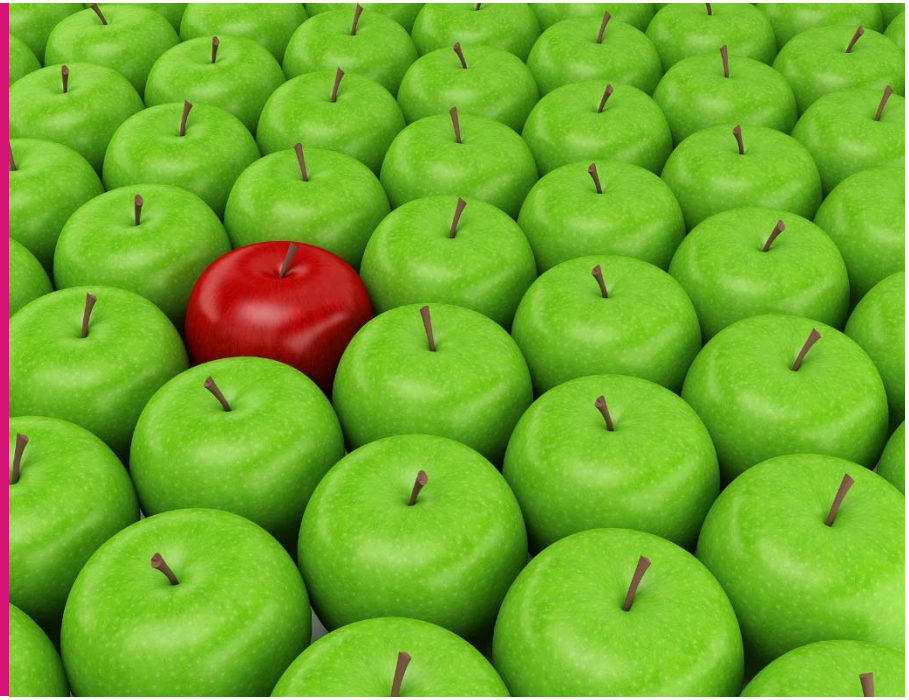
KCE REPORT 237Cs

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

SCIENTIFIC SUMMARY

GENE EXPRESSION PROFILING AND IMMUNOHISTOCHEMISTRY TESTS FOR PERSONALISED MANAGEMENT OF ADJUVANT CHEMOTHERAPY DECISIONS IN EARLY BREAST CANCER

A RAPID ASSESSMENT



Belgian Health Care Knowledge Centre

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KCE REPORT 237Cs
HEALTH TECHNOLOGY ASSESSMENT

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A RAPID ASSESSMENT

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COLOPHON

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FOREWORD

We can say it loud and clear: the survival rates of certain cancers have increased tremendously over the last decade. Breast cancer offers a good example of this, where progress has been the result of a whole bundle of different improvements including better detection, more effective drugs, more advanced surgical techniques, more targeted radiotherapy,… and above all, a multidisciplinary and evidence-based approach implemented by teams with more and greater experience.

In the recent years, genetics have gained importance in everyday clinical practice. Their novelty raises a number of new questions: The gene expression profiling and expanded immunohistochemistry tests analyzed in this report are not primarily aimed at increasing overall survival. Instead, they try to answer the questions: how could we avoid exposing a large proportion of women with early breast cancer to aggressive treatments such as chemotherapy? Would it be possible to do so without decreasing their chances of survival? In other words, if we could foresee which of these tumors are likely to be more aggressive, we could be more selective in chemotherapy treatment decisions. At least in theory…

However, one should not rush into that kind of betting if not sure of winning. In research, these new tests also require very rigorous methods. These, depend upon two-phase study approaches: First, it is necessary to discern if they offer a good prognostic value. Only then, arises the crucial question of whether such prognostic value would translate into better long-term patient outcomes. The answer is not straightforward. On the one hand, there is a possibility that we could reduce the amount of chemotherapy given thanks to the tests, without compromising survival or relapse rates. On the other hand, we may find that the risks had originally been sub estimated and end up providing more chemotherapy instead. Finally, there is as usual, the additional question of whether the benefits provided by these tests justify their cost (currently very high).

A last point: genetic testing is a rapidly evolving field. Before a technique has proven itself, another, newer technique appears, promising even better outcomes. The market is vast and competition is fierce. However, reimbursement decisions by the health insurance cannot be based on promises. A snapshot such as the one provided in this study, imperfect as it may be in this whirlpool of progress, still provides the most reliable point of reference we have. Moreover, and probably more importantly, the patient's interest is often better served by a technique whose added value is proven than by the promises linked to the latest innovation.

Christian LÉONARD
Deputy general director

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General director

ABSTRACT

CONTEXT AND AIMS

The aim of this report is to assess the clinical effectiveness and cost-effectiveness of selected gene expression profiling (GEP) and expanded immunohistochemistry (IHC) tests compared to alternative risk assessment methods for early breast cancer patients.

METHODS

A systematic search of the published literature up to the end of June 2014 on the efficacy, effectiveness and cost-effectiveness of GEP and expanded IHC tests versus current risk stratification tools in early breast cancer was undertaken by consulting electronic databases, including Medline, PreMedline, EMBASE and the Cochrane Library. The clinical evaluation was based on existing systematic reviews; the economic review included full primary and secondary economic evaluations. Bibliographies of articles found via our original search were also checked to identify further relevant studies. No time limitations were imposed.

RESULTS

Most evidence is available for Oncotype and MammaPrint. For some of these tests, there is good evidence supporting their prognostic ability, but very limited and weak information on their clinical utility. Direct evidence evaluating the effect of GEP or expanded IHC testing on clinical outcomes such as survival or recurrence, is generally lacking. No prospective RCTs studying the clinical utility of these tests were identified.

Overall, the results from the review of economic evaluations appear favourable to the tests analysed when these are compared to standard practice, with more unclear results found when comparing one test to another.

The positive results are nevertheless subject to important limitations mainly linked to the need to model different sets of data coming from different studies since there are up to date no prospective studies following patients from testing to long-term outcomes.

CONCLUSIONS

Although there is good evidence proving the prognostic ability of these tests further research is needed to clarify what their clinical utility is. Such research should also reduce the current uncertainties surrounding the potential cost-effectiveness of these tests.

SYNTHESIS

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1. CONTEXT AND OBJECTIVES

1.1. Breast cancer epidemiology, classification and prognosis

Breast cancer is the most commonly diagnosed cancer in women in Belgium and worldwide. In 2011 the Belgian Cancer Registry reported 10 490 cases of incident breast cancers in women and 75 in men. Incidence increases markedly with age with a peak in the 65-69 year age category in women. Mean age at diagnosis is 62 years in women.[1]

Breast cancers can be classified using different schemata and classification can influence treatment response and prognosis. These classifications include histopathological type, grade, stage, receptor status and the presence or absence of specific genes as determined by genetic testing.[2]

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.[3] However, mortality is still considerable with breast cancer accounting for approximately 20% of all cancer deaths in Belgian women.

1.2. Breast cancer treatment

Treatment usually involves primary surgery to remove the primary tumour and any involved lymph nodes. It might be followed by adjuvant therapy such as radiation therapy, endocrine therapy and/or chemotherapy with or without targeted biological treatment, all depending upon characteristics of tumour and patient.

Clinical practice guidelines recommend, in addition to the basic triple assessment (clinical assessment, imaging and tissue sampling) the analysis of hormonal receptors (ER, PR and HER2) in primary invasive breast cancers. Neoadjuvant and adjuvant therapies after surgery should be decided depending on tumour and patient characteristics in a multidisciplinary team and taking the preferences of the patient into account.[4]

1.3. Gene expression profiling

Gene expression profiling tests assess the identity and number of messenger ribonucleic acid (mRNA) transcripts in a specific tissue sample and give information about the activity of genes that give rise to these mRNA transcripts. The mRNA levels are associated with the protein composition of the cells, and consequently to changes in the properties and functions of tissues and cells (both normal and malignant) in the body.

1.4. Expanded immunohistochemistry

Immunohistochemistry tests measure protein synthesis levels in the tumour sample rather than mRNA or cDNA. IHC identifies the number of cancer cells synthesising specific proteins. The intensity of staining correlates with protein synthesis levels. Some of these tests (e.g. IHC4) offer the advantage of using existing immunohistochemical markers (ER, PR and HER2), which are routinely tested in early invasive breast cancer. The term 'expanded' is used to describe the fact that these tests are used in addition to the standard IHC receptor testing.

The aim of GEP and expanded IHC tests is to improve the targeting of adjuvant therapy by providing more accurate prognostic information for subgroups of patients.[5] These tests are typically indicated for women with ER+ and LN– tumours. They are intended to ultimately guide the decision on whether or not to offer chemotherapy.

1.5. Research questions

Our project team performed a systematic search (up to the end of June 2014) of the published literature, consulting databases including Medline, EMBASE, and the Cochrane Library, in order to answer the following questions:

- What is the efficacy/effectiveness of GEP and expanded IHC tests versus standard risk classification systems in early breast cancer patients?
- What is the cost-effectiveness of GEP and expanded IHC tests versus standard risk stratification systems in early breast cancer patients?
  - Are these tests more cost-effective for specific patient populations?
- How much would the introduction of these tests add in budgetary terms when compared to current risk stratification systems used in Belgium ?

2. HOW EFFECTIVE ARE GENE EXPRESSION PROFILING AND EXPANDED IMMUNOHISTOCHEMISTRY TESTS IN EARLY BREAST CANCER?

Our analysis, based on a review of systematic reviews highlighted an overall lack of evidence on the clinical utility of gene expression profiling or expanded IHC tests, with most of the studies included in the systematic reviews analysed[5-17] focusing purely on the prognostic ability (clinical validity) of such tests. For the quality appraisal of the systematic reviews, the AMSTAR checklist was used (http://amstar.ca). Appraisal was done by one reviewer.

2.1. Gene expression profiling (GEP) tests

Most of the evidence found referred to Oncotype DX and MammaPrint. For these tests there were studies judged to be of moderate to high quality supporting their clinical validity. However, important evidence gaps are still present with no prospective studies reporting on the impact of these tests on long-term outcomes such as overall survival or recurrence.[5] For Oncotype DX there was limited evidence indicating that the test leads to changes in decision making but further research is required before clear conclusions can be drawn on this regard.[5]

2.2. Expanded IHC tests

The evidence for Mammostrat appears to be of reasonable quality with regards to its prognostic ability (clinical validity) with studies including a large sample size.[5] Evidence for IHC4 is limited to one large study supporting its prognostic ability.[5]

As per the GEP tests, further evidence is required for expanded IHC tests regarding their clinical utility.

3. HOW COST-EFFECTIVE ARE GENE EXPRESSION PROFILING AND EXPANDED IMMUNOHISTOCHEMISTRY TESTS IN EARLY BREAST CANCER?

Our search identified 27 relevant evaluations most of which were published in the last four years (see Table 1). Only published full economic evaluations were included in our review. Grey literature or partial evaluations looking purely at costs were not included in our analysis.

Table 1 – Overview of economic evaluations on gene profiling (GEP) and expanded immunohistochemistry (IHC) tests in chemotherapy decisions for early breast cancer patients

Author	Year	Country	Type of economic evaluation	Perspective	Discount rate; both costs and outcomes (%)
Blomher[18]	2013	Germany	CUA/CEA	Healthcare payer	3%
Chen[19]	2010	USA	CUA/CEA	Healthcare payer	3%
Cosler[20]	2009	USA	CUA/CEA	Healthcare payer	NA
Davidson[21]	2013	Canada	CUA/CEA	Healthcare system	5%
Hall[22]	2012	UK	CUA/CEA	Healthcare system	3,50%
Hannouf[23]	2014	Canada	CUA/CEA	Healthcare system	5%
Hannouf[24]	2012	Canada	CUA	healthcare system	5%
Holt[25]	2013	UK	CUA/CEA	Healthcare system	3,50%
Hornberger[26]	2011	USA	CUA	Healthcare payer	3%
Hornberger[27]	2005	USA	CUA/CEA	Societal	3%
Klang[28]	2010	Israel	CUA	Healthcare payer	3%
Kondo[29]	2012	Japan	CUA/CEA	Healthcare system although presented as societal	3%
Kondo[30]	2011	Japan	CUA	Healthcare system although presented as societal	3%
Kondo[31]	2008	Japan	CUA/CEA	Healthcare payer	3%

Lamond[32]	2012	Canada	CUA	Healthcare system	3%
Mislick[33]	2014	USA	CUA/CEA	Healthcare payer	3% for costs only
Oestreicher[34]	2005	USA, Netherlands	CUA	Societal	3%
Paulden[35]	2013	Canada	CUA/CEA	Healthcare payer	5%
Reed[36]	2013	USA	CUA/CEA	Healthcare system and societal	3%
Retel[37]	2013	Netherlands	CUA/CEA	Healthcare system	4% for costs and 1,5% for effects
Retel[38]	2012	Netherlands	CUA/CEA	Healthcare system	4% costs and 1,5% for outcomes
Retel[39]	2010	Netherlands	CUA/CEA	Healthcare payer	costs:4%; benefits:1,5%
Tsoi[40]	2010	Canada	CUA/CEA	Healthcare system	5%
Valderlaan[41]	2011	USA	CUA	Healthcare payer	3%
Vataire[42]	2012	France	CUA/CEA	Societal	4%
Ward[5]	2013	UK	CUA	Healthcare system	3,50%
Yang[43]	2012	USA	CUA	Healthcare payer	3%

3.1. Gene expression profiling (GEP) tests versus standard practice

Six studies looked at MammaPrint,[19, 29, 34, 37-39] while the remaining covering GEP tests versus standard practice focused on Oncotype Dx.

Overall, the results appear favourable to the GEP tests when these are compared to standard practice, with 7/25 of the studies showing GEP test to be dominant (i.e. cheaper and more effective),[18, 26, 27, 37, 39, 41, 44] and the majority of the remaining studies displaying relatively low ICERs (<€25 000).

3.2. Expanded (IHC) tests versus standard practice

Ward et al. included in their analyses expanded IHC tests such as Mammostrat and IHC4,[5] and reported positive results for IHC4 versus current practice (dominant), but negative results when modelling Mammostrat versus current practice (not cost-effective at a threshold of GBP20 000/QALY when testing all patients, and dominated when testing NPI>3,4 only).

3.3. Comparisons between tests

Only four studies compared different tests. Amongst these, the two comparing MammaPrint versus Oncotype DX showed the former to be dominant (cheaper and more effective).The comparison of Oncotype DX versus Mammostrat showed the former to be more expensive while offering similar outcomes. Finally, the comparison by Ward et al. between Oncotype DX and IHC4 favoured IHC4.[5]

The available evidence suffered from important weaknesses to be borne in mind before clear conclusions can be drawn. More specifically, the lack of clinical studies looking at the long term consequences of testing represented the main limitation and made all evaluations rely on inputs from different sources which had to be modelled together resulting in important uncertainties surrounding the overall results.

4. BUDGETARY ESTIMATIONS FOR GENE EXPRESSION PROFILING TESTS

The use of these tests in early breast cancer patients has, so far, been limited in Belgium, with financial barriers hindering their widespread adoption. The main barrier for their use being the lack of public funding, which has resulted in a fragmented picture with very few centres using it.

4.1. Methodology

4.1.1. Data sources

Epidemiological data from the Belgian Cancer Registry coupled with IMA data for 2008 was used to identify the size of the relevant target population (ER+, LN-, HER2-) as well as the proportion of such patients who receive adjuvant chemotherapy (15% overall).

A review of the literature and consultation with experts facilitated an estimation of the cost of chemotherapy in Belgium for the target patient population.

Data on risk distribution were extracted directly from the independent economic evaluation performed by Ward et al.[5] for Oncotype DX and were based on TransATAC data and assumptions were made with regard to the proportion of those likely to be treated with chemotherapy if the test had been performed (i.e. all with high risk, 15% of those with an intermediate risk score and none of those with a low score). The reasons for focusing on Oncotype DX were two fold: First, most of the available evidence up to date is for this test and second, Oncotype has the highest price amongst the tests analysed, according to the literature, and thus focusing on it offers a more conservative approach.

4.1.2. Perspective and scenarios analysed

The perspective considered was that of the healthcare payer, and in particular that of the RIZIV/INAMI. However, considering the importance of absenteeism in cancer patients, we also presented estimations including sick-leave payments covered by the INAMI/RIZIV over the chemotherapy treatment period.

The availability of NPI data for the target population and the recent recommendations by the National Institute of health and Care Excellence (NICE) to limit GEP testing to patients with an intermediate risk of recurrence (3,4 < NPI <5,4) (http://www.nice.org.uk/guidance/dg10) made it possible and appropriate to study two different scenarios:

- in which all patients are tested independently of their NPI, or indeed any other current risk stratification systems
- in which only those with NPI>3,4 are tested and reclassified before chemotherapy treatment decisions are made.

4.1.3. Results

With an overall approximate annual population of 3266, and an approximated mean cost of chemotherapy treatment of €7 820 without considering sick leave and of €11 280 when the latter are included, the overall expected budgetary impact would be of €7 868 600 without sick leave costs or €7 733 780 including sick leave costs if used in all ER+, LN-, HER2- versus €2 238 200 without sick leave costs or €2 103 380 with sick leave, if testing is limited to only those with 3,4 < NPI <5,4.

5. DISCUSSION AND LIMITATIONS

5.1. Clinical validity and utility

5.1.1. The evidence

The present overview of systematic reviews on the effectiveness of gene expression profiling and expanded immunohistochemistry tests for early breast cancer shows that most evidence is available for Oncotype DX (RT-PCR) and MammaPrint (micro-array GEP). In general, the evidence is mainly limited to their clinical validity (i.e. prognostic ability), and no RCTs appear to be available yet. For several tests (e.g. Oncotype DX, MammaPrint, Mammostrat), the evidence supporting their prognostic ability is quite strong, but this only gives indirect information about the clinical utility of these tests. Direct evidence (e.g. test-and-treat RCTs, comparative observational studies) evaluating the effect of management strategies incorporating these tests on clinical outcomes (i.e. survival, recurrence, etc.) is generally lacking. Would the GRADE system have been used in this report to assign a level of evidence to the conclusions (see KCE processes, http://processbook.kce.fgov.be/node/51), the indirectness of the evidence concerning patient-important outcomes such as survival would have immediately led to a downgrading to low or very low level evidence, even though the level of prognostic evidence is high in itself. However, the GRADE Working Group has not yet developed a method to evaluate prognostic evidence, so no grading system was used in the present report. If a RCT would have been available, the GRADE methodology for therapeutic interventions would have been used.

5.1.2. Limitations

An important limitation of our review of the clinical literature is the pragmatic approach chosen by doing a review of reviews. The rationale behind this choice is that from a pre-assessment of the literature it was clear that on the one hand high-quality recent reviews are available and on the other hand the evidence is currently limited to observational studies. Important consequences of our approach are that interpretation bias (i.e. interpretation of data by other reviewers) is introduced and that the most recent observational studies are not included. However, our estimation is that these studies would only have a small impact on the present conclusions. For

example, experts consulted during the current project mentioned the study of Drukker et al.[72], being one of the few prospective studies on this topic. This observational study prospectively evaluated the clinical validity of MammaPrint in a cohort of 427 patients with T1-3N0M0 breast cancer. No significant difference was found in five-year distant-recurrence-free interval between systematically untreated patients with a concordant low risk assessment and patients with a MammaPrint low-risk result even with a high-risk assessment by Adjuvant! Online (95.3% vs. 98.4%, p=0.29). No data on clinical utility in terms of effect on clinical outcomes are available from this study. However, the authors reported that in the 70-gene signature low-risk group 15% (33/219) of the patients received adjuvant chemotherapy, versus 81% (169/208) in the high-risk group. A limitation of the study, which was acknowledged by the authors, is that the treatment decisions were based on the (restrictive) Dutch guidelines of 2004 and doctor's and patients' preferences. Equality of prognosis between groups that did or did not receive adjuvant chemotherapy could therefore not be guaranteed (selection bias).

An ideal design to evaluate GEP and/or expanded IHC tests would be a RCT where an eligible population of women with early breast cancer is randomized to a treatment arm where the results of the test are not taken into account and a treatment arm where the results are taken into account for management decisions. However, such trials are costly and require a large sample size [73]. At least three RCTs with a somewhat different but acceptable design are currently ongoing (TAILORx, MINDACT, GERICO 11), but their first results are not expected before the end of 2015. In the TAILORx study, women with node-negative, estrogen-receptor positive HER2-negative breast cancer meeting 'standard criteria' for adjuvant chemotherapy are evaluated with Oncotype DX. Those with Oncotype DX low risk receive endocrine therapy alone, those with Oncotype DX high risk receive chemotherapy and endocrine therapy, and those with an intermediate risk (i.e. score of 11-25) are randomized to endocrine therapy alone or a combination of adjuvant chemotherapy and endocrine therapy. Similarly, in the French GERICO 11 study, elderly women with node-negative, estrogen-receptor positive HER2-negative T1-3 breast cancer and a high risk based on the Genomic Grade are randomized to hormonal therapy or a combination of adjuvant chemotherapy and hormonal therapy. Finally, in the MINDACT study, women with node-negative or up to 3 positive nodes T1-3N0-1M0 breast cancer have their risk assessed by MammaPrint and a modified version of Adjuvant Online (which includes HER-2 status). Those with high risk by both risk assessment methods receive chemotherapy (and endocrine therapy if ER+) and those with low risk by both methods do not receive chemotherapy and receive endocrine therapy if ER+. Those with discordant results by both methods are randomized to method of risk assessment, i.e. to follow what MammaPrint indicates (high risk to receive chemotherapy and low risk not to receive) or follow what Adjuvant Online indicates (high risk to receive chemotherapy and low risk not to receive).

Once the results from these trials are made public, an update of this report would be recommended. The status of the present report should therefore be considered preliminary.

An additional limitation of our review was the fact that only one reviewer quality appraised the included reviews and performed the data extraction.

5.2. Cost-effectiveness

5.2.1. The evidence

Despite the lack of randomized controlled trials up to date, looking at the clinical utility of these tests, we decided to still review the economic evidence available up to date for two reasons. First, there is a need to highlight current data gaps for Belgium. For example, there are at present limited or no data on the baseline population receiving chemotherapy, the current risk stratification systems most commonly used and the proportion of patients for which risk is unclear under standard practice, as well as the proportion of patients who - following a testing strategy - would be treated with chemotherapy. Such data could be captured by means of a registry and would facilitate a better understanding of the role and value of these tests in the Belgian context.

Second, there is a growing body of cost-effectiveness studies in this field of high methodological quality that deserves some attention and interpretation. In this regard, there is a high level of consistency which appears to indicate that GEP or expanded IHC tests are likely to be cost-effective compared to standard practice and should help to reduce current chemotherapy levels by better targeting the treatment and limiting it to those most likely to benefit

from it. However, such results should be interpreted with great caution in view of the important limitations identified during our review.

5.2.2. Limitations

The main limitation relates to the need to combine and model multiple sources of data given the fact that there are no studies following patients from the time of testing to final health outcomes. Such combinations increase, as already mentioned on section 5 of our report, the uncertainty surrounding the 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, standard practice, etc). Furthermore, the importance of certain variables such as population characteristics or standard practices on the overall results makes the extrapolation and generalizability of those results to the Belgian context, not advisable.

The grey literature was excluded from our study.

5.3. Budgetary impact

5.3.1. Preliminary estimations

Our budgetary estimations show that limiting testing to a subpopulation of patients for which the risk of recurrence is unclear according to current methods of stratification (e.g. NPI score) is likely to be an economically more attractive option. Nevertheless, the introduction of these tests in clinical practice is not likely to bring in savings in the short term from a health insurance perspective. This is expected, given that budgetary impact models focus on the short term and, as such, rely completely on the cost of testing and chemotherapy spared. Thus, the cost of distant recurrence or long-term adverse events, important cost drivers in economic evaluations on cancer, are not included. A cost-effectiveness model taking into consideration these important factors would ideally be fed with data from the ongoing prospective RCTs on Oncotype DX, MammaPrint and Genomic Grade (TAILOR-X, MINDACT, and GERICO 11) combined with data from Belgian registries on patient characteristics and standard practices.

Our analysis is carried out from a healthcare payer perspective, although estimations taking into consideration sick-leave over the chemotherapy treatment period were also explored. If a societal perspective would have been preferred, full productivity costs would have been included, and the overall results would have been more positive towards testing, since following chemotherapy has been shown to be a crucial predictor of rates of return to work in primary breast cancer patients[74, 75]. On this same line, Broeckx et al.[76] found that productivity costs account for as much as 86% of the total mean costs of breast cancer in Belgium (€107 456 over a period of 6 years).

Our budget analysis focuses on Oncotype DX, given that it is the test for which there is up to date more evidence, but also because it is the most expensive test according to the literature reviewed. Bearing in mind these factors the illustrative calculations here included are likely to represent an overestimation of the real impact that the introduction of these tests are likely to have in Belgium.

5.3.2. Limitations

Our estimations are no exempt of limitations and in particular, there is a crucial factor that should be highlighted. This relates to patients classified as having an intermediate risk according to Oncotype DX. Although the clinical evidence from Paik et al[62]. does not appear to show a large benefit from treating this risk group with chemotherapy (relative risk 0,61; 95%CI 0,24-1,59; p=0,39), it is highly unlikely that none of them would be considered for such treatment. Furthermore, the low rates of chemotherapy, used for the overall target population, (i.e. 15% of ER+, LN-, HER2- early breast cancer patients in 2008 in Belgium), make the proportion of these intermediate risk patients to be treated with chemotherapy a determinant cost factor. If a large proportion of these patients was treated with chemotherapy, then the amount of chemotherapy offered overall may not diminish when compared to a strategy without GEP testing. Indeed, the chemotherapy treated population could even increase. This would be in contrast with the general findings from the published evidence in which a decrease in chemotherapy was consistently reported. In this regard, it should be stressed that the departing chemotherapy rates used in the economic evaluations summarised in section 5 for ER+, LN- populations were noticeably higher, (from 26%[54] to 69%[52]), than those shown in the data from the Belgian Cancer Registry, which makes reducing current chemotherapy rates in this country more challenging than in others where the approach appears to be more aggressive.

Despite the negative short term budgetary impact that an increase in the number of patients receiving chemotherapy could have, it is important to highlight that, if the tests helped to identify patients at high risk of recurrence and likely to benefit from chemotherapy treatment, who would otherwise not have been identified and treated, this could in turn still bring savings in the long-term as it can be illustrated with an example from the published literature in this topic with Holt et al. 2013 concluding that Oncotype DX is cost-effective but finding that its use was linked to an increase in terms of budgetary impact when compared to not testing patients.

Further limitations include the need to use expert opinion in order to populate our model and estimate the cost of these tests in the Belgian context. There are at present no real Belgian data available on specific chemotherapy regimens for this specific population, and according to the discussions held with the experts, clinical practice differs greatly from one centre to another. Thus, our calculations provide a very simplified vision of what truly happens in clinical practice. The data used to identify the size of the target population as well as the proportion of them currently receiving adjuvant chemotherapy dates from 2008 and these could have changed to a certain extent in the last years.

At present, there is no agreement either on the proportion of the target population for which it is difficult to make decisions regarding chemotherapy treatment. During our discussions with experts, a proportion of 10% was mentioned, but this was thought to differ from one centre to another depending on their current risk stratification systems or their chemotherapy treatment approach amongst other factors. In our estimations we used the NPI tool as an objective measure of patients with an intermediate risk of recurrence, but whether this is commonly used in Belgium and how much influence it has on current treatment decisions is to this date unknown.

All of the above mentioned limitations highlight the importance of considering our calculations as an approximation to the real impact that these tests are likely to have in budgetary terms. Nevertheless, they offer a good insight into the current data gaps that would still need to be filled to ensure the Belgian situation can be modelled and studied in enough detail. Those data gaps have been taken into consideration at the time of drafting our recommendations to policy makers, health care providers and researchers.

5.4. Other limitations

Overall, the rapid nature of this review has as a further implication, i.e. the limited consideration of the ethical aspects that the use of these tests may bring. The extent to which patients may be willing to accept the test results, as a fundamental part of treatment decisions, as well as the inequalities that could potentially arise if these tests are only available to patients who can afford them, are important factors that should be further explored and debated.

RECOMMENDATIONS[a]

To the Minister of Public Health and Social Affairs

In view of the available evidence on the prognostic value of Gene expression profiling and expanded IHC tests but the lack of data on their clinical utility, we recommend to temporarily fund a pilot study evaluating these tests only in ER+, LN-, HER2- early breast cancer patients.

The types of laboratories participating in the pilot study should reflect the reality of the Belgian current situation (mix of sizes, academic versus non-academic, etc.)

Participation in the pilot study should be conditional to the collection of data on:

- **Risk stratification scores by means of validated tools (such as NPI or Adjuvant Online !) for the whole ER+, LN-, HER2- early breast cancer population**
- **A declaration of intention to treat (chemo yes/no) prior to using the test, and justification of that intention, after discussion in a Mutidisciplinary Oncological Consultation (MOC)**
- **Choice of test and risk score obtained, for each patient in which the test is used. The choice of test should be left open to drive competition, but the laboratory performing the test should be ISO15189 accredited for performing the test.**
- **A clear mention of the treatment offered post-test and details on the specific adjuvant chemotherapy regimen provided.**

To the research community:

- **A full HTA should be undertaken as soon as the data from the ongoing prospective RCTs become available (results not expected before the end of 2015 – MINDACT; 2016-2017 – GERICO 11 and end of 2017 – TAILORx trials). The data from the pilot study should facilitate the development of a cost-effectiveness evaluation for Belgium.**
- **The clinical validity and utility as well as the economic value of these tests on the LN+ population should be further explored (very limited evidence available up to date).**
- **The reproducibility and reliability of IHC4 should continue to be explored in order to facilitate a wider acceptance and use of this more economical testing option**

[a] The KCE has sole responsibility for the recommendations.