Research Article

Journal of Comparative Effectiveness Research

Long-term cost–effectiveness of Oncotype DX® versus current clinical practice from a Dutch cost perspective

Introduction: This study analyzes the incremental cost–effectiveness of Oncotype DX® testing to support adjuvant chemotherapy recommendations, versus current clinical practice, for patients with estrogen receptor-positive (ER+), node-negative or micrometastatic (pN1mic) early-stage breast cancer in The Netherlands. **Methods:** Markov model projecting distant recurrence, survival, quality-adjusted life years (QALYs) and healthcare costs over a 30-year time horizon. **Results:** Oncotype DX was projected to increase QALYs by 0.11 (0.07–0.58) and costs with €1236 (range: -€142–€1236) resulting in an incremental cost–effectiveness ratio of €11,236/QALY under the most conservative scenario. **Conclusion:** Reallocation of adjuvant chemotherapy based on Oncotype DX testing is most likely a cost-effective use of scarce resources, improving long-term survival and QALYs at marginal or lower costs.

Keywords: adjuvant chemotherapy • breast cancer • economic evaluation • gene expression • healthcare costs • life expectancy • quality of life

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Approximately 14,000 women in The Netherlands are diagnosed with breast cancer each year. Breast cancer remains the most common type of cancer in women and is one of the most common causes of death for women between the ages of 30 and 59 years in The Netherlands [1,2]. Patients presenting with early-stage, estrogen receptor-positive (ER+) breast cancer preferentially benefit from adjuvant endocrine therapy, as demonstrated in large randomized controlled trials [3,4]. The benefit from chemotherapy in terms of preventing or delaying distant recurrence after primary surgery, however, is uncertain and present in a small group of patients with this type of cancer. Despite this, current Dutch consensus guidelines, based on standard clinical-pathological criteria, still recommend adjuvant chemotherapy plus endocrine therapy for the majority of these patients [5]. Consequently, a complex decision concerning this patient category is whether to prescribe adjuvant chemotherapy treatment in addition to endocrine therapy [6–12]. On the one hand, this complexity is due to difficulties in capturing disease heterogeneity, incorporating tumor size, patient age and histology as risk factors [13–15]. On the other hand, adverse events related to chemotherapy treatment are experienced by almost all patients, varying in severity from hair loss to death [13]. Besides the clinical pros and cons, the use of chemotherapy is associated with high costs [16,17]. The high rate of chemotherapy prescription in early-stage ER+ breast cancer patients indicates that a significant number of patients might undergo chemotherapy treatment despite a low recurrence risk, and therefore have only a limited possibility of achieving the health benefits. Consequently, there is a need for a predictive tool to help guide the decision to prescribe adjuvant chemotherapy, which may reduce both the burden and cost of breast cancer management [15–17].

Recently, molecular assays to predict risk and treatment response for early stage breast cancer patients have become commercially available [18]. Of these, the Oncotype DX®

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assay has shown to provide both predictive and prognostic information, beyond traditional parameters, in node-negative (N0) and node-positive (N+) hormone receptor-positive disease [19–23]. This assay predicts both the 10-year recurrence risk of breast cancer as well as the expected benefit of adjuvant chemotherapy treatment [2]. The recurrence score (RS) is expressed in a numeric value between zero and 100 using a proprietary algorithm. This score is used to stratify patients in three risk groups: low, intermediate and high risk of disease relapse [24]. The correlation between the Oncotype DX Recurrence Score (RS) and both distant recurrence and/or survival, and the benefit from chemotherapy, has been reported by Paik *et al.* in two prospective analyses of archived tissue from randomized clinical trials (NSABP B-14 and B-20) [19,20]. Results of this analysis indicated that Oncotype DX independently predicts the 10-year recurrence risk of breast cancer, as well as the response to adjuvant chemotherapy treatment [17,20]. Recently, Carlson *et al.* (2013) reported that, based on a meta-analysis of 21 studies, Oncotype DX changed overall treatment recommendations in 33.4% of patients [25]. They also found that high RS patients were significantly more likely to follow the treatment suggested by Oncotype DX than low RS patients (RR: 1.07 [95% CI: 1.01–1.14]). While the clinical and patient benefits of Oncotype DX are compelling, these have to be balanced against the costs of the Oncotype DX assay (€3180), and the potential downstream cost impacts. This study analyzed the incremental cost–effectiveness of Oncotype DX testing to support adjuvant chemotherapy decision-making versus current clinical practice in treatment of patients with ER$^+$, node-negative or micrometastatic (pN1 mic) early-stage breast cancer in The Netherlands.

Methods

Analytical framework

A Markov model was developed using Microsoft Excel (Redmond, WA, USA) to model the recursive disease processes, including the annual risk of recurrence and mortality. The model is based on the original model structure by Hornberger *et al.* [18], which was initially developed for a NICE submission in England and Wales and has been adapted to the Dutch setting, in accordance with the applicable pharmacoeconomic guidelines [26]. The analysis was performed from a

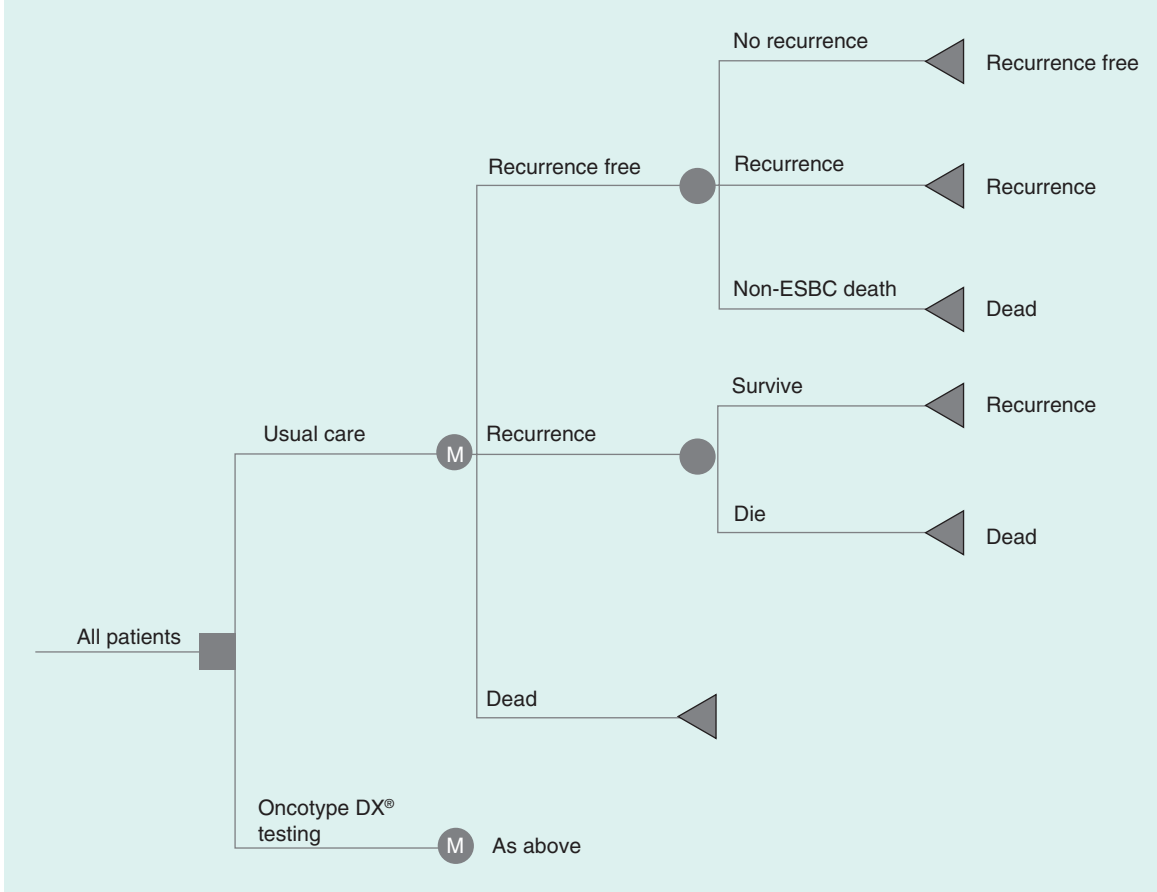

Figure 1. Overview of model structure.
ESBC: Early-stage breast cancer.

Table 1. Summary of clinical input parameters.

Variable	Mean	SE (minimum; maximum)	Distribution	Study (year)	Ref.
Age (years)	60.55	6.06 (18; 80)	Normal	Dutch Cancer Registration (2013)	[28]
Net change in chemotherapy use with low RS (%)	-18.60	1.86 (-20.50; -9.30)	Normal	Albanell (2012)	[29]
	-20.95	2.10 (-20.50; -10.48)		Holt (2013)	[31]
	-20.00	2.00 (-20.50; -10.00)		Eiermann (2013)	[30]
	-18.67	1.87 (-20.50; -9.34)		Carlson (2013)	[25]
Net change in chemotherapy use with intermediate RS (%)	7.5	0.75 (3.75; 11.25)	Normal	Albanell (2012)	[29]
	1.90	0.19 (0.95; 2.86)		Holt (2013)	[31]
	-0.50	0.05 (-0.75; -0.25)		Eiermann (2013)	[30]
	-3.21	0.32 (-4.82; -1.61)		Carlson (201)	[25]
Net change in chemotherapy use with high RS (%)	1.90	0.19 (0.95; 2.85)	Normal	Albanell (2012)	[29]
	4.76	0.48 (2.38; 7.14)		Holt (2013)	[31]
	1.60	0.16 (0.80; 2.40)		Eiermann (2013)	[30]
	4.42	0.44 (2.21; 6.63)		Carlson (2013)	[25]
10-year risk of recurrence (low RS) on endocrine therapy (%)	3.20	1.60 (1.60; 4.80)	Normal	Paik (2006)	[20]
10-year risk of recurrence (intermediate RS) on endocrine therapy	9.10	4.30 (4.55; 13.65)	Normal	Paik (2006)	[20]
10-year risk of recurrence (high RS) on endocrine therapy (%)	39.50	7.30 (19.75; 59.25)	Normal	Paik (2006)	[20]
RRR with chemotherapy (low RS) (%)	0	N/A (0.00; 20.00)	Fixed	Assumption based on Paik (2006)	[20]
RRR for chemotherapy (intermediate RS) (%)	39.0	4.43 (19.5; 58.5)	Normal	Paik (2006)	[20]
RRR for chemotherapy (high RS) (%)	74.0	3.95 (37.0; 100.0)	Normal	Paik (2006)	[20]
Postrecurrence survival (years)	3.3	0.330 (1.65; 4.95)	Normal	Thomas (2009)	[32]
Mortality rates	Indexed by age	N/A	N/A	Central Bureau of Statistics of The Netherlands (2012)	[33]

HT: Hormone/endocrine therapy; N/A: Not applicable; RRR: Relative risk reduction; RS: Recurrence Score; SE: Standard error.

Dutch healthcare payer's perspective comparing the clinical outcomes and costs of 'Oncotype DX testing' to 'current clinical practice' involving clinical–pathological assessment, over a time horizon of 30 years. The model made projections of life expectancy, quality-adjusted life expectancy and direct costs, based on recurrence rates for low-, intermediate- and high-risk patients as well as country-specific mortality data. The model structure is outlined in Figure 1.

Three Markov health states are defined to estimate the cumulative costs and QALYs based on hypothetical cohorts of 100 women with ER$^+$, node-negative, or single node positive early-stage breast cancer. All patients in the model start in the 'recurrence-free' state, and in each 1-year cycle of the simulation, patients might experience either a recurrence or mortality event, and might therefore transition to either the 'recurrence' or the 'dead' state (absorbing state). Transition probabilities between the three health states are based on Hornberger *et al.* [27]. To avoid systematic over- or underestimation of survival in the model, half-cycle correction was performed.

Patient population & comparators

Starting age of the cohort was 60 years, which is the median age of incident breast cancer cases as reported

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Table 2. Chemotherapy costs and adverse events.

Description	Dose/comment
50% patients 3× FEC 3× docetaxel treatment regimen	Mean 180 mg per patient per session (derived from expert)
50% patients 6× TAC treatment regimen	Taxotere/doxetaxel = 1.8 × 75 = 135 mg per session per patient Adriamycine/doxorubicine = 1.8 × 50 = 90 mg per session per patient
G-CSF use with docetaxel	Included in DRG
G-CSF use with TAC	Included in DRG
Add-on DRG for docetaxel	€4.07 per mg [36]
Add-on DRG for doxorubicine	€23.56 per mg [36]
DRG for intravenous/intrathecal chemotherapy in nonmetastatic tumors, nonclinical	95% of patients (derived from expert), average tariff of €1225.64 as derived from publicly available data of 73 Dutch hospitals. Six DRGs per chemotherapy
DRG for intravenous/intrathecal chemotherapy in nonmetastatic tumors, with side effects requiring hospitalization	5% of patients (derived from expert), average tariff of €4409.91 as derived from publicly available data of 73 Dutch hospitals. Six DRGs per chemotherapy

DRG: Diagnosis-Related group; FEC: Fluorouracil, epirubicin, cyclophosphamide; TAC: Docetaxel, adriamycine, cyclophosphamide.

by The Netherlands Cancer Registration [28]. In current clinical practice, patients receive endocrine therapy and 3rd-generation chemotherapy regimens according to Adjuvant! Online and the Nottingham Prognostic Index. Therapy recommendations in current clinical practice for low, intermediate and high risk were based on the study of Albanell *et al.* [29]. The net change in the percentage of chemotherapy (CT) use following Oncotype DX testing was also extracted from Albanell *et al.* for the base case analysis. In addition, we modeled the net change in % CT use as reported in a German cohort (Eiermann *et al.* [30]), in a British cohort (Holt *et al.* [31]) and based on additional data from the Carlson *et al.* [25] meta-analysis as provided by the authors. Data input for the base case (Albanell) and alternative analyses (Eiermann, Holt and Carlson) are specified in Table 1 [25,29–31].

Event rates

Data on recurrence risks associated with endocrine therapy and relative risk reduction associated with chemotherapy, were derived from the NSABP B-20 cohort. These data were evaluated for each simulated patient in each cycle of the model, based on their RS (low, intermediate, or high), as shown in Table 1 [20]. These risks were adjusted based on whether patients were receiving chemotherapy as per the initial recommendation (in the current clinical practice arm) and based on the RS (in the Oncotype DX arm). Relative risk reduction of distant recurrence among low risk patients receiving chemotherapy was assumed to be zero. All recurrence rates are assumed to be independent of age. Nonbreast cancer death was captured as a competing risk in the model. These data were derived from The Netherlands Cancer Registration and based on Dutch female life tables for 2007–2009 [28,33]. For patients experiencing distant recurrence, survival was assumed to be 3.3 years [32]. Long-term adverse events associated with chemotherapy are not captured in the model (including cardiotoxicity, leukemia, and mild cognitive impairment).

Costs

The Markov model incorporates cost of endocrine therapy, cost of chemotherapy and cost of distant recurrence. Cost of endocrine and chemotherapy, and cost of accompanying adverse events, were derived from tariffs of The Netherlands Healthcare Authority (NZA) and expressed in Euros [34]. Costs of endocrine therapy were derived from the NZA and from the official website of the National Health Care Institute, listing medication costs [35]. Endocrine treatment costs are incurred over 8 years, with higher annual costs in years 1–5 and lower costs in years 6–8, reflecting change in treatment intensity over time. One hundred percent therapy compliance was assumed. The treatment cost of the two most commonly used third-generation CT regimens were applied assuming a 50–50 distribution among all patients recommended for CT, as based on communication from physicians of the Leiden University Medical Center in The Netherlands. The first regimen involves six cycles

of TAC (T = docetaxel, A = adriamycine, C = cyclophosphamide), combined with primary G-CSF therapy. The second one involves three cycles of FE100C (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2), and three cycles of docetaxel. For those patients receiving chemotherapy, the costs of chemotherapy and endocrine therapy are both incurred in the first year, indicating an overlap of costs of approximately 3.5 months. Costs of chemotherapy and G-CSF are included in the relevant diagnosis related group (DRG) tariff, which further includes all in- and out-patient activities that a hospital performs following an ICD-10 diagnosis as well as the honorarium for the medical specialists involved. Some medications are not included in the DRGs and, therefore, considered as DRG add-ons. In this case, costs of docetaxel and doxorubicin are add-ons to the DRG, and costs have been derived for an average patient (135 mg docetaxel, 90 mg doxorubicin) [36]. A summary of all costs associated with chemotherapy costs, its adverse events and the corresponding data sources is provided in Table 2.

Other drug costs were derived from the Pharmacotherapeutic Compass [37]. Adverse events associated with endocrine therapy are effectively set to zero, because these costs are incorporated in the DRG tariff. Costs of distant recurrence were derived from a study by Thomas *et al.* including active, supportive and end of life care, and recalculated to 2012 Euros [32]. Total cost of recurrence is incurred at the time of recurrence. Thomas *et al.* stated that the population currently under consideration (ER$^+$ and HER2$^-$), incurred lower treatment costs than ER$^+$ and HER$^+$ patients. While their estimation of mean cost across all groups may thus be an overestimate for this population, it is still lower than that reported elsewhere [38]. Following Dutch pharmacoeconomic guidelines, future costs were discounted at 4% and clinical benefits at 1.5% annually. A summary of the cost variables used is provided in Table 3.

Health utilities

Health utility values were obtained from published literature and were used to calculate the quality-adjusted life-years (QALYs). These scores are quantitative representations of the desirability of a particular health outcome, with a utility of 0 being equivalent to death and a value of 1 equaling perfect health. Health-related quality of life associated with recurrence is taken from Milne, who reported an analysis in New Zealand women with advanced breast cancer, and assumed treatment via endocrine therapy [39]. In addition, a disutility associated with chemotherapy of 0.07 was applied to capture the health-related quality of life impact of chemotherapy in the first model cycle (for those patients recommended chemotherapy in each treatment arm), and this value was taken from Peasgood *et al.* [40]. The health utility associated with one year in the recurrence free state was assumed to be the same during and after endocrine therapy (Connor-Spady *et al.*) [41]. The util-

Table 3. Summary of cost variables in the cost–effectiveness modeling analysis.

Item	Mean cost (€)	SE	Distribution	Ref.
Oncotype DX® test	3180.00	318	Gamma	Genomic Health (2014 list price)
Endocrine therapy (years 1–5)	877.71	87.77	Gamma	DRG tariff derived from the NZa and medicijnkosten.nl [34,35]
Endocrine therapy (years 6–8)	114.27	11.43	Gamma	DRG tariff derived from the NZa and medicijnkosten.nl [34,35]
Chemotherapy	16,433.13	1643.31	Gamma	DRG tariff derived from the NZa and Pharmacotherapeutic Compass [34,35]
Distant recurrence (monthly)	1133.46	113.35	Gamma	Thomas *et al.* (2009) [32]
Endocrine therapy adverse events (years 1–5)	0.01	0.00	Gamma	Not taken into account, conservative
Endocrine therapy adverse events (years 6–8)	0.01	0.00	Gamma	Not taken into account, conservative
Chemotherapy adverse events	0.01	0.00	Gamma	Not taken into account, conservative

SE: Standard error.

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Table 4. Utility scores used in the modeling analysis.

State or event	Mean utility score	SE	Distribution	Study (year)	Ref.
1 year in recurrence-free state	0.78	0.03	Beta	Conner-Spady (2005)	[41]
1 year in recurrence state	0.60	0.03	Beta	Milne (2006)	[39]
Chemotherapy treatment (six cycles)	-0.07	0.01	Beta	Peasgood (2010)	[40]

SE: Standard error.

ity scores used in the modeling analysis are reported in Table 4.

Sensitivity analyses

One-way and probabilistic sensitivity analyses (PSA) were conducted. In the one-way sensitivity analysis, key drivers of model outcome were identified by varying each of the individual input parameters over its predetermined range. Both costs and clinical parameters were varied, and the impact of each on the incremental cost–effectiveness ratio (ICER) was noted. The impact of five (*a priori* determined) key-parameters will be shown in a tornado diagram, namely the mean starting age of the patient cohort, the cost of Oncotype DX, the net change in chemotherapy use following Oncotype DX testing, the ten year risk of recurrence with hormonal therapy, the relative risk reduction (RRR) of recurrence with use of chemotherapy. For the latter three parameters, the sensitivity is evaluated for low, intermediate and high risk separately.

The joint decision uncertainty surrounding the model outcomes was quantified by means of a probabilistic sensitivity analysis (PSA), which employs random draws from predetermined parameter distributions that were defined using the method-of-moments approach [42]. Where reported, distribution parameters (such as standard error [SE] and minimum and maximum values) were taken from literature. When insufficient information was available, the standard error was assumed to be 10% of the mean; maximum and minimum values are assumed at ± 50% of the mean. These assumptions were considered conservative since they are likely to exceed the true variance. The appropriate number of runs to be included in the PSA was estimated based on the mean ICER plotted against the number of iterations of the PSA. Variation in sampling was found to be sufficiently minimized when running the PSA 1000 times.

The model was validated by a third party health economic modeler, who reviewed both the face-validity of the model structure and the formulas used. No further sensitivity analyses were performed to investigate structural uncertainty. An internal validation exercise was performed, to compare model outcomes against the study on which it was based. Results from the NICE model and the validation exercise were found to closely match in both treatment arms (data not shown).

Results

Oncotype DX testing was associated with a notable change in treatment recommendations, of which our base case reflects the most conservative scenario with 18.6% less CT use in low risk patients, and 7.5% and 1.8% more CT use in intermediate and high risk patients, respectively (Table 5). The data from Eiermann *et al.* reflect the scenario with the highest impact of Oncotype DX on the net change in CT use, with -20, -0.5 and +1.6% for low-, intermediate- and high-risk patients, respectively [30].

A scatter plot presenting the base case results from the PSA is shown in Figure 2, depicting the incremen-

Table 5. Summary of changes in adjuvant therapy recommendations with Oncotype DX®.

Recurrence score	Initial recommendation		Post Oncotype® DX		Net change CT (%)
	ET (%)	ET + CT (%)	ET (%)	ET + CT (%)	
Actual treatment					
Low	37.4	20.5	56.1	1.9	-18.6
Intermediate	24.3	8.4	16.8	15.9	+7.5
High	1.9	7.5	0	9.3	+1.8
Total	63.6	36.4	72.9	27.1	

CT: Chemotherapy; ET: Endocrine therapy.
Data taken from [29].

tal costs and QALYs for a cohort of 100 patients. The mean difference in quality-adjusted life expectancy for Oncotype DX versus current clinical practice is 0.11 QALYs per patient, and comes at an incremental cost of €1236 per patient, yielding an ICER of €11,236 per QALY gained. A cost–effectiveness acceptability curve was plotted based on the findings of the PSA with willingness to pay thresholds ranging from €0 per QALY gained to €40,000 per QALY gained. At a willingness to pay threshold of €30,000 per QALY there is a 99.5% probability that Oncotype DX is cost effective versus current clinical practice (data not shown).

Table 6 shows per patient costs, QALYs, life years (LYs) and ICERs for the base case and the alternative analyses. Incremental costs are negative in the analysis based on Eiermann *et al.* data [30] (-€124 per patient) and positive in the three other analyses (range: €325–1236). In all analyses, incremental QALYs and LYs are higher for the Oncotype DX versus the current clinical practice strategy, varying from +0.07 QALYs and +0.07 LYs (Eiermann *et al.* [30]) to 0.58 QALYs and +0.73 LYs (Holt *et al.* [31]). The ICERs range from +€11.236/QALY and +€9.508/LY gained (based on Albanell *et al.* [29]) to dominance (based on Eiermann *et al.* [30]).

The tornado diagram in Figure 3 shows that varying the starting age of the patient cohort has the highest impact on the model outcome, followed by the cost of the Oncotype DX assay, and the net change in chemotherapy use following Oncotype DX testing.

Discussion & conclusion

This cost–effectiveness analysis contributes to the evidence that Oncotype DX is likely to be cost effective compared with current clinical practice in The Netherlands. Oncotype DX testing was associated with a notable change in treatment recommendations based on the data reported in three different original studies and a meta-analysis. Based on these changes, and modeling the long-term risk of distant recurrence based on published trial data, Oncotype DX was projected to improve quality-adjusted life expectancy per patient with 0.11 QALYs and 0.13 life years in the base case analysis, which is also the most conservative.

PSA showed that there was a 99.5% probability that Oncotype DX would be cost effective, at a willingness to pay threshold of €30,000 per QALY gained. One-way sensitivity analyses showed that the cost–effectiveness of Oncotype DX testing was most sensitive to variations in patient age, cost of the Oncotype DX assay and net changes in chemotherapy use in low risk patients. Regarding the latter, it is notable that the studies underpinning this model are very consistent regarding the percentage change in treatment recommendation in the total patient group (varying between 27% [31] and 33% [25,30]), but less so regarding the net change in chemotherapy in the intermediate- and high-risk groups. While we cannot provide a full explanation for this based on the reported data, we observe that a positive net change in chemotherapy in the intermediate-risk group [25,30], and a higher positive net change in the high-risk group [25,31], coincides with a relatively higher proportion of patients classified in each of these groups. That said, in all sensitivity analyses, Oncotype DX was associated with ICERs in the range (€20,000–€80,000) that would be considered cost effective by commonly quoted standards in The Netherlands.

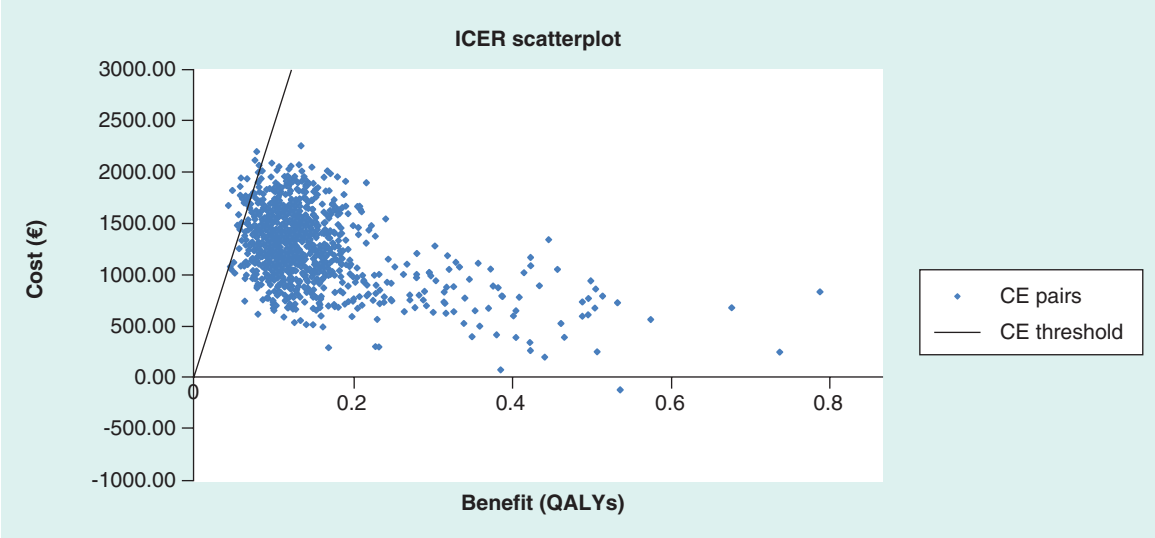

Figure 2. Incremental cost–effectiveness scatterplot.
CE: Cost–effectiveness; ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.

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Table 6. Summary of cost–effectiveness results for the four studies.

	Study	Current clinical practice	Oncotype DX® testing	Difference	Ref.
Cost (€)	Albanell	€13,973	€15,209	€1236	[29]
	Eiermann	€13,973	€13,831	€-142	[30]
	Holt	€13,973	€14,767	€794	[31]
	Carlson	€13,973	€14,298	€325	[25]
Quality-adjusted life expectancy (QALYs)	Albanell	14.66	14.78	0.11	[29]
	Eiermann	14.66	14.73	0.07	[30]
	Holt	14.66	15.24	0.58	[31]
	Carlson	14.66	15.10	0.43	[25]
Life expectancy (years)	Albanell	18.91	19.04	0.13	[29]
	Eiermann	18.91	18.98	0.07	[30]
	Holt	18.91	19.64	0.73	[31]
	Carlson	18.91	19.45	0.54	[25]
ICER (cost per QALY gained)	Albanell	€11,236			[29]
	Eiermann	Dominant			[30]
	Holt	€1369			[31]
	Carlson	€756			[25]
ICER (cost per life year gained)	Albanell	€9508			[29]
	Eiermann	Dominant			[30]
	Holt	€1088			[31]
	Carlson	€602			[25]

Values shown are per patient.
ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.
Data taken from [25,29–31].

The cost–effectiveness analysis can be considered conservative in some regards. First, this analysis did not capture some of the long-term adverse effects of chemotherapy treatment (including cardiotoxicity, secondary leukemia or effects on cognitive impairment). Local recurrence was not captured in the modeling analysis and, given the purported benefits in terms of treatment recommendations with Oncotype DX testing, this may also have led to an underestimation of the clinical benefit of Oncotype DX.

A potential weakness of the analysis is that, in absence of Dutch data sources, it had to rely on long-term clinical data from the USA to estimate the risk of distant recurrence. Also, health-related quality of life utility scores were not Dutch-specific. Ideally, clinical data from a Dutch setting addressing both of these aspects would have been available to support the modeling analysis. Furthermore, information on variance around many of the model inputs was limited and, therefore, assumptions have been made regarding the shape and, in certain cases, the parameters defining distributions for PSA. In most cases, these assumptions have been conservative (overestimating the likely variance). Although sensitivity analyses have not been performed to investigate the impact of changing these assumptions, it is unlikely that any changes within plausible limits would notably alter the findings of the analysis, although specific results and estimates of uncertainty may be influenced.

Although recommending a similar study in the Dutch setting, comparing Oncotype DX versus current clinical practice, might seem obvious, the added value of such research is questionable. First of all, the results of this analysis were generally consistent with those observed in multiple other countries [43,44], with different clinical practices and other cost levels. Second, the high costs associated with performing those studies, and the inevitable burden to patients for participating in a study, are serious considerations to be made. Although no formal Value of Information analysis has been performed, the current analysis shows little decision uncertainty and the one-way sensitivity analyses indicate that other values for key-inputs are unlikely to change the overall recommendation. Instead, with

more prognostic tests coming to the market nationally and internationally, for example, the Mammaprint®, MammaTyper®, PAM50, Endopredict and others [45], head-to-head studies regarding their impact on treatment decisions would provide important and timely information for appropriate, value-based, adoption and reimbursement decisions. Furthermore, while the Oncotype DX is furthest along the validation pathway compared with the other genetic tests mentioned above, the need remains for evaluating the accuracy of the results and predictions of the proprietary algorithms of these tests before definitive conclusions can be drawn on any of them. Prospective studies are needed to do so, while longitudinal (observational) studies can help to understand the relationship between predicted risk and observed risk and hence its real-word impact on clinical outcomes [46].

When recommending more research, urgent attention is also required to the situation that payments for diagnostics do not reflect the cost of evidence generation or the value created [47]. Currently, payments to drug manufacturers are typically based on projections of likely impacts on QALYs and costs, while diagnostic reimbursement tends to be based on cost only. As a consequence, neither the full benefits nor costs of effective stratification are fully reflected in the pricing and reimbursement systems for drugs and diagnostics in most EU healthcare systems including The Netherlands. A system of flexible pricing has been proposed by the Academy of Medical Sciences (2013) that is based on value both for drugs and for diagnostics, to overcome the challenges mentioned above. Yet, in order to base pricing on value, it is necessary that the definition of value also captures the benefits of diagnostics appropriately [48]. The implementation of pricing flexibility could be facilitated by risk-sharing schemes, such as Oncotype DX and the US payer UnitedHealthcare agreed to, whereby they collected information on whether women actually forego chemotherapy when recommended to do so by the diagnostic.

Finally, diagnostic reimbursement is in many countries, including The Netherlands, not always included in the cost of care for outpatients, and is commonly spread across multiple siloed budgets. This means that a test developer may face high barriers to getting a test adopted because of budget constraints and costs falling on other budget silos than those where the gains are enjoyed, even when it has good evidence of cost–effectiveness [49]. Detailed budget impact analyses, which project the potential financial impact of the adoption and diffusion of a new technology into a healthcare system with finite resources, are a means to generate insight in which budget holder is paying for the diagnostic and which one absorbs the downstream cost savings [50]. Potential disincentives can herewith be identified and when budget holders are (held) accountable they could use this information to align the incentives and find a way to adopt a highly cost-effective diagnostic. In The Netherlands, health insurers are particularly well positioned to play a leading role in this, as they negotiate prices for each Diagnostic Related Group with hospitals and primary care groups on an annual

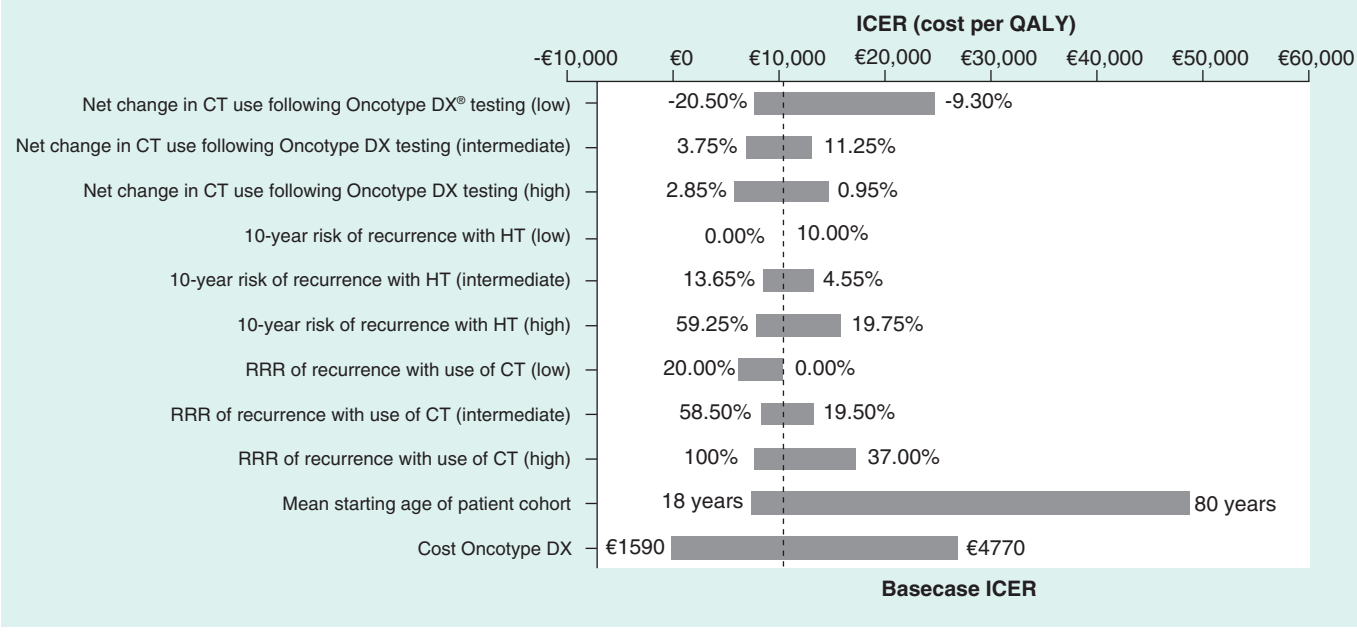

Figure 3. Tornado diagram of one-way sensitivity analyses.
CT: Chemotherapy; HT: Hormone/endocrine therapy; ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year; RRR: Relative risk reduction.

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basis. Given they are one of the major beneficiaries of the significant cost savings due to expensive and ineffective chemotherapies avoided by diagnostics such as Oncotype DX, they have generally been unresponsive as to play a constructive role in this debate.

Future perspective

The Oncotype DX test is currently considered for reimbursement in The Netherlands and other EU countries. In the USA, it is already included in major treatment guidelines for breast cancer and it receives a value-based reimbursement, which is based on clinical data demonstrating the test's ability to restrict healthcare costs. The test is often considered the poster child for other genomic tests that are not linked to one specific drug and herewith encounter the typical drug-diagnostic co-development model. Notwithstanding the appeal of such tests, most countries, except the UK, do not currently have a framework for calculating the added value of stratification and separating the rewards for this between the therapeutic and diagnostic part [47]. Another current challenge is generating the evidence base for the clinical utility and predictive value of these tests. While Oncotype DX and some other genetic assays have been shown to effectively guide treatment decisions, the use of such prognostic tests is not necessarily predictive, and long-term patient outcomes are still unknown. Generating such evidence, requires large prospective studies that take time and substantial investments (from often fairly small diagnostics companies) to be performed. Given the speed at which technology as well as usual care changes for this sector, a strict insistence on randomized control trials, for instance, is increasingly unfeasible and likely leaves a new diagnostic outdated by the time premarket evidence is generated. Therefore, a flexible approach to evidence generation, which balances the need for high-quality evidence with appropriate incentives for innovation, will receive more attention in the future. Adaptive or observational trials designs and the application of advanced analytics to real-world data may well be the way forward, and there is large potential for big data analytics to support such comparative effectiveness studies. As such, Health Technology Assessment bodies, regulators and payers must (re-)consider not only the evidence requirements for informed decision-making, but also the consequences of such demands to healthcare innovation, sustainability and population health.

Acknowledgements

The authors gratefully acknowledge Dr Roth of the Fred Hutchinson Cancer Research Institute and Dr Carlson of the University of Washington (Seattle, WA, USA) to share the crude data of their previously published systematic review and meta-analysis [25] for reanalysis in this cost–effectiveness model.

Disclaimer

All views expressed in this paper are the author's and the author's only.

Financial & competing interests disclosure

Monteban Value Services b.v. and PANAXEA b.v. received funding from Genomic Health Inc. for developing and analyzing the model for The Netherlands. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Rationale

- Oncotype DX® is likely to be cost effective compared with current clinical practice in The Netherlands.
- The assay is expected to improve survival and quality-adjusted life expectancy.

Findings

- The assay comes at an incremental costs of €1236 per patient, yielding an ICER of €11,236 per QALY gained.
- The cost–effectiveness of testing is most sensitive to variations in patient age, assay cost and net changes in chemotherapy use in low-risk patients.
- The results of this analysis were consistent with those observed in multiple other countries.

Discussion

- Even cost-effective diagnostics face high barriers to adoption and reimbursement because their costs and benefits fall on separate budget silos.
- Currently, neither the full benefits nor costs of effective patient stratification are fully reflected in the pricing and reimbursement systems for drugs and diagnostics.

Recommendation

- Future studies should focus on head-to-head comparisons of various assays to provide timely information for adoption and reimbursement decisions.

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