of their results, although two of them limited their tests to one-way sensitivity analyses,[24, 27] and a further presented results univariate and multivariate sensitivity analysis[18]. Finally, a recent French study engaged in a probabilistic sensitivity analysis[16] but did not pursue one or two-way sensitivity analysis.

The remaining studies undertook both one way and probabilistic sensitivity analyses and overall, important uncertainties were found when it came to comparisons between MammaPrint® and other prognostic tools. Results appeared to be primarily sensitive to long-term recurrence and survival rates,[18, 24, 27] the distribution of risk scores, thresholds and chemotherapy decisions,[18, 24, 25] costs of chemotherapy[17, 24, 25, 27] and test costs.[16, 24, 25, 27].

Two of the evaluations comparing MammaPrint® to Oncotype concluded that their results were robust[17, 26], while the third one found uncertain results that varied depending on the compliance levels for discordant test results.[22]

4.3.10 Conflict of interest

All 10 studies but one[26] included in their manuscripts a declaration of conflict of interest for their authors. Of the remaining nine, only two[16, 27] reported no conflict of interest. The existence of conflicts of interest may introduce a bias which could affect the validity of the study results, although there is, up to date, no hard evidence on this.

4.4 Discussion and conclusions

Despite relatively consistent results found in the published literature evaluations up to date, in favour of MammaPrint® when compared to A!O there are a number of important points worthwhile considering.

Sources of clinical data

The main limitation of the economic evaluations reviewed relates to the fact that all of them were published before the data from the MINDACT study[2] became available. The full results from the first prospective RCT on the utility of gene expression profiling testing (i.e MammaPrint®), saw the light in August 2016, while the most recent economic evaluations here reviewed date from 2014. Therefore, all economic evaluations had to combine and model multiple sources of data derived mostly from retrospective (with small sample sizes) studies. Such a combination increases the uncertainty surrounding model assumptions, since important factors which could play a role in the final results are not kept constant from one study to another (e.g. population characteristics, tumour characteristics, prognostic tool used, etc). For MammaPrint®, most of the models used data from Buyse et al.,[30] Bueno de Mesquita et al.[31] and Van de Vijver[32]. The most recent of these[31], refers to the RASTER, the first prospective study evaluating MammaPrint® on similar outcomes to the ones studied in the MINDACT study over a 5 year follow-up period.

The RASTER study

The microarRAy-prognoSTics-in-breast-cancER (RASTER) study(Drukker 2013) was the first prospective study evaluating the performance of the MammaPrint®, in 427 patients, aged 18-60, with a histologically confirmed operable, invasive adenocarcinoma of the breast (cT1-3N0M0).

Adjuvant systemic treatment decisions were based on the Dutch CBO 2004 guidelines, the 70-gene signature and doctors' and patients' preferences. 5-year DMFS probabilities were compared between subgroups based on MammaPrint® and Adjuvant! Online (A!O).

The 5-year DMFS for the genomic low-risk (n = 219) and genomic high-risk (n = 208) groups were 97.0% and 91.7% respectively. The 5-year DMFS probabilities for A!O low-risk (n = 132) and high-risk (n = 295) groups were 96.7% and 93.4%.

For clinical high-risk/genomic low-risk patients (n = 124), of whom a majority (76%) did not receive adjuvant chemo, 5-year DMFS was 98.4%. Focusing purely on the proportion of that clinical high/genomic low-risk population who did not receive adjuvant chemotherapy, the 5-year DMFS was slightly higher (98.9%, 95%CI 96.9-100). This last rate appears to be higher than those found in the MINDACT study[2] for the same patient group (94.0% in the PPS analysis and 94.4%; in the ITT analysis).

The authors also reported a potential reduction in the proportion of patients receiving chemotherapy on the clinical high risk group, if MammaPrint® was used to guide adjuvant treatment decisions, of 32% (versus a reduction of 46% in the MINDACT trial[2]).

In September 2017 the 10-year data from the RASTER was presented in the form of a poster at the ESMO congress[34]. Although no full article is currently available and thus, the publicly available data remains limited, the results appear to show a 10 year DMFS for the genomic low risk (according to MammaPrint) of 93.7%

The difference in the populations, with the RASTER study focusing on patients under 60 in the Netherlands, compared to a more international European patient population aged below 71 in the MINDACT[2], could be responsible for the differences in DMFS.

In addition, the RASTER study is not a randomised trial which limits the possibility to draw conclusions on the clinical benefit of the Mammaprint® test.

For Oncotype, there was more variation in the sources used (see Table 18 in Appendix for more information).

Model structure

Furthermore, the model structure chosen in all cases was also different to the one that could have been informed after the publication of the MINDACT RCT[2]. As already mentioned, the evaluations here included, primarily compared the use of MammaPrint® to other prognostic tool (eg A!O) for treatment decision-making in the whole of the target population.

However, the conclusions of the MINDACT study[2] showed that the use of MammaPrint® to possibly signal the need for chemotherapy in patients at low clinical risk according to A!O does not result in any advantage, since those patients do not appear to derive a benefit from the use of adjuvant chemotherapy and thus, the test should be kept for those patients at “high clinical risk” of recurrence according to A!O, supporting a more targeted approach.

As a consequence, the most appropriate comparison would require a model structure that compares the strategy of using just A!O to a further arm in which patients are first assessed by means of A!O and only those shown to be at high “clinical” risk of recurrence would be tested with MammaPrint®. This would allow to limit the use of this expensive tests to those patients more likely to benefit from it. Such design would also be more appropriate for the Belgian context.

Modelling/assumptions

Most of the studies included important assumptions not well backed-up with literature. In particular, most models assumed that all patients categorised as having a “high clinical risk” of recurrence (according to the comparator) would be treated with chemotherapy, while none of the “low clinical risk” patients would receive such treatment. The extent to which this represents a relevant clinical approach that could be applied in practice in these early breast cancer patients, remains unclear, since there are aspects like age, comorbidities, frailty or patients preferences that were often not studied and that could play an important role in the choice to give chemotherapy or not.

It is important to note that a similar assumption would nevertheless, be derived from any models using the results from the MINDACT study[2] due to its design. In the comparative arm where no MammaPrint® is used, all patients at high-clinical risk according to the modified A!O, would receive chemotherapy.

The price of the test as well as the size of the target population are two crucial factors likely to have an important influence on the overall economic impact of the test.

Transferability of results to the Belgian situation

Despite the weaknesses and limitations linked to the available evidence on the effectiveness of MammaPrint® already explained in the clinical chapter, the authors of this review considered an analysis of Belgian practice/data necessary to better understand the transferability of the MINDACT[2] results to the Belgian context. In turn, this should facilitate an adaptation of any decisions adopted regarding these tests, once the 10 year OS and the AEs data from the MINDACT study are published.

Conclusions

- **All economic models published up to date presented a crucial limitation: no economic evaluation was yet based on the MINDACT RCT data and thus, all studies relied on inputs from different sources, mostly retrospective analyses, modelled together resulting in important uncertainties.**
- **No economic evaluations up to date used the relevant comparison: MammaPrint® in addition to Adjuvant!Online versus Adjuvant! Online alone.**
- **The increments seen in LYG when using MammaPrint® in these studies do not reflect the small (non significant) decreases in the DMFS point estimates found in the MINDACT trial. Nevertheless, some gains in QALYs by avoiding chemotherapy, specially in the short term are possible.**
- **Sources for one of the most important factors in the evaluations (QoL) were relatively old and were derived in all cases from studies with small sample sizes.**
- **Although the awaited 10-year results from the MINDACT study should offer more robust data on overall survival and AEs, they will not fill in the current evidence gaps regarding QoL.**

5 THE BELGIAN CONTEXT

The aim of this exercise was to analyse the Belgian situation by:

- firstly, estimating the overall target population for the MammaPrint® test based on the size of the "early breast cancer" population in Belgium;
- secondly, classifying early breast cancer patients (based on the available data on tumour characteristics) according to their clinical risk of recurrence by means of the same tool applied during the MINDACT trial (i.e. modified A!O) as presented in the supplement of the NEJM publication.[2]
- finally, analysing data on their treatment, and more specifically on whether they received chemotherapy or not, in order to map out the situation in this country.

5.1 Database description

The Belgian Cancer Registry (BCR) is a national population based cancer registry, collecting data on a national level since 2004. Cancer registration in Belgium has a firm legal basis. In 2003 the Royal Decree on the oncological care programs[k] describing the reimbursement of the multidisciplinary oncological consult (MOC) was enacted. Later on, in 2006, the specific law on the Cancer Registry[l] was created, making cancer registration compulsory for the oncological care programs and for the laboratories for pathological anatomy. Collected information covers a broad range of patient and tumor characteristics, such as incidence date, age, sex, topography, morphology and stage. Furthermore, the law authorizes the use of the national Social Security Identification Number (NISS/INSZ) as the unique identifier of the patient. Through linkage with the Crossroads Bank for Social Security, the NISS/INSZ enables the Registry to perform active follow-up on vital status and date of death of the patients.

Since 2009, the BCR is authorized to link data from the BCR database with data on cancer-related diagnostic and therapeutic procedures and pharmaceuticals, which are obtained from all seven Belgian sickness funds via the Intermutualistic Agency (IMA–AIM). Via this linkage procedure, the Belgian Cancer Registry receives for each registered patient, health insurance data starting from January 1st of the year preceding the incidence year, until December 31st of the fifth year after the incidence year.

Information about the incidence date came from the BCR database and data about surgery and chemotherapy were found in the IMA data.

5.2 Patients' selection

Patients for the analyses were firstly selected according to the following criteria:

- Incidence date 2014
- Diagnosis of invasive breast cancer
- Country of residence at incidence date: Belgium
- Only women
- Only the first invasive breast tumor recorded at the Belgian Cancer Registry
- Surgery between one month before and 9 months after incidence date

[k] Koninklijk Besluit houdende vaststelling van de normen waaraan het zorgprogramma voor oncologische basiszorg en het zorgprogramma voor oncologie moeten voldoen om te worden erkend. Belgisch Staatsblad 21 maart 2003. / Arrêté Royal fixant les normes auxquelles le programme de soins de base en oncologie et le programme de soin d'oncologie doivent répondre pour être agréés. Moniteur Belge, 21 mars 2003.

[l] Wet houdende diverse bepalingen betreffende gezondheid van 13 december 2006, artikel 39. Belgisch Staatsblad. 22 december 2006. / Loi portant dispositions diverses en matière de santé du 13 décembre 2006, article 39. Moniteur Belge, 22 décembre 2006.

- Pathological size and extent of the primary tumor stage : pT1 or pT2
- Coupling with IMA data should be possible

In addition to the above, a sample of patients was created by selecting only patients with a verified ER and HER2 status (as declared by a subset of hospitals or derived from the pathology reports) in order to perform the economic analyses.

Despite the fact that the MINDACT RCT[2] included some ER- and HER2+ patients (ER- 11,6%; HER2+ 9,5%), the experts consulted during this project believed that the indication for chemotherapy in these patients is often clearer and thus, the test was thought to be of less interest in these populations. Therefore, a limitation of our sample to ER+, HER2- patients was thought to be appropriate.

Table 8 illustrates the modified Adjuvant! Online as shown in the supplement of the MINDACT trial publication.[2] The highlighted area (ER+, HER2-) illustrates the part of the Table that we aimed to populate with Belgian data to offer a map of the Belgian situation and the size of the potential target for MammaPrint® use.

Table 8 – Clinical risk assessment according to modified Adjuvant!Online[m]

ER status	HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
ER positive	HER2 negative	well differentiated	N-	≤ 3 cm	C-low
				3.1-5 cm	C-high
			1-3 positive nodes	≤ 2 cm	C-low
				2.1-5 cm	C-high
		moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	Well differentiated OR moderately differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated OR undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
ER negative	HER2 negative	Well Differentiated	N-	≤ 2 cm	C-low
				2.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		Moderately differentiated OR poorly differentiated OR undifferentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
	HER2 positive	Well differentiated OR moderately differentiated	N-	≤ 1 cm	C-low
				1.1-5 cm	C-high
			1-3 positive nodes	Any size	C-high
		poorly differentiated or undifferentiated	Any	Any size	C-high

[m] Table S 13 from the supplement of the MINDACT trial NEJM publication

A limitation of BCR database is that the ER and HER2 status are not available as a variable but are included in the pathology reports as a free-text field. For a subset of hospitals, ER-status and HER2 status is based on the data delivered electronically by the hospital itself. For a subset of hospitals, ER and HER2 status are based on data delivered by the hospital itself. For other hospitals, the ER and HER2 status were retrieved for some of the patients manually from the pathology reports by the BCR datamanagers. As the ER and HER2 status were crucial information for the identification of the target population for MammaPrint®, the authors of this report decided to work with only a sample, but in order to have accurate results, the sample should be a representative sample of the full set of patients on some specific characteristics: age, c-Stage, p-Stage, pN and pT categories, WHO performance status, differentiation grade and type of adjuvant chemotherapy as well as on center size (regarding the number of patients treated for early breast cancer by a surgical intervention).

For the HER2 status, in situ hybridization results were prioritized over information based on HER2-immunohistochemistry.

5.3 Variables description and limitations

5.3.1 Variables description and methodology

The following section describes the methodology used as well as any encountered limitations.

All data regarding the tumour or patient characteristics were taken from the database of the cancer registry, while data on chemotherapy use were extracted from the IMA data. Therefore, to gather all relevant information for our analysis, coupling of both data sets was required.

Tumour grade is the description of a tumour based on how abnormal the tumor cells and the tumour tissue look under a microscope. It is an indicator of how quickly a tumour is likely to grow and spread. Tumour can be well differentiated, moderately differentiated or poorly differentiated/undifferentiated. Information on grade was available from the BCR database.The International Union Against Cancer (UUICC) reports that the classification of cancer by anatomic disease extent, i.e. stage, is the major determinant of appropriate treatment and prognosis. Stage is an increasingly important component of cancer surveillance and cancer control and an endpoint for the evaluation of the population-based screening and early detection efforts[n]. The clinical and pathological stage were defined according to the TNM classification, 7th Edition.

- **Clinical Staging (c-Stage)** determines how much cancer there is based on the physical examination, imaging tests, and biopsies of affected areas.
- **Pathologic Staging (p-Stage)** can only be determined from individual patients who have had surgery to remove a tumor or explore the extent of the cancer. Pathologic staging combines the results of both the clinical staging (physical exam, imaging test) with surgical results.

Given that the Belgian Cancer Registry did not have data on the specific **number of nodes** needed in the Modified Adjuvant!Online tool, this was replaced by an overview of the pN-category as follows:

[n] https://www.uicc.org/resources/tnm

pN category	Nodal status
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis identified histologically
pN	Micrometastases or metastases in one to three axillary lymph nodes
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1 to 3 axillary lymph nodes, at least one metastasis greater than 2.0mm)
pN1b	Metastases in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph nodes biopsy but not clinically detected.
pN1c	Metastases in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph nodes biopsy but not clinically detected.
pN2	Metastases in four to nine axillary lymph nods or in clinically detected internal mammary lymph nodes.
pN2a	Metastases in 4 to 9 axillary lymph nodes (at least one tumour deposit greater than 2.0mm).
pN2b	Metastases in clinically detected internal mammary lymph nodes in absence of axillary lymph node metastasis.

pN2a patients were practically excluded from the MINDACT study[2] (0,1%) and thus, clear conclusions could not be drawn for this subgroup. Furthermore, the experts considered that these are patients in which the chemotherapy indication is clearer and thus, of limited interest for our analysis. Therefore, the description of the Belgian context took into consideration only pN0-/pN1 (no lymph nodes involved, or 1-3 lymph nodes involved.

Tumour size used in needed in the Modified Adjuvant!Online tool was not directly available in the BCR data but was derived by means of pT-category data.

pT category	Tumor size
pT0	No evidence of primary tumor
pT1	Tumor ≤20 mm in greatest dimension
pT1mi	Tumor ≤1 mm in greatest dimension
pT1a	Tumor >1 mm but ≤5 mm in greatest dimension
pT1b	Tumor >5 mm but ≤10 mm in greatest dimension
pT1c	Tumor >10 mm but ≤20 mm in greatest dimension
pT2	Tumor >20 mm but ≤50 mm in greatest dimension
pT3	Tumor >50 mm in greatest dimension
pT4	Tumor of any dimension with direct extension to chest wall and/or to the skin

The **WHO score** or performance status is a measure of the quality of life / the patient's condition at time of diagnosis. Valid values range from 0 (asymptomatic) to 4 (bedbound) with increasing gravity of the patient's performance.

After experts' consultation, the population under study was restricted to pT1 and pT2 patients.

On the basis of the above-mentioned data, the clinical risk according to the modified A!O was estimated for the Belgian MammaPrint® target population.

Regarding chemotherapy use, only adjuvant chemotherapy in the 9 months following surgery was taken into account. Surgery was defined as either breast conserving surgery or mastectomy, from one month before incidence date until 9 months after incidence date.

The nomenclature codes used for Breast conserving surgery and mastectomy are presented in an Appendix (

Table 20 and Table 21 respectively).

The region and number of the centers is based on the center of primary surgery. The number of patients per centers referred to the total number of patients in the center with an early breast cancer who had a surgery.

5.4 Results

5.4.1 Characteristics and representativity of the sample

The analysis was aimed to be performed on the full set of patients selected according to the previously mentioned criteria. However, as explained in the limitations, we used a sample of the full set of patients for whom ER and HER2 status was available. The representativity between the full and the sample set was assessed through a statistical test (chi-square test) but due to the sample size (5 758 patients), this test was overpowered and therefore differences between expected percentage and calculated percentage of more than 1% were considered statistically significant at the 5% significance level, i.e. would always reject the hypothesis of representativity of the sample for all variables except for age). This is the pitfall of the statistical significance versus clinical significance. As shown in Appendix (Table 22), differences in the distribution of the different variables between the full set and the sample of patients was less than 1% in the majority of the cases with a maximum of 4.6% in one category (for pstage III). We therefore conclude that the sample was “clinically” representative enough to be used for our analysis of the Belgian situation. There is, in median (Q1 – Q3), 74 patients (29 – 94) per center (see Appendix Table 23). Around 25% of the hospitals have less than 30 patients with early breast cancer and inclusion criteria who were surgically treated (see selection criteria) and 25% of the hospitals treat more than 100 of those patients a year. The proportion were similar in the sample.

5.4.2 Characteristics of the subset of patients for the Belgian context

As explained in 5.2, we aimed to describe the size of the potential target population for the MammaPrint® based on the modified A!O Tool (Table 8) which is used in the MINDACT trial publication. [2] The selection of patients was therefore done on patients with the following characteristics:

- ER positive
- HER2 negative
- Non-missing differentiation grade
- pN0 or pN1 (up to 3 nodes)

The characteristics of this subset of patients with ER positive and HER2 negative status were similar in the sample and the overall population (see Table 9). In this subset of patients with positive ER status and negative HER2 status, 19.6% underwent adjuvant chemotherapy. The difference with the overall population, where the percentage of adjuvant chemotherapy was of higher (see Table 22) is due to the selection of less severe cases (pN0 or pN1) in our analyses.

Table 9 – Characteristics of patients included in the Belgian analyses – patients with ER+, HER2-, pN0 or pN1 and non-missing differentiation grade

Characteristics	Descriptive statistics	Subset population
Number of patients		**N = 3 303**
Age	mean (sd)	61.5 (12.2)
	Q1-Q3	52 – 70
	min –max	26 – 95
Age category	Less than 35 years	28 (0.8%)
	35 to 50 years	558 (16.9%)
	50 to 70 years	1 835 (55.6%)
	70 years or older	882 (26.7%)
(c)Stage	0	19 (0.6%)
	I	1 773 (53.7%)
	II	897 (27.2%)
	III	44 (1.3%)
	IV	9 (0.3%)
	Unknown	561 (17.0%)
(p)Stage	I	1 997 (60.5%)
	II	1 305 (39.5%)
	III	0 (0.0%)
	IV	1 (0.0%)
	Unknown	0 (0.0%)
pN-category	0	2 527 (76.5%)
	1	776 (23.5%)
pT-category	1	20 (0.6%)
	1mi	9 (0.3%)
	1a	115 (3.5%)
	1b	632 (19.1%)
	1c	1 512 (45.8%)
	2	1 015 (30.7%)
WHO PFS	0 – Asymptomatic	2 032 (61.5%)
	1 – Symptomatic but completely ambulatory	1 049 (31.8%)
	2 – Symptomatic. <50% in bed during the day	12 (0.4%)
	3 – Symptomatic. >50% in bed. but not bedbound	2 (0.1%)
	4 – Bedbound	1 (0.0%)
	Missing	207 (6.3%)
Differentiation grade	1 – Well-differentiated	746 (22.6%)
	2 – Moderately differentiated	1 793 (54.3%)
	3 – Poorly differentiated	764 (23.1%)
Adjuvant Chemotherapy	Yes	648 (19.6%)
	No	2 655 (80.4%)
Type of adjuvant chemo	Cyclophosphamide + epirubicin + paclitaxel	277 (42.7%)
	Cyclophosphamide + epirubicin + docetaxel + fluorouracil	130 (20.1%)
	Cyclophosphamide + docetaxel	56 (8.6%)
	Cyclophosphamide + epirubicin + docetaxel	35 (5.4%)
	Paclitaxel	17 (2.6%)
	Cyclophosphamide + epirubicin + paclitaxel + fluorouracil	30 (4.6%)
	Cyclophosphamide + paclitaxel + doxorubicin	30 (4.6%)

	Cyclophosphamide + epirubicin	21 (3.2%)
	Cyclophosphamide + epirubicin + fluorouracil	15 (2.3%)
	Cyclophosphamide + docetaxel + doxorubicin	0 (0.0%)
	Other	37 (5.7%)
Number of centers		98
Number of patients per center*	mean	75.31
	Q1-Q3	33 – 94
	min –max	3 – 377
Number of centers in Belgium*	<100 patients	74 (75.5%)
	100-149 patients	12 (12.2%)
	150+ patients	12 (12.2%)

*Source: Belgian Cancer Registry – 2014; *based on the total number of patients with breast cancer undergoing surgery (and not only based on the sample).*

5.4.3 Target population and projection

The purpose of this part was to estimate the potential target population for Mammaprint® based on a clinical risk estimation – modified A!O

Some transformations of the variables were performed (see section on variable description and methodology) in order to have the tumor size (based on the pT-stage) and the nodal status (pN-stage). Those transformations do not match exactly the definition of the Clinical Risk in MINDACT[2] for 2 special cases:

- Well differentiated, no nodes with tumor size 3.1-5cm (91 cases with pT2 (i.e. tumor size 2-5cm) were attributed to this category);
- Poorly differentiated, no nodes with tumor size 1.1-5 cm (4 cases with pT1 (i.e. tumor size <2cm) were attributed to this category).

In those case, the conservative approach was taken and it was decided to put those few cases under C-high risk. A check was performed placing these patients under C-low risk, but the overall picture did not differ much from the base case assumption.

The analysis on the available sample of 3303 patients for the target population (ER+, LN(0-3), HER2-) in Belgium for the year 2014 is displayed on Table 10

From these, approximately 20% received adjuvant chemotherapy. Looking at clinical risk levels (according to the modified A!O), it is clear that patients classified as having a “clinical high-risk”, have a higher probability of receiving chemotherapy, while few of those at “clinical low-risk” of recurrence, received chemotherapy (35% for high versus 5% for low clinical risk patients).

Table 11 extrapolates the results seen in the sample analysis to the overall Belgian target population, estimated to be of 6367 patients overall in 2014. An extrapolation factor of 0.85 was applied, based on the MINDACT study [2]. Thus, ER positive, HER2 negative patients were estimated to account for 85% of the early stage breast cancer population.

Thus, following the findings from MINDACT[2], if the MammaPrint® test was used in the Belgian population described in the Belgian Cancer Registry data of 2014, 3069 patients overall would represent its target population (i.e. those at a high-clinical risk). From those, according to the MINDACT study, 46% (≈1412), could be reclassified as "genomic low-risk" by means of the MammaPrint® test and could therefore, avoid chemotherapy, while the remaining 1657 patients would have the most benefit from chemotherapy.

However, when comparing these results with the Belgian IMA data on the proportion of chemotherapy use, we see that: while in MINDACT all high clinical risk patients were offered chemotherapy, only 35% of those classified as "clinical high-risk" by the same prognostic tool in Belgium did, in fact, receive such therapy.

While this raises some questions regarding the applicability/generalisability of the MINDACT results to the Belgian situation, the lack of clear standardised approaches or tools to estimate the risk of recurrence in Belgium for these patients made it impossible to further investigate these differences in detail.

Nevertheless, some reflections are listed below:

1. Could the inclusion in our sample of patients older than 70 (age limit in the MINDACT study[2]), to better reflect the reality on the ground, have significantly influenced the results of our analysis, given their weight on the BCR database (i.e. 26.7%).

   A check was done excluding from the sample patients aged 71 or older. Although the proportion of chemotherapy use rose to 23.8% overall (i.e. 46.9% in clinical high-risk patients and 5.6% in clinical low-risk patients), the age limit in isolation did not appear to be a crucial factor that could explain the relatively low proportion of chemotherapy used in the clinical high-risk (according to A!O) early breast cancer Belgian population, although it is clearly a factor with some weight in adjuvant treatment decisions.

2. Did the characteristics of the population studied in the MINDACT trial[2] (aside from the age limits) differ greatly from those of the BCR registry population? If so, could certain of these differences explain a relatively low rate of chemotherapy treatment in the Belgian BCR population?

   A comparison of both populations (using the sample of BCR patients aged below 71 years), showed that the characteristics of the two populations are somewhat different:

   - There were more patients in the age category of 50 to 70 years in the BCR sample than in the MINDACT population (+7.8%);
   - There were more patients with smaller tumour size (<1 mm) in the BCR evaluation than in the MINDACT population (+13.2%);
   - There were more patients with grade 3 (poorly differentiated) in the MINDACT population compared to the BCR sample (+6.4%);
   - There were more patients LN- in MINDACT, compared to the BCR sample population (but difference of +2% only);
   - The majority (96.1%) of patients in the MINDACT population had a good performance status (WHO score = 0) compared to 61.5% in the BCR sample population.

The differences were statistically significant (see Table 24 in appendix) but one should remain cautious when interpreting such differences due to the large sample sizes compared, given that with large samples, even small differences might be statistically significant, but still not clinically meaningful.

Apriori, no obvious explanation for the lower chemotherapy rates for clinical high-risk patients in Belgium could be derived from this analysis, but some influence of certain patient characteristics cannot be excluded.

Overall, the proportion of clinical high-risk patients, according to the modified A!O, found in the MINDACT and the BCR populations were similar (50% in the MINDACT versus 48% in the BCR sample).

3. Would most of the “clinical high-risk” patients re-classified as “genomic low-risk” by MammaPrint® in the MINDACT study already coincide with the 65% (53% in those aged 70 or younger) “clinical high-risk” patient population currently not receiving chemotherapy in our country?

   And if so, how have these patients been identified? Is MammaPrint® or other GEP tests already used in the field, even if not reimbursed? What other clinical tools/approaches are currently utilised in Belgian hospitals and what additional factors do these tools (or specialists on the field) consider in addition to the ones already included in the modified A!O tool?

   Although the use of such tests in the absence of reimbursement is likely to remain very limited, some influence could be a reality. Nevertheless, an analysis of chemotherapy use per centre size (used as an approximation to larger university hospitals more likely to use prognostic tests versus smaller hospitals) did not show any differences that could point in this direction.

4. What is the weight of patient preferences on the final decisions and at what point these place an important role?

5. An analysis of MOC forms showed that the proportion of chemotherapy recommended in those forms is very similar to that finally observed in the IMA data. These appears to illustrate that the decision on whether adjuvant chemotherapy should be given for a specific patient depends mainly on the specialist’s decisions, although it is hard to say whether patients preferences may have already played a role in treatment decisions pre-MOC.

   Based on the available data, chemotherapy treatment that could have potentially been safely omitted, based purely on A!O (i.e chemotherapy given to “clinical low-risk” patients), appears to be relatively limited, (i.e. 5% of the overall population for the whole sample, and 5,6% in those aged 70 or younger).

Table 10 – Clinical risk estimations Belgium 2014 (modified A!O) and chemotherapy use – Sample population (patients with ER+, HER2-, pN0 or pN1 and non-missing differentiation grade)

ER status	HER2 status	Grade	Nodal Status	Tumor Size	Clinical Risk	Total Number of patients	With chemotherapy	% patients on chemotherapy
Positive	Negative	Well-differentiated	None	<=3cm	C-low	542	7	1.3%
				3.1 - 5cm	C-high	91	5	5.5%
			1-3 positive nodes	<=2cm	C-low	68	17	25.0%
				2.1 - 5cm	C-high	45	13	28.9%
		Moderately differentiated	None	<=2cm	C-low	1025	53	5.2%
				2.1 - 5cm	C-high	343	47	13.7%
			1-3 positive nodes	Any size	C-high	425	186	43.8%
		Poorly differentiated	None	<=1cm	C-low	76	9	11.8%
				1.1-5cm	C-high	450	171	38.0%
			1-3 positive nodes	Any size	C-high	238	140	58.8%
Total						**3303**	**648**	**19.6%**

Source: Belgian Cancer Register. 2014.

Table 11 – Chemotherapy use in estimated target Belgian population 2014 (patients with ER+, HER2-, pN0 or pN1 and non-missing differentiation grade)

	Number with no adj. chemo (%)	Number with adj. chemo (%)	Total
High c risk	1986 (65%)	1083 (35%)	3069
Low c risk	3132 (95%)	0166 (5%)	3298
Total	5118 (80%)	1249 (20%)	6367

6 CHEMOTHERAPY USE AND RELATED COSTS IN EARLY BREAST CANCER PATIENTS IN BELGIUM

In order to complete our overview of the Belgian situation this section illustrates the chemotherapy combinations most commonly used in our country in the MammaPrint® target population and provides a preliminary estimation of chemotherapy-related costs.

6.1 Chemotherapy combinations

The most common chemotherapy combinations administered in Belgium for the specific patient target population of interest were extracted from the IMA 2014 data - (see Table 12 for a detailed description).

For simplification, infrequent chemotherapies (used in less than 2% of the target patient population), were grouped under “other”. After checking the available data with a panel of experts, the treatment with Paclitaxel-only, used according to the available data in around 2.6% of the Belgian target population, was put into question. The experts pointed out that Paclitaxel as monotherapy is unlikely to be used in these patients. A possible explanation regarding its appearance in the registry may include the possibility that patients captured under that group could have been receiving other chemotherapy agents not yet reimbursed (as part of clinical studies).

Looking at the summary table, it can be noticed that the two most common combinations:

1. Four cycles of Cyclophosphamide and Epirubicin (EC), followed by 12 cycles of Paclitaxel.
2. Three cycles of Cyclophosphamide, Epirubicin and Fluorouracil (FEC), followed by a further three of Docetaxel,

are used in 63% of cases, representing a marked preference of Belgian specialists for these two treatment approaches in 2014.

However, discussions with the experts revealed that the combination of FEC+Docetaxel, used in 20% of all patients in 2014, has since then been used much less frequently in favour of the Cyclophosphamide Docetaxel (TC) combination. This switch was a consequence of recent evidence showing that the TC approach is as effective and better tolerated than the FEC → Docetaxel combination.[35]

An estimation of the costs linked to each of the pharmaceutical regimens in Belgium is presented in Table 13. Prices were extracted from the CBIP/BCFI database (www.cbpi.be). The cheapest alternative for a specific product was selected for the purpose of our calculations.

Prices and costs for the latest available year (i.e. 2017) were considered.

On the table we can see that the most frequently used combination: EC→Paclitaxel, is also the most expensive at approximately €4545. Such high costs are mainly a consequence of the price of Paclitaxel and the fact that this combination administers such a product over 12 weekly cycles.

The two other most common combinations show lower costs with TC costing €1374 and FEC→Docetaxel €1732.

Data on use of dose dense (dd) chemotherapy regimens (cycles separated by two-week periods as opposed to the three-week periods for conventional chemotherapy) in Belgium was missing, although input from the experts regarding the two most frequently used regimens at present (EC→Paclitaxel and TC), pointed out to a high proportion of dd chemotherapy for the former (estimated at 75%), while no dd was used in patients on TC.

The overall, mean pharmacological cost of chemotherapy excluding the “other” and the Paclitaxel as monotherapy categories appears to be of €3005. However, it is important to highlight that there are many other costs linked to the administration of these agents. The following section explores these.

Table 12 – Chemotherapy use in target population in Belgium BCR-IMA 2014 data

CHEMOTHERAPY REGIMENS - 2014	CYCLES	N. (%) OF PATIENTS ON CHEMO
1. EC → Paclitaxel		277 (42.7%)
Cyclophosphamide	4	
Epirubicin	4	
Paclitaxel	12	
2. FEC → Docetaxel		130 (20.1%)
Cyclophosphamide	3	
Epirubicin	3	
Docetaxel	3	
Fluorouracil	3	
3. TC		56 (8.6%)
Cyclophosphamide	4	
Docetaxel	4	
4. EC → Docetaxel		35 (5.4%)
Cyclophosphamide	4	
Epirubicin	4	
Docetaxel	4	
5. FEC → Paclitaxel		30 (4.6%)
Cyclophosphamide	4	
Epirubicin	4	
Paclitaxel	4	
Fluorouracil	4	
6. Cyclo/Paclitaxel/Doxorubicin		30 (4.6%)
Cyclophosphamide	4	
Paclitaxel	12	
Doxorubicin	4	
7. EC		21 (3,2%)
Cyclophosphamide	4	
Epirubicin	4	
8. Paclitaxel		17 (2,6%)
Paclitaxel	4	
9. FEC		15 (2.3%)
Cyclophosphamide	6	
Epirubicin	6	
Fluorouracil	6	
Other		37 (5.7%)

6.2 Other non-pharmacological chemotherapy-related costs

Table 14 offers an illustration of non-pharmacological costs, most of which, are dependent on the number of cycles of chemotherapy received.

6.2.1 Chemotherapy administration

Belgian hospitals receive a maximum lump sum, per chemotherapy cycle, covering costs linked to the administration of the therapy. This maximum lump sum varies from one hospital to another with a weighted mean cost in 2014 of €135.9. However, the code was changed in March 2017 into a pseudo-code specific for combi chemotherapy[o] evaluated by RIZIV – INAMI at €161.

Most often a central venous access line is placed at the beginning of treatment (one-off procedure) in order to facilitate the administration of the chemotherapy at each cycle. However, the price of the implant cannot be costed for separately, in those cases in which the lump sum for chemotherapy administration (combi or mono) is already considered.

Thus, a cost of approximately €161 per chemo cycle should be added to the pharmacological chemo costs to account for their administration.

6.2.2 Blood tests

Day care and blood test costs are also incurred in at every chemotherapy cycle and thus, their weight on the overall costs of chemotherapy administration depends not only on the specific treatment regimen used but once more, on the number of cycles required to complete a full course of treatment. Although the cost of blood tests can vary significantly depending on specific patient needs, a minimum cost aimed at offering a conservative estimate, can be represented by the lump sum per day for clinical biology (i.e. €20.69), plus an assumed 20% additional blood tests needed to be performed for various clinical reasons (e.g. nadir control after first cycle if not dose dense, extra blood count for clinical problems).

[o] Code: Pseudo-code for combination therapy: 767896/767900

Some imaging tests or other patient-specific tests could also be required either at the beginning of the chemotherapy or throughout the treatment.

6.2.3 Costs of prophylaxis or management of common chemotherapy related adverse events (AEs)

Regarding frequent early AEs following administration of a chemotherapy cycle, prophylactic treatment for nausea and vomiting is often administered for every patient receiving chemotherapy. Although the specific products could vary form one chemotherapy regimen to another, the experts consulted identified Akynzeo (300mg netupitant and 0,5mg palonosetron) as the most common approach for preventing such AEs. This has a cost of €63 per chemotherapy cycle. For combinations in which Docetaxel, Litican, is often used at a price of €7.61 for 6 x 50mg. Although Litican can be taken up to 6 days if needed; most patients take them only a few times per cycle. For simplification, and given its low cost, 6 doses were used for the costing illustration presented in Table 14. Akynzeo was assumed to be used for all patients for which the chemotherapy did not include Docetaxel, (see Table 10 for details). For those receiving Docetaxel Litican was assumed to be the choice. The mean per patient cost of anti-emetics in Belgium was therefore, estimated to be of €42.

Neutropenia is also a relatively common consequence of chemotherapy treatment. For this, the experts and the published evidence were consulted/checked in order to define rates of neutropenia in early breast cancer patients receiving chemotherapy with or without prophylactic treatment.

Primary prophylactic treatment for neutropenia with growth factors is currently limited in Belgium to patients receiving dd chemotherapy or to elderly patients, aged 65+, following the recommendation of international guidelines.

As previously mentioned, the experts estimated that approximately 75% of patients on EC→Paclitaxel, received dd chemotherapy and thus, will receive primary prophylactic treatment for neutropenia. Similarly, from the remaining patients on conventional treatment (non-dd), approximately 10% were estimated to be 65+ and would therefore also received growth factors.

From the patients on TC 20%-30% were estimated to be over 65+ and therefore to receive primary prophylaxis.

Secondary prophylaxis is estimated to be provided to approximately 20% of patients younger than 65 on TC, and to 1/3 of those on conventional EC→Paclitaxel regime (non-dd), below 65 (based on expert opinion).

Secondary prophylaxis often starts from the second cycle, since neutropenia appears to develop mostly over the first chemotherapy cycles[36].

For illustration, an assumption was made that 50% of all patients would receive primary prophylaxis, for 4 cycles, while from the remaining, 20% would be administered secondary prophylaxis from the 2nd cycle.

The price of the growth factors is of €1169 based on a single injection of Neulasta 6mg/0,6ml. Therefore, given the recommended dose of a single injection per cycle, prophylactic treatment for neutropenia could add approximately €2689 per patient. (4 cycles at €1169, for 50% of the population + 3 cycles of €1169 for 10% of the population).

Overall rates of neutropenia based on the previously published report[1], the literature [36, 37]Barcenas, 2014 #221} and expert input were estimated to be from 5-10% for those on dd (or on prophylactic treatment) and from 10-20% for those on conventional chemotherapy and not subject to prophylaxis. For the purpose of this exercise, rates of 7.5% and 15% were assumed for patients on dd or with prophylactic treatment, and for those without it respectively. Therefore, an approximate rate of neutropenia of 10.5% was estimated in the MammaPrint® target population in Belgium.

Taking the overall costs of a neutropenia episode, from a Belgian study by Somers 2012[38] and updating such costs to the year 2017 using the official Belgian Health care index (http://statbel.fgov.be), the mean cost of a febrile neutropenia episode was estimated at €5930.

Thus an approximate mean per patient cost of €623 could be linked to the management of chemotherapy-related neutropenia.

6.2.4 Other costs

Rates for chemotherapy-related hospitalisation within 6 months of chemotherapy treatment were recently studied by Barcenas et al. in 2014[39]. Although a majority of those hospitalisations appeared to be linked to neutropenia, fever and other infections, (i.e. 6% of patients aged 65 or younger; and 12.4% of those 65+), approximately 3% of patients were hospitalised within 6 months of chemotherapy initiation for other chemotherapy related problems (1.87% of those aged 65 or younger and 6.47% of those aged 65+).

Taken into consideration the age groups of the MammaPrint® target population, the mean hospitalisation rate for causes other than neutropenia in Belgium in 2014 would be of approximately 3%. Bearing in mind the 2014 per diem price of €462.77[p] and assuming a mean length of stay of 5 days[40], this could add €2314 to the overall costs linked to chemotherapy use.

Other costs such as transport costs are difficult to estimate (public reimbursement dependant on kilometres from and to the hospital where treatment takes place), but nevertheless, their weight is likely to remain limited and thus were left out from the illustration.

Finally out of pocket costs (payment co-payments) in Belgium were excluded from the estimations. Nevertheless, these were expected to remain limited, given that most chemotherapy-related medication in breast cancer appears to be covered by the public health insurance in this country.

Sick leave

Table 14 also considered absenteeism, given its importance in cancer patients.

Assumptions on the sick-leave entitlement were based on the mean gross salary for a working woman in Belgium (i.e. €3209 from statistics of the FPS Economy), and the proportion of the salary paid for by the RIZIV – INAMI (http://www.riziv.be) in case of sick leave. Only the costs covered by the Health Insurance were considered. At present in Belgium, patients are entitled to a monthly payment of 60% of their gross salary for the first year of sick leave. An assumption was made that a mean sick-leave period of six months (the first of which is paid by the employer), would apply for those patients receiving chemotherapy, although this could depend on regimen and more specifically, on whether dose dense regimens are applied versus longer, conventional treatments. This was thought to apply only for patients aged below 65 (around 60% of the early breast cancer population) and actively working (i.e. 62.90% of all women aged less than 65 according to Eurostats -http://epp.eurostat.ec.europa.eu)

This would result on an additional €3 633 that would need to be added to chemotherapy related costs in order to account for direct payer payments for sick leave costs.

[p] Reported per diem hospitalisation costs are based on the 100% weighted average per diem price for all acute beds nationally and were extracted from the technical cell hospital data (https://tct.fgov.be).

6.2.5 Limitations

Because of the limited detailed data currently available regarding non pharmacological chemotherapy related costs, the figures here mentioned represent an approximation to the real costs and are aimed at illustrating the fact that chemotherapy-related costs are much more than purely the pharmacological agents used at every cycle.

Although the cost of managing AEs may appear low these reflect only the most common AEs (i.e. including hospitalisation and treatment costs within 6 months of chemotherapy). Other, long-term AEs already mentioned in the clinical chapter of this review, such as chronic heart failure or acute Myeloid Leukaemia, have not been included in this illustrative exercise, since limited evidence exists on their incidence in early breast cancer patients (≈2% of patients exposed to chemotherapy according to the clinical chapter of this review), which is on the other hand, dependent on the regimen administered. Nevertheless, they represent very severe conditions and their management can be very costly. The publication of the 10-year MINDACT data on AEs should add valuable information in this regard, which should be considered in any future full economic evaluations in this field. Given all the uncertainties identified in the clinical chapter, a cost effectiveness evaluation was considered premature by the authors of this review. Its pertinence should be revisited after the publication of the 10 year MINDACT data.

Table 13 – Mean costs of pharmacological chemotherapy regimens in Belgium 2014

Regime 1: EC → Taxol	Dose mg/sqm	Dose mg*/patient	Price/mg	Drug price/cycle	N. of cycles	Drug price/chemo
Epirubicin	90	158	1	104	4	416
Cyclophosphamide	600	1050	0	15	4	62
Paclitaxel	175	306	1	339	12	4067
Regime 2: FEC → Docetaxel	**Dose mg/sqm**	**Dose mg*/patient**	**Price/mg**	**Drug price/cycle**	**N. of cycles**	**Drug price/chemo**
Cyclophosphamide	500	875	0	13	3	39
Epirubicin	100	175	1	116	3	347
Docetaxel	100	175	3	438	3	1313
Fluorouracil	500	875	0	12	3	35
Regime 3: TC	**Dose mg/sqm**	**Dose mg*/patient**	**Price/mg**	**Drug price/cycle**	**N. of cycles**	**Drug price/chemo**
Docetaxel	75	131	3	328	4	1313
Cyclophosphamide	600	1050	0	15	4	62
Regime 4: EC → Docetaxel	**Dose mg/sqm**	**Dose mg*/patient**	**Price/mg**	**Drug price/cycle**	**N. of cycles**	**Drug price/chemo**
Cyclophosphamide	600	1050	0	15	4	62
Epirubicin	90	158	1	104	4	416
Docetaxel	100	175	3	438	4	1750
Regime 5: FEC → Paclitaxel	**Dose mg/sqm**	**Dose mg*/patient**	**Price/mg**	**Drug price/cycle**	**N. of cycles**	**Drug price/chemo**
Cyclophosphamide	500	875	0	13	4	52
Epirubicin	100	175	1	116	4	462
Paclitaxel	175	306	1	339	4	1356
Fluorouracil	500	875	0	12	4	46
Regime 6: Cyclo Paclitaxel Doxo	**Dose mg/sqm**	**Dose mg*/patient**	**Price/mg**	**Drug price/cycle**	**N. of cycles**	**Drug price/chemo**
Cyclophosphamide	600	1050	0	15	4	62
Paclitaxel	80	140	1	155	12	1859
Doxorubicin	60	105	1	67	4	269
Regime 7: EC	**Dose mg/sqm**	**Dose mg*/patient**	**Price/mg**	**Drug price/cycle**	**N. of cycles**	**Drug price/chemo**
Cyclophosphamide	600	1050	0	15	4	62
Epirubicin	90	158	1	104	4	416
Regime 8: FEC	**Dose mg/sqm**	**Dose mg*/patient**	**Price/mg**	**Drug price/cycle**	**N. of cycles**	**Drug price/chemo**
Cyclophosphamide (500mg)	500	875	0	13	6	77
Epirubicin (100mg)	100	175	1	116	6	693
Fluorouracil (500mg)	500	875	0	12	6	70

**Surface area for a mean body weight of 70kg: 1,75m2 assumed*[41]

Table 14 –Mean chemotherapy related costs in Belgium 2014

Drug chemo costs	Catheter	Admin costs	Clinical biology	Prophylaxis anti-emetics	Prophilaxis neutropenia	Neutropenia costs	Hospitalisation costs (non neutropenia)	Sick leave costs
3005	300	1759	271	450	2689	623	2314	3633

Adding all these costs gives an approximate adjuvant chemotherapy related-costs in Belgium in 2017 of €11 411 without considering sick leave costs and a cost of €15 044 when the latter are included. Despite the preliminary nature of these estimations, they appear to be similar to those recently reported for other EU countries, with Laas et al.[41] quoting a cost of €15 740 including sick leave in France and Blohmer et al. reporting costs of €19 263 in Germany[42], including absenteeism costs of €5 600. All of these studies highlight the limited weight of the pharmacological agents within the overall costs linked to chemotherapy. These estimates are higher than the ones calculated in our 2015 report[1, 41, 43]. The differences come mainly from the higher use of dose dense chemotherapy currently seen in Belgium according to the experts, which result in a higher use of prophylactic treatment for neutropenia. Nevertheless, detailed data on dose dense use is currently missing and thus, the assumptions presented here should be explored further and put to the test, once a full economic evaluation is undertaken.

A comparison with the adjuvant chemotherapy-related costs shown in the economic evaluations included in this review was in most cases difficult to perform since not enough detail was given regarding the costs included under “chemotherapy costs”. An exception was the French study by Bonastre et al,[16] which displayed costs of €7486 and thus, lower than those presented here for Belgium. Looking at the differences, once more the assumptions regarding growth factors use for preventing neutropenia appear to play an important role on the variation. Using the assumptions on that regard used by Bonastre et al. (3 injections of Pelfilgrastim in 22% of the population), our Belgian costs without sick leave would be reduced to €9495.

Assumptions surrounding the management of rare but severe long-term AEs, such as chronic heart failure or acute Myeloid Leukaemia have not been included in this overview due to the scarce existing data on that regard.

Conclusions

- **The overall ER+ HER2- early breast cancer population in Belgium in the year 2014 was of approximately 6367 patients, of which 3069 are classified as high-clinical risk patients (≈48%)**
- **From the potential target population of MammaPrint®, (i.e. high-clinical risk patients according to the modified A!O), 35% received chemotherapy treatment in Belgium in 2014 overall (or 47% excluding patients aged 71+ as per the MINDACT trial).**
- **Our estimates show an approximate mean chemotherapy-related costs in Belgium of €11 411 without considering sick leave costs and of €15 044 when the latter are included**
- **Given the uncertainties surrounding the limited data on the clinical utility of MammaPrint®, no reliable increamental cost effectiveness ratio could be calculated**

7 DISCUSSION AND LIMITATIONS

This section focusses on the clinical utility and the economic evidence of MammaPrint®. Other aspects such as ethical considerations are briefly covered in an appendix of the EUnetHTA clinical assessment[3] carried out by ZiN, in which KCE acted as dedicated reviewer.

7.1 Clinical utility of MammaPrint®

The discussion here included regarding the clinical evidence from the MINDACT study[2] mirrors the discussion of the more extensive EUnetHTA assessment[3]. For more details in each of the points here mentioned see the full EUnetHTA assessment and discussion.

7.1.1 The evidence

In general a prerequisite when considering reimbursement decisions is that added benefit in health-related outcomes should be proven when an intervention or test is added to standard care. It has been claimed that MammaPrint® has a substantial, positive effect on the health and wellbeing of women with early breast cancer by limiting the number of patients receiving adjuvant chemotherapy and, as a consequence, related adverse events, without negatively affecting overall survival. For this purpose, the MINDACT authors predefined a non-inferiority threshold as the cut-off for the benefit of using MammaPrint® for the decision of administering chemotherapy: among patients with clinical high-risk and genomic low-risk who did not receive chemotherapy, the lower boundary of the confidence interval (CI) of the five-year DMFS should be 92% or higher.

According to the MINDACT study authors, DMFS was not negatively affected in the primary test population of women with the clinical high/genomic low-risk profile when the genomic profile (MammaPrint®) was followed. However, based on the assessment of the research team involved in the EUnetHTA clinical assessment[3], data are insufficient to determine that it is safe to omit chemotherapy in the clinical high/genomic low-risk population of early breast cancer patients. Their conclusions are supported by the following observations.

7.1.1.1 Non-inferiority threshold

From a reimbursement perspective, it is necessary that a comparison is made between the new and the standard approach, because added value has to be proven in case a test or intervention is added to standard care. The risk of distant metastasis of women in the groups with and without chemotherapy should have been compared instead of evaluating only one arm. This issue was already mentioned in Bogaerts et al. in 2006, as a major criticism to the primary analysis of the MINDACT.[44] So despite the aim to prove non-inferiority for the endpoint 5-year DMFS, the MINDACT does not have a formal non-inferiority design. A trial with a non-inferiority design would need to have a very large sample size or present a very long follow-up. Bogaerts et al. proposed that if the primary test is significant and the gene signature does select fewer patients to be treated with chemotherapy while not adversely affecting DMFS, then this can be taken to be equivalent to proving that the signature has a very good sensitivity, as well as a specificity that is better than the clinical-pathologic method.

This assumption would be acceptable in the situation that the 5-year DMFS of the subgroup of patients with a clinical high-risk and genomic low-risk who received chemotherapy was reliably known. However, this subgroup could not be selected from the SEER database. Because these data were not available at the start of the MINDACT study, TRANSBIG Consortium members decided on a non-inferiority threshold of 92% derived from a 10-year breast cancer survival probability using Adjuvant! Online. This choice for non-inferiority threshold is a rational one, and a threshold had to be pre-specified. However, three criticisms can be made of this assumption.

First, the MINDACT study design had the potential to directly compare the outcomes in patients with treatment guided by the MammaPrint® versus outcomes in patients with treatment guided by clinicopathologic criteria. However, now that the MINDACT data are available, comparing the DFMS outcomes, it can be concluded that the lower boundary of the CI of the five-year DMFS in the clinical high/genomic low-risk group receiving chemotherapy is 94.1%, higher than the predefined threshold of 92%. To prove added value, the lower boundary of the 95% CI should be at least 94.1% among patients in whom chemotherapy was omitted. Second, the 92% of A!O is the overall survival probability after ten years, and a strong

correlation between five-year DMFS and ten-year OS has yet to be shown. Third, Thewes and Prins et al. recently wrote a comment on the MINDACT study suggesting that most patients with breast cancer are willing to accept adjuvant chemotherapy for very small survival gains (≤1%).[45] Hamelinck et al.[46] also concluded that most patients judged small to moderate benefits sufficient to consider adjuvant systemic therapy worthwhile, but individual preferences varied widely. These criticisms make the 92% 5-year DMFS non-inferiority boundary of the MINDACT trial controversial (for a more detailed discussion on non-inferiority threshold see the full EUnetHTA report[3]).

7.1.1.2 Magnitude of clinical relevance

In the first secondary MINDACT analyses, outcomes were compared in patients in the discordant risk groups according to whether they were assigned to the chemotherapy group or the non-chemotherapy group. This is the direct comparison that is of primary importance for reimbursement decisions. The MINDACT authors stated that the five-year DMFS (the primary study endpoint) was not significantly different and that the study was not sufficiently powered to assess these differences. However, this finding should not be interpreted as evidence of absence of a difference for the specific endpoints.[47] Furthermore, since the per-protocol analysis of five-year DFS was highly significant (p=0.009), we assume that the investigated group was large enough to reveal an effect in DFS even without the power calculation targeting this secondary analysis. While the possibility of a chance finding always exists, since all outcome measures point in the same direction, it is doubtful that this effect arose by chance. Instead, we believe that this effect reveals a true difference between the two groups. This treatment effect may become more pronounced over the next five years because more events ((distant) recurrences and deaths) will occur.

7.1.1.3 PP or PPS analysis

Due to the temporary change in risk as a result of assay problems, all risk groups as enrolled in that particular period are somewhat biased due to incorrect risk assessment. Next to the prespecified PP analyses, also so-called PPS analysis is presented in the the MINDACT publication, in which all patients enrolled during the period of change in risk were excluded. This PPS analysis is presented as sensitivity analysis, but in fact this PPS analysis represents the least biased and therefore most conservative PP analysis. Because the supplement of the MINDACT in which the PPS analysis was presented may not have undergone peer review, it could be argued that it should not be used primary analysis in this assessment. But even if it is used in the way it is presented, i.e. as a sensitivity analysis it is of complementary and confirmative information in order to assess the robustness of the findings and herewith an important way to assess the final impact of the study results for clinical practice. Unfortunately, the PPS analysis points in the direction in which the MP group scores worse, thereby casting doubt on the robustness of the pre-specified PP analysis.

7.1.1.4 Surrogate endpoints for ten-year OS

In general there is no consensus on the use of surrogate endpoints to assess (added) clinical benefit of a health technology, because the relationship between a patient-relevant clinical endpoint and its various surrogates has rarely been investigated in such depth that one particular surrogate is universally accepted as a replacement.[q] Each country/ HTA organisation, need to decide individually which surrogate endpoint is considered best for their assessment.

MINDACT's primary endpoint is five-year DMFS in the clinical high/genomic low discordant risk group. According to the study authors, five-year DMFS is the primary endpoint as distant metastasis from breast cancer represents a virtually incurable disease with almost 100% mortality, and the benefit of adjuvant chemotherapy is primarily limited to reducing recurrences within the first five years. The MINDACT authors stated that five-year DMFS was

[q] www.eunethta.eu/eunethta-guidelines

not significantly different and that the five-year results can be considered as mature data. However, as noted above, the wide 95% CI show that there is a lot of uncertainty and a possibility that many patients could be harmed. Furthermore, there is an on-going risk of distant recurrence after five years. This is especially the case in ER-positive/HER2-negative (luminal-type) breast cancer, where recurrences occur after five years in approximately one half of all distant recurrence cases.[48] This is the main MINDACT study population and thus, further distant metastasis cases might be expected. Adjuvant chemotherapy primarily prevents early metastasis,[49-51] and it is unclear whether these late recurrences are prevented by adjuvant chemotherapy. Therefore, the planned evaluation of the ten-year follow-up data is necessary.

7.1.1.5 Quality of life/short- and long-term side effects of chemotherapy

It is generally recognised that OS is the least ambiguous and most clinically relevant endpoint in clinical trials for cancer therapy. Beyond OS, the QoL endpoint is also very relevant. Unfortunately, QoL was not included in the MINDACT trial. According to the investigators, adding QoL questionnaires would be too burdensome for patients as they had to comprehend the complexities of the trial, including information on genomic testing. In addition, according to the investigators, no validated instrument was available at the time of study. Therefore, the TRANSBIG consortium, which involved patients and advocates, decided not to include a QoL evaluation in the overall study population.

Although, long term QoL is not directly measured in the MINDACT trial, it may be argued that some aspects of QoL are reflected by other outcomes. It is well recognised that the QoL of patients receiving adjuvant chemotherapy will be reduced due to chemotherapy side-effects during and shortly after treatment compared to patients who do not receive chemotherapy. The benefit in quality of life during the administration period chemotherapy is indirectly known from empirical evidence. In addition, the MINDACT study shows that refraining from chemotherapy leads to a significant and clinically relevant worse five-year DFS. All kind of recurrences are stressful to patients even in the case of a curable disease. This distress will have its repercussions on quality of life. Retel et al.[52] conclude in their QoL assessment 6-8 weeks after their decision regarding adjuvant chemotherapy that patients were generally satisfied with the information they received about recurrence risk based on the MammaPrint®, but clinicians should be aware that genomic test results may be associated with greater distress levels, especially for patients with high recurrence risk or discordant test results. Because long term QoL is not available in the MINDACT, the added value of the MammaPrint in terms of QoL in the long term cannot be quantified.

Toxicity data are measured in the MINDACT trial but are not yet published. When looking at the protocol, future analyses will be limited to a comparison between side-effects of the two regimens of chemotherapies and endocrine therapy. At this time, we only know from previous publications that chemotherapy has an absolute risk of heart failure or leukaemia of approximately 2% %.[53, 54] The absence of data on AEs will not be critical when data on OS and QoL would be available, as AEs will have its repercussions on QoL and/or OS.

7.1.1.6 Clinical utility of MammaPrint®

Taking everything into consideration, it has not yet been demonstrated that patient outcomes (ten-year OS and QoL) are improved by withholding adjuvant chemotherapy based on MammaPrint® testing in the clinical high/genomic low-risk group. This conclusion is based on the absence of evidence on added value in terms QoL and on the fact that non-inferiority in terms of OS (surrogates five-year DMFS, five-year DFS and five-year OS) is not shown. Next to that there are concerns about the certainty of DMFS because of the imprecision (very wide 95% CI's). Therefore the results do not rule out the possibility of a small but possibly clinically relevant increase in distant metastasis and hence risk of death.

The quality of the evidence for the critical ten-year OS endpoint was rated as low to very low. Therefore, the confidence in the OS effect estimate after ten years is limited.

If a revision of A!O becomes available, as is expected, this could have an impact on the baseline risks of recurrence and hence may potentially limit the clinical applicability of the MINDACT results.

Ultimately, the decision to receive or forgo chemotherapy (or any other treatment) lies with each patient who is properly informed about the potential side effects and the potential benefits of such treatment. For the same risk–benefit scenario, different patients may make different decisions. However, well informed decision making would ideally require that both parameters (OS and QoL) are quantified.

7.2 Generalizability of economic evaluations to the Belgian context

The discussion here included regarding the economic evidence and the transferability of the available evidence to the Belgian context is based on the analysis performed by KCE in this report.

Given the uncertainties surrounding the limited evidence on the clinical utility of MammaPrint® previously discussed, the research team believe it would be premature to engage in a full economic evaluation of MammaPrint®. Nevertheless, they consider there would be value in reviewing the economic evidence available to date, primarily to highlight important data gaps and factors that could encourage the development of more relevant economic evaluations, making use of the MINDACT data. Aside from the fact that none of the available economic evaluations make use of the MINDACT data yet and therefore rely on multiple sources often reflecting small retrospective studies, there are still data gaps as well as questions regarding current practice in Belgium that the MINDACT data cannot yet answer.

In particular, the reasons why an important proportion of “high clinical risk patients” (according to A!O) do not receive chemotherapy in Belgium remains unknown. In order to further investigate these differences which could facilitate the application of the MINDACT results to the Belgian landscape, a better understanding of current risk stratification systems is necessary. In particular, what characteristics/parameters other than the ones already included in A!O are currently used in Belgium? In addition to this, it remains unclear to which extent the current chemotherapy treated population in Belgium already covers the “high-clinical”/ “high-genomic” risk population and, if that was the case, how such patients were “rightly” identified in the absence of the MammaPrint® test (e.g. ki67?). The question thus remains: who in this subgroup should be tested in Belgium and in what proportion of patients tested will the test lead to a change in the decision to use or not use chemotherapy?

The claims of the test most often shown in the literature are linked to its capacity to limit chemotherapy treatment to those needing it the most, minimising AEs and saving resources. However, based on the available data we cannot exclude the possibility for MammaPrint® to be a valuable tool to increase the number of patients receiving chemotherapy, in case of under treatment.

Thus, if the test helps to identify patients at high risk of recurrence and likely to benefit from chemotherapy, who would otherwise not have been identified and treated, the test may ultimately result in better clinical outcomes and end up being cost-effective, even if cost-additive.

Further questions include the need to use expert opinion in order to outline a picture of the Belgian situation. Although good data was available on the size of the population, their clinical risk (according to the modified A!O) and the proportion and type of chemotherapy used, more data on dose dense chemotherapy use as well as on prophylactic or therapeutic strategies to prevent/manage AEs as well as hospitalisations linked to the chemotherapy administered would be of great value before a full economic evaluation is pursued.

In addition to the above, our review of the economic literature highlighted an important gap regarding data on quality of life. Although it is well accepted that the QoL of patients could be affected by the administration of chemotherapy, not only in the short term but also in longer time horizons, utilities in this regard have only be published as part of small studies. Most of the economic evaluations, referred to a Swedish study by Lidgren et al. dating from 2007 studying health related QoL specifically in breast cancer. Although the completeness of this study makes it the most relevant evidence found on that regard, the sample size was limited to 361 patients. From those, only a small proportion received chemotherapy and thus, the

decrements in utility due to chemotherapy treatment were based on a very limited sample of patients.

All of these limitations make our review an exploratory exercise that should nevertheless, encourage discussion on how to best respond to the current data challenges to ensure a timely response once the 10-year OS and AEs data from the MINDACT study is published.

The current data gaps have been taken into consideration at the time of drafting our recommendations to policy makers, health care providers and researchers (see the synthesis of this report for recommendations).

APPENDICES

APPENDIX 1. ECONOMIC REVIEW

Appendix 1.1. Search strategies – update 2014-2017

Appendix 1.1.1. MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Breast Neoplasms/ (250811)

2 exp Gene Expression Profiling/ (100725)

3 mammaprint.mp. (158)

4 (70 genes or 70-genes).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (303)

5 2 or 3 or 4 (101028)

6 exp Economics/ (541260)

7 exp Health Care Costs/ (54861)

8 exp "Value of Life"/ (5550)

9 (cost or cost analysis or cost-analysis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (402796)

10 (cost-effectiveness or cost effectiveness).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (45983)

11 (cost-utility or cost utility).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3534)

12 exp Cost-Benefit Analysis/ (69137)

13 exp Quality-Adjusted Life Years/ (9099)

14 exp Health Expenditures/ (17991)

15 (buget* or budget* impact).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (984)

16 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (761760)

17 1 and 5 and 16 (124)

18 limit 17 to yr="2014 -Current" (47)

Appendix 1.1.2. EMBASE

SEARCH QUERY

'breast tumor'/exp and (('gene expression profiling'/exp and [embase]/lim) or ('dna microarray'/exp and [embase]/lim) or ('mammaprint'/exp or 'mammaprint' and [embase]/lim) or ('70 gene' or '70-genes' or '70 genes' and [embase]/lim)) and (('economics'/exp and [embase]/lim) or ('health care cost'/exp and [embase]/lim) or ('health economics'/exp and [embase]/lim) or ('health care financing'/exp and [embase]/lim) or ('cost benefit analysis'/exp and [embase]/lim) or ('cost effectiveness analysis'/exp and [embase]/lim) or ('cost of illness'/exp and [embase]/lim) or ('cost control'/exp and [embase]/lim) or ('hospital cost'/exp and [embase]/lim) or ('cost utility analysis'/exp and [embase]/lim) or ('cost minimization analysis'/exp and [embase]/lim) or ('price'/exp or price or 'prices'/exp or prices or 'pricing'/exp or pricing and [embase]/lim)) and [2014-2017]/py

Appendix 1.1.3. EconLit

Database: Econlit <1886 to February 2017>

Search Strategy:

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1 (breast adj neoplasm*).mp. [mp=heading words, abstract, title, country as subject] (0)

2 (breast adj cancer).mp. [mp=heading words, abstract, title, country as subject] (252)

3 (gene adj expression adj profiling).mp. [mp=heading words, abstract, title, country as subject] (1)

4 (gene adj expression).mp. [mp=heading words, abstract, title, country as subject] (89)

5 test.mp. [mp=heading words, abstract, title, country as subject] (48452)

6 1 or 2 (252)

7 3 or 4 or 5 (48525)

8 6 and 7 (37)

9 limit 8 to yr="2014 -Current" (8)

Appendix 1.1.4. CRD NHS databases

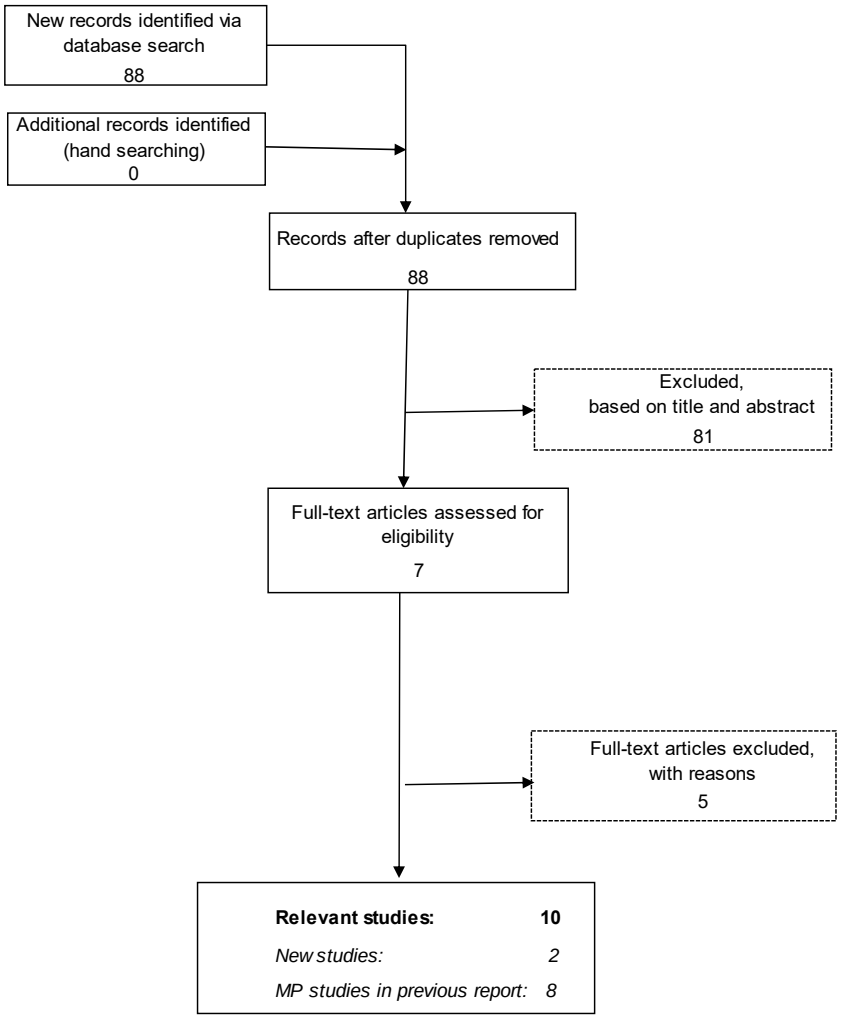
1.MeSH DESCRIPTOR Gene Expression Profiling EXPLODE ALL TREES (49)

2.MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES (1783)

3.#1 AND #2 (31)

Limit to NHS EED & NHS HTA Flow chart selection of Economic Evaluations

Figure 1 – Flow chart Economic Evaluations



Appendix 1.2. Template table for data extraction – Economic evaluations

Table 15 – Data Extraction Template for Economic Evaluations

1	Title
2	Reference (including all authors)
3	Conflict of interest and/or study funding
4	Country
5	Study question – clear and complete including statement of problem
6	Need for modelling – justified
7	Type of analysis (analytic technique)
8	Specific model design –complete description
9	Population – full description
10	Intervention
11	Comparator
12	Time horizon – appropriate and justified
13	Discount rate – inclusion and justification of rates used
14	Perspective
15	Costs
	• Cost items included
	• Measurement of resource use
	• Valuation of resource use
	• Data sources and references
	• Currency and cost year
16	Outcomes

	• Endpoints taken into account and/or health states
	• Valuation of health states
	• Treatment effect and Extrapolation
	• Utility assessment (Quality of Life)
	• Data sources for outcomes and references –values used in base case scenario and justification
17	Uncertainty
	• Scenario analysis
	• Sensitivity analysis – univariate and or multidimensional – ranges of values used and justification
18	Assumptions and discussion regarding their impact on the results
19	Results
	• Cost-effectiveness and/or cost-utility (base case)
	• Scenario analysis
	• Sensitivity analysis
20	Conclusions and applicability
21	Remarks – ongoing research which could affect results

APPENDIX 2. DATA INPUTS ECONOMIC EVALUATIONS

Table 16 – Costs as reported in published economic evaluations of MammaPrint

Study	Cost item	Mean patient cost	Basis/asumptions on costs	Source
Bonastre 2014	MammaPrint test	2675		Manufacturer (Agendia)
	Chemo costs	7486		
	CT administration	2184	6 cycles at €364 per cycle	DRG28Z07Z (weighted mean. Includes pharmaceutical agents)
	Venous port implantation (cetheter)	685	One off cost	DRG05K14Z (weighted mean)
	G-CSF	749	Based on 3 injections of Pelfilgrastim for 22% of patients	PACS01 trial - Roché 2006
	Concomitant medication	342	Aprecipant and Ondansetron orally for 6 cycles	Assumption
	Transportation	240	€80 per course for 50% of paitents	Assumption
	Biologic workup	219	Blood count, hepatic test, etc	French National insurance reimbursement tariffs
	Cardiac ultrasound	96		French national insurance system reimbursement tariff
	Acute toxicities	566	Mean cost per hospital stay for CT-induced hematologic toxicity for 15% of patients	Proportion of patients with at least 1 serious AE from PACS01 (Roché 2006). Hospital costs from French national cost survey
	Hair wig	125		French national insurance reimbursement tariff
	Sick leave	2280	40% of employed women mean duration 5 months. Cost per day €38	French National Insurance System
	Distant recurrence costs	36516	Mean cost per patient from metastasis to death	Bonastre 2012

Study	Cost item	Mean patient cost	Basis/asumptions on costs	Source
Segui 2014	MammaPrint test	2675		Manufacturer price
	Chemo costs	2825 (960; 5248)	Includes drug costs and costs of AEs	Expert opinion; Gisbert 2013; General council of pharmaceutical associations of Spain Database
	Free of recurrence 1st yr	645 (549; 742)		Expert opinion; Martin Jimenez2009
	Free of recurrence 2nd yr	597 (508; 687)		Expert opinion; Martin Jimenez2009
	Free of recurrence 3rd+ yrs	258 (219; 297)		Expert opinion; Martin Jimenez2009
	Recurrence per year	6358 (5404; 7311)		Expert opinion; Martin Jimenez2010
Retel (2010, 2012 and 2013)	MammaPrint test	2675		Manufacturer price
	Chemo costs - FEC regime	4421	Includes drugs, day care costs, lab costs for 80% of patients	Oostenbrink 2006; Health care insurance board 2006
	Chemo costs- TAC regime	19340	Includes drugs, day care costs, lab costs and G-CSF costs for 10% of patients	Oostenbrink 2006; Health care insurance board 2006
	Chemo cost - PAC regime	31257	Includes drugs, day care costs, lab costs and G-CSF costs for 10% of patients	Oostenbrink 2006; Health care insurance board 2006
	Oral endocrine treatment	822	Includes cost of drugs+ consultations+lab tests + scan	Oostenbrink 2006; Health care insurance board 2006
	Trastuzumab	36298		Lidgren 2008
	Chronic congestive heart failure	3453		Lidgren 2008
	Follow-up costs low risk	1179	Includes drugs and in-outpatient costs	Assumption
	Follow-up costs high risk	2359	Includes drugs and in-outpatient costs	Lidgren 2008
	Relapse 1st yr	12181		Lidgren 2008
	Relapse from 2nd yr +	2359		Lidgren 2008

Study	Cost item	Mean patient cost	Basis/asumptions on costs	Source
	Distant metastasis	14303		Lidgren 2008
	Distant metastasis last year of life	6813		Lidgren 2008
Kondo 2012	MammaPrint test	380000		Manufacturer
	Chemo therapy	343001		Kondo 2011 & 2008
	Endocrine therapy per yr	534610		Kondo 2011 & 2008
	Treatment for major toxicity	173352		Kondo 2011 & 2008; Iwata 2005; Papaldo 2006
	Annual monitoring costs - after adjuvant treatment w/o recurrence	25340		Kondo 2011 & 2008
	Treatment for distant recurrence - adjuvant chemo &endocrine therapies	558458		Kondo 2011 & 2008; Iwata 2006; Japanese Breast cancer Society 2010; Japan Society of Clinical Oncology 2005
	End of life -after disant recurrence (per year)	1315143		Kondo 2011, 2009 & 2008
Yang 2012	MammaPrint test	4200 (3150-5250)		Slodkowska 2009
	Adjuvant chemo	19618 (14714-24523)		Hornberger 2005
	Other chemo related costs - pre-medication per cycle	15 (11-18)		Elkin 2004
	Other chemo related costs - oncology visit per cycle	44 (33-55)		Elkin 2005
	Other chemo related costs - monitoring AEs per year	668 (501-835		Elkin 2006
	Recurrence per year	10837 (8128-13546)		Hilner & Smith 1991
	Treatment of AEs - Minor	2709 (2032-3386)		Hilner & Smith 1991
	Treatment of AEs - Major	18061 (13546-22576)		Hilner & Smith 1991
	Treatment of AEs - Fatal	45153 (33865-56441)		Hilner & Smith 1991
	End of life	34778 (26084-43473)		Hilner & Smith 1991
Chen 2010	MammaPrint test	4200 +/-50%		Manufacturer

Study	Cost item	Mean patient cost	Basis/asumptions on costs	Source
	Endocrine therapy per yr	1383 +/-50%	Tamoxifen	Red Book 2007
	Adjuvant chemo	35964 +/-50%	Includes drugs, administration costs, and hospitalisations, and costs of AEs	Hassett 2006
	Annual care for patints w/o recurrence	5928 +/-50%		Lamerato 2006
	Treatment of recurrence	57424 +/-50%		Lamerato 2006
	Terminal care for death from cancer	76557 +/-50%		Lamerato 2006
	Terminal care for death from other causes	65016 +/-50%		Lamerato 2006
Oestreicher 2005	Gene expression profiling	US$3460 (1960-4860)		College of American Pathologists 2005
	Adjuvant chemo	US$21984 (17930-26037)		Reimbursement tariffs from a managed care organisation' Barlow 2001; Hillner & Smith 1991; Warren 2002; Smith 1993; Lokich 1996
	Distant recurrence costs	US$50300 (40300-60300)		Hillner & Smith 1991; Hillner 1992; Coslet 2004; Warren 2002; Taplin 1995; Riley 1995; Fireman 1997
Ward 2013	MammaPrint test	GBP2675		Manufacturer
	6monthly costs endocrine therapy (yrs1-5)	GBP334		BNF; NICE guidance and assumptions
	6monthly costs endocrine therapy (remaining 3 yrs)	GBP65		BNF; NICE guidance and assumptions
	6monthly cost of monitoring in recurrence-free state (yr 1)	GBP151		NHS reference costs 2010/11 and assumption
	6monthly cost of monitoring in recurrence-free state (yrs2-5)	GBP87		NHS reference costs 2010/11 and assumption
	Chemotherapy cost (one-off)	GBP4099	Drug, administration and monitoring	BNF; NHS reference costs 2010/2011 and assumption

Study	Cost item	Mean patient cost	Basis/asumptions on costs	Source
	Short-term adverse events £276 NHS reference costs 2010/11175 and	GBP276		NHS reference costs 2010/2011 and assumption
	G-CSF	GBP485		NHS reference costs 2010/2011 and assumption
	Long-term AEs - AML	GBP11500	Assumes 8 yr probability of AML 0,37% and time spent on AML health state 8 months	NICE STA 18
	Recurrence costs - 6-monthly	GBP4082		Thomas et al. 2009
	End-of-life costs - death from BC (one off)	GBP4038		Campbell et al. 2011
	Local recurrence costs (one off)	GBP14132		Karnon et al. 2007 and Curtis 2010 (PSSRU)

Table 17 – Adverse events as reported in the economic evaluations of MammaPrint

Adverse events as reported in the literature	Reported events	Incidence (SE)	Mean cost per patient (if available)	Original source
Bonastre 2014	Acute toxicity (CT-induced hematologic toxicities)	15%	3775	Incidence: PACS01 trial (Roche 2006); Costs: French national cost survey
Segui 2014				Martin 2010; Jones 2009, Burnell 2010
Retel (2010, 2012 and 2013)	Chronic congestive heart failure - yr 1	0,030 (0,03)	3453	Keefe 2002 and Lidgren 2008
	Chronic congestive heart failure - yr 2-20	0,007 (0,01)		
Kondo 2012	Minor chemo toxicity	60%		Hilner 1991
	Major chemo toxicity	5%		
	Fatal chemo toxicity	0,50%		
Yang 2012	Minor chemo toxicities	60%		Hillner 1991
	Major chemo toxicity	5%		
	Fatal chemo toxicity	0,50%		

Chen 2010	NA - included in the chemo costs			
Oestreicher 2005	NA - not specified in the chemo costs?			
Ward 2013	Short term - Anaemia	1,40%	GBP21,41	PACS-01 trial - Roche 2006
	Short term - Trombocytopenia w/o complications	0,3	GBP4,06	
	Short term - Neutropenia	1,6	GBP36,58	
	Short term - Nausea/vomiting	24,20%	GBP142,34	
	Short term - Stomatitis	4%	GBP71,22	
	Long-term severe AEs - Acute Myeloid Leukaemia	0,37% (0,13-0,61%)	GBP11500	Praga 2005

Table 18– Sources for clinical inputs as reported in published economic evaluations of MammaPrint

Clinical inputs	MammaPrint	Oncotype
Bonastre 2014	Buyse et al. 2006	NA
Segui 2014	Buyse et al. 2006	Paik 2006
	Drukker et al. 2013 (RASTER)	Tang 2011
	Hartmann 2012	Ademuyiwa 2011
	Rutgers 2011	Partin 2011
Retel (2010, 2012 and 2013)	Van de Vijver 2002; Buyse 2006; Bueno de-Mesquita 2009	Thomassen 2007; Fan 2006
Kondo 2012	Van de Vijver2002; Buyse 2006; Bueno-de-Mesquita 2009	NA
Yang 2012	Buyse et al. 2006; Marchionni 2008	Tsoi 2010; Marchionni 2008
Chen 2010	Buyse et al. 2006	NA
Oestreicher 2005	Van de Vijver 2002	NA
Ward 2013	Bueno-de-Mesquita 2009	NA

Table 19 – Utility values as reported in published economic evaluations of MammaPrint

Utility values	State	Value (mean)	Original source
Bonastre 2014	Free of disease - 1st yr with CT	0,62	Hall et al 2012, and Ward 2013
	Free of disease - 1st yr w/o CT	0,74	
	Free of disease subsequent yrs	0,78	
	Distant recurrence	0,69	
Segui 2014	Free of recurrence	0,8	Oestreicher 2005
	Recurrence	0,5	Whyte 2011
	Patients on chemo	0,5	Oestreicher 2005
Retel (2010, 2012 and 2013)	Disease free survival - 1st yr w/o chemo	0,935	Lidgren 2008; Lidgren 2007
	Disease free survival - yr subsequent yrs	0,935	
	Disease free survival - 1st yr with CT	0,62	
	Disease free survival - Endocrine therapy yr 1-5	0,744	
	Disease free survival - Chronic congestive heart failure	0,7	assumption by author
	Recurrence	0,779	Lidgren 2008; Lidgren 2007
	Distant metastasis	0,685	
Kondo 2012	After CT with no distant recurrence	0,98	Kondo 2011, Kondo 2008; Earle 2000
	Minor toxicity	0,9	
	Major toxicity	0,8	
	Distant recurrence - chemo 6 months only	0,5	
	Distant recurrence - If respond to treatment	0,84	
	Distant recurrence - stable	0,7	
	Distant recurrence - progression of disease	0,49	
Yang 2012	No chemo	1	assumption by author
	No recurrence with or w/o chemo	0,98	Earle 2000
	Recurrence with or w/o chemo	0,75	Earle 2000
	No toxicity from chemo	1	assumption by author
	Minor toxicity from chemo	0,8	Gold 1996

	Major toxicity from chemo	0,7	Gold 1996
Chen 2010	Recurrence free survival	0,98	Earle 2000
	Receiving chemo for 6 months	0,7	Hornberger et al 2005
Oestreicher 2005	Post diagnosis - no chemo	0,8 (0,6-1)	de Haes 1991
	Post diagnosis - chemo	0,5 (0,3-0,9)	de Haes 1991, Hillner 1991 & 1992
	No evidence of disease	0,9 (0,8-1)	Hall 1992, de Haes 1991; Hayman 1997, Hutton 1996; Brown 2001
	Distant recurrence	0,3 (0,2-0,5)	Hall 1992; Hutton 1996; Brown 2001; Cosler 2004
Ward 2013	Recurrence Free	0,824 (0,785-0,857)	Lidgren et al. 2007
	Distant recurrence	0,685 (0,62-0,735)	Lidgren et al. 2007
	Local recurrence (decrement per patient)	-0,108	Campbell et al. 2011
	Acute Myeloid Leukaemia (AML)	0,26	Younis et al. 2008
	Chemotherapy (decrement per patient)	-0,038	Campbell et al. 2011
	Patients dying from cancer (3 last months)	0,159 (SE 0,04)	Campbell et al. 2011

Table 20 – Nomenclature codes for Breast conserving surgery

code	Label (Français)	Label (Nederlands)
227032	Exérèse d'une tumeur ou d'un kyste de la glande mammaire	Verwijderen van een gezwel of cyste uit de borstklier
227043	Exérèse d'une tumeur ou d'un kyste de la glande mammaire	Verwijderen van een gezwel of cyste uit de borstklier
227054	Mammectomie partielle ou tumorectomie associée à un curage ganglionnaire axillaire	Gedeeltelijke mammectomie of tumorectomie. geassocieerd met een curage van de okselklieren
227065	Mammectomie partielle ou tumorectomie associée à un curage ganglionnaire axillaire	Gedeeltelijke mammectomie of tumorectomie. geassocieerd met een curage van de okselklieren
227732	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge
227743	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge

227754	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. non-palpable. avec résection d'une marge de sécurité macroscopiquement suffisante. après procédure de localisation	Volledige. borstsparende. resectie van een bewezen kwaadaardig. niet voelbaar borstletsel met macroscopisch voldoende veiligheidsmarge. na localisatieprocedure
227765	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. non-palpable. avec résection d'une marge de sécurité macroscopiquement suffisante. après procédure de localisation	Volledige. borstsparende. resectie van een bewezen kwaadaardig. niet voelbaar borstletsel met macroscopisch voldoende veiligheidsmarge. na localisatieprocedure
227776	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante et résection du ganglion sentinelle	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge. en resectie van schildwachtlymfeklier
227780	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante et résection du ganglion sentinelle	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge. en resectie van schildwachtlymfeklier
227791	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante et résection du ganglion sentinelle avec examen anatomo-pathologique peropératoire du ganglion sentinelle	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge. en resectie van schildwachtlymfeklier. met peroperatoir anatomo-pathologisch onderzoek van de schildwachtlymfeklier
227802	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante et résection du ganglion sentinelle avec examen anatomo-pathologique peropératoire du ganglion sentinelle	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge. en resectie van schildwachtlymfeklier. met peroperatoir anatomo-pathologisch onderzoek van de schildwachtlymfeklier
227813	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante et résection du ganglion sentinelle qui en cas d'envahissement tumoral démontré à l'examen anatomo-pathologique	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge. en resectie van schildwachtlymfeklier. die wanneer tumoraal ingenomen bij peroperatoir anatomo-pathologisch onderzoek gevolgd wordt door
227824	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante et résection du ganglion sentinelle qui en cas d'envahissement tumoral démontré à l'examen anatomo-pathologique	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge. en resectie van schildwachtlymfeklier. die wanneer tumoraal ingenomen bij peroperatoir anatomo-pathologisch onderzoek gevolgd wordt door
227835	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante. et un évidement ganglionnaire de l'aisselle	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge. en een okseluitruiming
227846	Résection complète. conservatrice du sein. d'une tumeur maligne démontrée. avec résection d'une marge de sécurité macroscopiquement suffisante. et un évidement ganglionnaire de l'aisselle	Borstsparende volledige resectie van een bewezen kwaadaardig borstletsel met macroscopisch voldoende veiligheidsmarge. en een okseluitruiming

Table 21 – Nomenclature codes for Mastectomy

code	Label (Français)	Label (Nederlands)
226951	Intervention selon Urban	Ingreep volgens Urban
226962	Intervention selon Urban	Ingreep volgens Urban
226973	Intervention selon Halsted ou Pattey avec examen anatomo-pathologique extemporané	Ingreep volgens Halsted of Pattey met ex tempore pathologisch-anatomisch onderzoek
226984	Intervention selon Halsted ou Pattey avec examen anatomo-pathologique extemporané	Ingreep volgens Halsted of Pattey met ex tempore pathologisch-anatomisch onderzoek
226995	Intervention selon Halsted ou Pattey	Ingreep volgens Halsted of Pattey
227006	Intervention selon Halsted ou Pattey	Ingreep volgens Halsted of Pattey
227010	Exérèse d'une tumeur située au-dessus du fascia dans les parties molles mais avec résection totale de l'organe dans lequel se situe la tumeur	Verwijderen van een gezwel uit de weke weefsels boven de spierfascia maar met volledige resectie van het orgaan waarin het gezwel is gelegen
227021	Exérèse d'une tumeur située au-dessus du fascia dans les parties molles mais avec résection totale de l'organe dans lequel se situe la tumeur	Verwijderen van een gezwel uit de weke weefsels boven de spierfascia maar met volledige resectie van het orgaan waarin het gezwel is gelegen
227636	Résection complète du sein (mastectomie) pour tumeur maligne	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor
227640	Résection complète du sein (mastectomie) pour tumeur maligne	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor
227651	Résection complète du sein (mastectomie) pour tumeur maligne et résection du ganglion sentinelle	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor en resectie van schildwachtlymfeklier
227662	Résection complète du sein (mastectomie) pour tumeur maligne et résection du ganglion sentinelle	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor en resectie van schildwachtlymfeklier
227673	Résection complète du sein (mastectomie) pour tumeur maligne et résection du ganglion sentinelle avec examen anatomo-pathologique peropératoire du ganglion sentinelle	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor en resectie van schildwachtlymfeklier met peroperatoir anatomo-pathologisch onderzoek van de schildwachtlymfeklier
227684	Résection complète du sein (mastectomie) pour tumeur maligne et résection du ganglion sentinelle avec examen anatomo-pathologique peropératoire du ganglion sentinelle	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor en resectie van schildwachtlymfeklier met peroperatoir anatomo-pathologisch onderzoek van de schildwachtlymfeklier
227695	Résection complète du sein (mastectomie) pour tumeur maligne avec évidement axillaire	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor met okseluitruiming
227706	Résection complète du sein (mastectomie) pour tumeur maligne avec évidement axillaire	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor met okseluitruiming

227710	Résection complète du sein (mastectomie) pour tumeur maligne et résection du ganglion sentinelle qui en cas d'envahissement tumoral démontré à l'examen anatomo-pathologique peropératoire est suivi d'un évidement ganglionnaire de l'aisselle	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor en resectie van schildwachtlymfeklier die wanneer tumoraal ingenomen bij peroperatoir anatomo-pathologisch onderzoek gevolgd wordt door een okseluitruiming
227721	Résection complète du sein (mastectomie) pour tumeur maligne et résection du ganglion sentinelle qui en cas d'envahissement tumoral démontré à l'examen anatomo-pathologique peropératoire est suivi d'un évidement ganglionnaire de l'aisselle	Verwijderen van de volledige borstklier (mastectomie) voor kwaadaardige tumor en resectie van schildwachtlymfeklier die wanneer tumoraal ingenomen bij peroperatoir anatomo-pathologisch onderzoek gevolgd wordt door een okseluitruiming

Table 22 – Patients characteristics and representativity analyses

Characteristics	Descriptive statistics	All patients	Patients with ER and/or HER2 status available	Difference	p-value
Number of centers		101	100		
Number of patients		N=7 491	N=5 758		
Age	mean (sd)	61.2 (12.9)	60.8 (12.8)		
	Q1-Q3	52 - 71	51 - 70		
	min –max	20 - 95	21 - 95		
Age category	Less than 35 years	108 (1.4%)	82 (1.4%)	0%	0.0555
	35 to 50 years	1 385 (18.5%)	1 114 (19.3%)	+0.8%	
	50 to 70 years	3 922 (52.4%)	3 005 (53.1%)	+0.7%	
	70 years or older	2 076 (27.7%)	1 507 (26.2%)	-1.5%	
c-Stage	0	95 (1.3%)	47 (0.8%)	-0.5%	<0.0001
	I	3 423 (45.7%)	2 756 (47.9%)	+2.2%	
	II	2 319 (31.0%)	1 703 (29.6%)	+0.4%	
	III	184 (2.5%)	100 (1.7%)	-0.8%	
	IV	39 (0.5%)	21 (0.4%)	-0.1%	

Characteristics	Descriptive statistics	All patients	Patients with ER and/or HER2 status available	Difference	p-value
	Unknown	1,431 (19.1%)	1131 (19.6%)	+0.5%	
p-Stage	I	4 101 (54.7%)	3 346 (58.1%)	+3.4%	<0.0001
	II	2 851 (38.1%)	2 262 (39.3%)	+1.2%	
	III	516 (6.9%)	135 (2.3%)	**-4.6%**	
	IV	16 (0.2%)	9 (0.2%)	0%	
	Unknown	7 (0.1%)	6 (0.1%)	0%	
pN-category	0	5 136 (68.6%)	4 177 (72.5%)	+3.9%	<0.0001*
	1	1 648 (22.0%)	1 321 (22.9%)	+0.9%	
	2	59 (0.8%)	8 (0.1%)	-0.7%	
	2a	298 (4.0%)	90 (1.9%)	-2.1%	
	2b	1 (0.0%)	1 (0.0%)	0%	
	3	21 (0.3%)	5 (0.1%)	-0.2%	
	3a	140 (1.9%)	29 (0.5%)	-1.4%	
	3b	2 (0.0%)	2 (0.0%)	0%	
	3c	1 (0.0%)	0 (0.0%)	0%	
	Unknown	185 (2.5%)	125 (2.2%)	-0.3%	
pT-category	1	49 (0.7%)	40 (0.7%)	0%	0.0043
	1mi	72 (1.0%)	54 (0.9%)	-0.1%	
	1a	357 (4.8%)	1 264 (4.6%)	-0.2%	
	1b	1 261 (16.8%)	1 044 (18.1%)	+1.3%	
	1c	3 143 (42.0%)	2 483 (43.1%)	+1.1%	

Characteristics	Descriptive statistics	All patients	Patients with ER and/or HER2 status available	Difference	p-value
	2	2 609 (34.8%)	1 873 (32.5%)	-2.3%	
WHO PFS	0 – Asymptomatic	4 408 (58.8%)	3 476 (60.4%)	+1.6%	0.1099
	1 – Symptomatic but completely ambulatory	2 467 (32.9%)	1 834 (31.9%)	-1.0%	
	2 – Symptomatic, <50% in bed during the day	38 (0.5%)	25 (0.4%)	-0.1%	
	3 – Symptomatic, >50% in bed, but not bedbound	10 (0.1%)	8 (0.1%)	0%	
	4 – Bedbound	4 (0.1%)	2 (0.0%)	-0.1%	
	Missing	564 (7.5%)	413 (7.2%)	-0.3%	
Differentiation grade	Well differentiated	1 236 (16.5%)	1 010 (17.5%)	+1.0%	0.1345
	Moderately differentiated	3 454 (46.1%)	2 637 (45.8%)	-0.3%	
	Poorly differentiated	2 345 (31.3%)	1 773 (30.8%)	-0.5%	
	Unknown	456 (6.1%)	338 (5.9%)	-0.2%	
ER status	Positive	3 147 (42.0%)	3 147 (83.0%)	na	
	Negative	395 (5.3%)	395 (10.4%)		
	Unknown	3 949 (52.7%)	249 (6.6%)		
HER2 status	Positive	569 (7.6%)	569 (15.0%)	na	
	Negative	2 638 (35.2%)	2 638 (69.6%)		
	Equivocal	307 (4.1%)	307 (8.1%)		
	Unknown	3,977 (53.1%)	277 (7.3%)		
Adjuvant Chemotherapy	Yes	2 453 (32.6%)	1 778 (30.9%)	-1.7%	0.0032

Characteristics	Descriptive statistics	All patients	Patients with ER and/or HER2 status available	Difference	p-value
	No	5 064 (67.4%)	3 980 (69.1%)	+1.7%	
Type of adjuvant chemo		**N=2 453**	**N=1 778**		0.9884
	Cyclophosphamide + epirubicin + paclitaxel	1 019 (41.5%)	731 (41.1%)	-0.4%	
	Cyclophosphamide + epirubicin + docetaxel + fluorouracil	489 (19.9%)	364 (20.5%)	+0.6%	
	Cyclophosphamide + docetaxel	171 (7.0%)	122 (6.9%)	-0.1%	
	Cyclophosphamide + epirubicin + docetaxel	142 (5.8%)	107 (6.0%)	+0.2%	
	Paclitaxel	132 (5.4%)	89 (5.0%)	-0.4%	
	Cyclophosphamide + epirubicin + paclitaxel + fluorouracil	125 (5.1%)	97 (5.5%)	+0.4%	
	Cyclophosphamide + paclitaxel + doxorubicin	95 (3.9%)	74 (4.2%)	+0.3%	
	Cyclophosphamide + epirubicin	61 (2.5%)	43 (2.4%)	-0.1%	
	Cyclophosphamide + epirubicin + fluorouracil	48 (2.0%)	35 (2.0%)	0%	
	Cyclophosphamide + docetaxel + doxorubicin	7 (0.3%)	6 (0.3%)	0%	
	Other	164 (6.7%)	110 (6.2%)	+0.5%	

Table 23 – Number of patients per centers

Characteristics	Descriptive statistics	All patients	Patients with ER and/or HER2 status available
Number of patients		N=7,491	N=5,758
Number of centers		101	100
Number of patients per center	Mean Q1 – Q3 min – max	74.2 29 – 94 1 – 377	74.9 31 – 95 3 – 377
Number of centers in Belgium with	0-100 patients	77 (76.2%)	76 (76.0%)

100-150 patients	12 (11.9%)	12 (12.0%)	
>150 patients	12 (11.9%)	12 (12.0%)	

Table 24 – Comparison between MINDACT and BCR population on demographic and tumor characteristics

Variable		Mindact population N=6693		BCR population (ER +/HER - & <70y) N=2491		Difference (MINDACT – BCR)	p-value (Chisquare test)
Age	<35	122	1.8%	28	1.1%	0.7%	<0.0001
	35-50	2104	31.4%	558	22.4%	**9.0%**	
	50-70	4411	65.9%	1 835	73.7%	**-7.8%**	
	Other	56	0.8%	0	0.0%	0.8%	
Tumor size	<1	920	13.7%	672	27.0%	**-13.2%**	<0.0001
	1 to 2	3875	57.9%	1 190	47.8%	**10.1%**	
	>2 to 5	1819	27.2%	629	25.3%	1.9%	
	>5	78	1.2%	0	0.0%	1.2%	
Tumor grade	1	1447	21.6%	582	23.4%	-1.7%	<0.0001
	2	3287	49.1%	1 350	54.2%	**-5.1%**	
	3	1927	28.8%	559	22.4%	**6.4%**	
	Missing	32	0.5%	0	0.0%	0.5%	
Lymph node status	Negative	5288	79.0%	1 916	76.9%	2.1%	0.0227
	1 to 3	1396	20.9%	575	23.1%	-2.2%	
	4+	8	0.1%	0	0.0%	0.1%	
				N=3303	(includes 70+)		
WHO PFS	0	6434	96.1%	2 032	61.5%	**34.6%**	<0.0001
	1	257	3.8%	1 049	31.8%	**-27.9%**	
	2	2	0.0%	12	0.4%	-0.3%	
	3			2	0.1%	-0.1%	
	4			1	0.0%	0.0%	

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