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Original article

Early stage cost-effectiveness analysis of a BRCA1-like test to detect triple negative breast cancers responsive to high dose alkylating chemotherapy

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ABSTRACT

Purpose: Triple negative breast cancers (TNBC) with a BRCA1-like profile may benefit from high dose alkylating chemotherapy (HDAC). This study examines whether BRCA1-like testing to target effective HDAC in TNBC patients can be more cost-effective than treating all patients with standard chemotherapy. Additionally, we estimated the minimum required prevalence of BRCA1-like and the required positive predictive value (PPV) for a BRCA1-like test to become cost-effective.
Methods: Our Markov model compared 1) the incremental costs; 2) the incremental number of respondents; 3) the incremental number of Quality Adjusted Life Years (QALYs); and 4) the incremental cost-effectiveness ratio (ICER) of treating TNBC women with personalized HDAC based on BRCA1-like testing vs. standard chemotherapy, from a Dutch societal perspective and a 20-year time horizon, using probabilistic sensitivity analysis. Furthermore, we performed one-way sensitivity analysis (SA) to all model parameters, and two-way SA to prevalence and PPV. Data were obtained from a current trial (NCT01057069), published literature and expert opinions.
Results: BRCA1-like testing to target effective HDAC would presently not be cost-effective at a willingness-to-pay threshold of €80.000/QALY (€81.981/QALY). SAs show that PPV drives the ICER changes. Lower bounds for the prevalence and the PPV were found to be 58.5% and 73.0% respectively.
Conclusion: BRCA1-like testing to target effective HDAC treatment in TNBC patients is currently not cost-effective at a willingness-to-pay of €80.000/QALY, but it can be when a minimum PPV of 73% is obtained in clinical practice. This information can help test developers and clinicians in decisions on further research and development of BRCA1-like tests.

Introduction

The human and economic consequences of resistant triple negative breast cancer (TNBC) are substantial. In the Netherlands, first-line anthracycline-based treatment is ineffective in approximately 40% [1] of 2.797 TNBC women [2], generating additional therapy costs of €17 Million (when treated, for instance, with Erbulin) [3]. Increasing first-line treatment effectiveness seems a promising way forward to decrease both patient morbidity and healthcare costs.

As TNBC is a heterogeneous disease [4], treatment effectiveness could possibly be increased by basing its therapeutic management on sub-classifications. One important example is the absence of BRCA1 gene functionality, also known as BRCA1-like tumors [5]. Approximately 68% of TNBC have this defect, which seems to confer them sensitivity to alkylating agent-based regimens. The largest published study so far (using carboplatin, thiotepa and cyclophosphamide) reports a protective effect of the alkylating regimen vs.

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standard (anthracyclines-based) chemotherapy (SC) in these tumors, yielding a hazard ratio of relapse free survival (RFS) of 0.17 (95% CI: 0.05–0.60, p = 0.05) [6]. Whether this positive result is due to the chemo-sensitivity of BRCA1-like tumors to one specific agent (e.g., carboplatin), the combination, or the fact that the drugs were given at high doses is not known. Yet, a similar patient series treated with high dose ifosfamide, carboplatin and epirubicine (a different intensive regimen containing two alkylators) and retrospectively tested for BRCA1-like, yielded similar promising results (hazard ratio of disease free survival (DFS) of 0.05, 95% CI: 0.01–0.38, p = 0.003)[7]. Thus, it seems that the BRCA1-like profile could serve as a predictive biomarker for high dose alkylating chemotherapy (HDAC) in TNBC.

Prevalence of BRCA1-like is approximated to be 68.000 per 100.000 TNBC [8]. Targeted use of HDAC in this subgroup could substantially improve health outcomes and reduce healthcare spending on ineffective treatment. Yet, HDAC requires peripheral blood progenitor cell transplant (PBPCT) with mean costs per patient of €53.600 [9]. Added to the BRCA1-like testing costs, these represent the additional direct medical costs to society of testing and treating one BRCA1-like patient with personalized HDAC compared to SC. The question therefore is whether these additional costs are offset by the health benefits and the reduction in spending on ineffective treatments. A timely investigation of the relationship between the expected test performance characteristics, its potential clinical consequences and potential cost-effectiveness, is thus warranted.

In order to inform clinicians and developers of BRCA1-like tests that predict response to HDAC in TNBC, we performed an exploratory cost-effectiveness analysis to examine whether BRCA1-like testing to personalize HDAC can be cost-effective compared to current clinical practice. Additionally, we estimated the minimum prevalence of BRCA1-like and the positive predictive value (PPV) required for a BRCA1-like test to render this strategy cost-effective.

Methods

Model overview and structure

We developed a Markov model (2010; Microsoft Corporation, Redmond, WA) to compare the health economic consequences of treating two identical cohorts of TNBC women aged 40 [8] by one of the following strategies: BRCA1-like testing followed by targeted treatment with HDAC (i.e., "BRCA1-like strategy") or no testing and standard (anthracycline based) chemotherapy treatment (i.e., "current practice"), from a Dutch societal perspective over a 20-year time horizon. Costs were calculated in 2013 Euros (€). Future costs and effects were discounted at a rate of 4% and 1.5% per year respectively, according to Dutch pharmacoeconomics guidelines [10].

BRCA1-like strategy: Patients were initially tested for BRCA1-like. Those with the biomarker were assigned to HDAC (4*FEC: Fluorouracil, epirubicin and cyclophosphamide, followed by 1*CTC: Cyclophosphamide, thiotepa and carboplatin), and those without the biomarker to SC (5*FEC). *Current practice*: All patients received 5*FEC. The mean duration of the intervention was of one year. Regimens were based on a previously published randomized clinical trial (RCT) comparing HDAC and SC efficacy in high risk breast cancer (BC) patients [11].

Patients were classified as "respondents" to the assigned chemotherapy when no relapse or death occurred within the first 5-years, and "non-respondents" in the case such an event occurred within the first 5-years. This time-frame was considered a reasonable limit to include all events related to chemotherapy response [1,12,13].

After the intervention, patients entered in the DFS health state of the Markov model (Fig. 1). From this state, transitions to the relapse (R, including local, regional, and distant relapse), death (D) and the same DFS health state were modeled. In year one, patients were assigned the costs and the health related quality of life (HRQoL) weights of the administered chemotherapy. During this year patients could die from toxic events (septicemia and heart failure [11]) or non-BC related events, but they could not relapse. From this year onwards, disease-free patients could relapse or die from a non-BC related event. Patients with a relapse received treatment and could 1) remain in this state and accrue the costs and HRQoL weights of the DFS health state, representing a "cured" relapse; or 2) die from BC or other unrelated cause. We assumed that patients could only develop one relapse.

Model input parameters

Model inputs for clinical effectiveness, transition probabilities (tp), and HRQoL-weights are presented in Table 1.

The BRCA1-like baseline prevalence was assumed 68%, as presented in literature [8]. The test's PPV (proportion of BRCA1-like patients responding to HDAC within the first 5-years) was assumed 72%. This was the average PPV of the BRCA1-like array comparative genomic hybridization (aCGH) test and the BRCA1-like multiplex ligation-dependent probe amplification (MLPA) tests. Both tests have been tested in the 60 TNBC samples from the publication of Vollebergh et al. [6]. The MLPA data is still internal data from the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NKI-AVL). Based on patient level data from the same publication, we estimated the proportion of non-BRCA1-like patients and unselected TNBC patients respondents to SC to be 35%. The proportion of patients with toxic deaths after HDAC were derived from the previously mentioned RCT, which compared HDAC and SC efficacy in high risk BC [11].

The tp of RFS, the tp of BC specific survival (BCSS) and the tps of all-cause mortality for years 1, 2, 5, 10 and 20 were estimated as follows:

- *tp of RFS for respondents* were considered zero over the 20-year time horizon reflecting that respondents, by definition, do not relapse during the first 5-years, and having a relapse later on is unlikely [12].
- *tp of RFS for non-respondents* and the *tp of BCSS for all patients* were derived from two hypothetical survival curves of RFS and BCSS. These were constructed by making use of an exponential model and the assumption that at 5 years, 95% of the patients had an event, relapse or BC death respectively; $S(t) = \exp\{-kt\}$, where k is the hazard rate and t is time. This assumption was confirmed by an experienced oncologist of the NKI-AVL.
- *tp of all-cause mortality* on the survival curve of the cohort were modeled using Dutch life tables [14].

HRQoL weights were obtained from sources using the EuroQoL-5D questionnaire, and attributed to the DFS and R health states [15,16]. The HRQoL-weight for R is the average of local and distant relapse. We assumed that HRQoL was not affected by BRCA1-like testing.

Model costs include testing, chemotherapy, and health state specific costs, all calculated accounting for direct medical, direct non-medical - (i.e., traveling expenses), and productivity losses. Direct medical and direct non-medical costs were derived from literature, the NKI financial department, and Dutch sources on resource use and unit prices [9,10,17,18]. Productivity losses were calculated using the friction cost method [19]. Foreign currencies were exchanged to 2013 euros [20], and the consumer price index was used to account for inflation [21]. A detailed cost break-down is presented in Table 2 and a textual description in the annex.

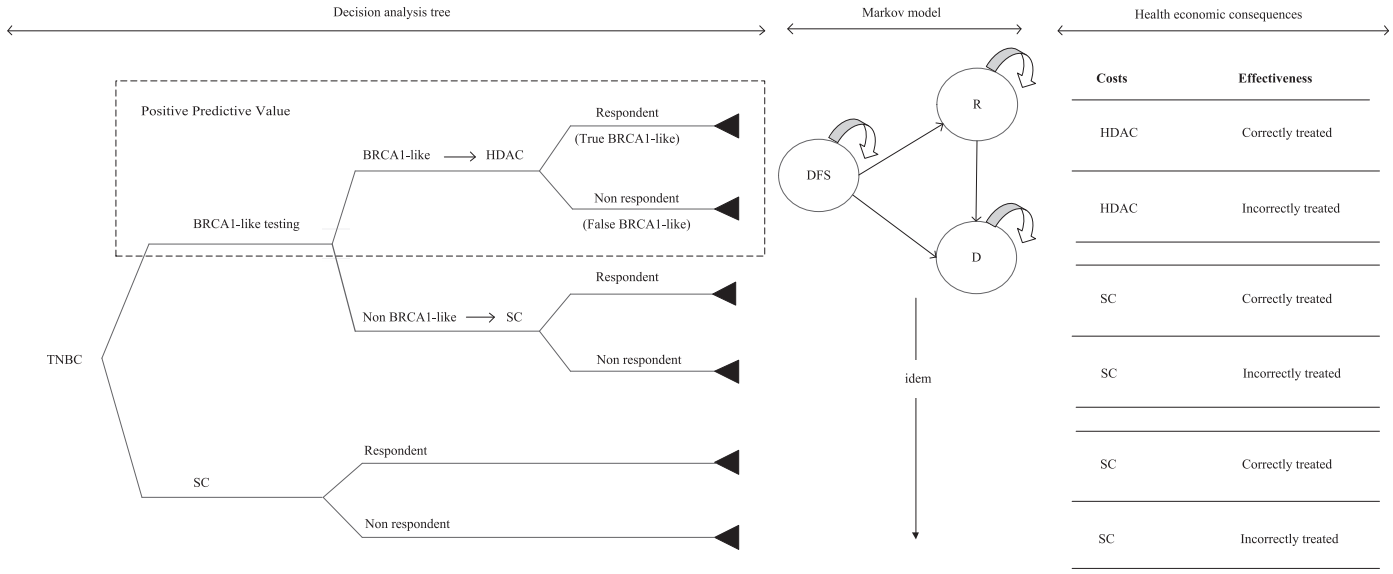

Fig. 1. Decision tree, Markov model and potential health economic consequences of BRCA1-like testing followed by personalized HDAC vs. current clinical practice. The decision analytic tree illustrates the two treatment pathways under study: 1) BRCA1-like testing followed by personalized HDAC and 2) treating all patients with (anthracycline based) SC. After the intervention, all patients enter the Markov model in the DFS state and they accumulate life years, QALYs and costs over a 20-year period based on the assigned transition probabilities. In the end, we expect the main heath economic consequences to be driven by the costs and effectiveness of the treatment received in each patient subgroup. TNBC = triple negative breast cancer; HDAC = high dose alkylating chemotherapy, SC = standard chemotherapy; DFS = disease free suvival; R = relapse.

Table 1
Baseline values for clinical effectiveness parameters, transition probabilities and HRQoL-weights included in the Markov model.

Parameter		Baseline	SE	Distribution parameters	Distribution	Source
Clinical effectiveness						
Positive predictive value (PPV) of the BRCA1-like test		72%	23.00%	2.12, 1.01	Beta	[6], NKI-AVL
Prevalence of BRCA1-like in TNBC		68%	23.00%	2.01, 0.77	Beta	[8]
Non BRCA1-like respondents to standard chemotherapy		35%	23.00%	1.13, 2.14	Beta	[6]
TNBC respondents to standard chemotherapy		35%	9.00%	9.00, 17.00	Beta	[6]
Toxic deaths due to high dose alkylating chemotherapy						
Septicemia		0.004	0.32%	2.00, 441.00	Beta	[11]
Heart failure		0.004	0.32%	2.00, 441.00	Beta	[11]
Transition probabilities						
Relapse free survival (RFS)						
Respondents	Transition probability 1, 2, 5, 10 and 20 years	0.000	–	–	–	Expert opinion
Non-respondents	Transition probability 1 year	0.451	8.00%	18.31, 22.31	Beta	Expert opinion
	Transition probability 2 year	0.248	0.41%	2800.35, 8510.93	Beta	Expert opinion
	Transition probability 5 year	0.092	1.00%	80.50, 793.22	Beta	Expert opinion
	Transition probability 10 year	0.010	0.50%	4.40, 449.57	Beta	Expert opinion
	Transition probability 20 year	0.0002	0.04%	0.43, 1727.13	Beta	Expert opinion
Breast cancer specific survival (BCSS)						
Respondents & non-respondents	Transition probability 1 year	0.000	–	–	–	Expert opinion
	Transition probability 2 year	0.451	7.71%	18.31, 22.31	Beta	Expert opinion
	Transition probability 5 year	0.112	0.84%	157.11, 1251.14	Beta	Expert opinion
	Transition probability 10 year	0.018	0.63%	7.89, 432.11	Beta	Expert opinion
	Transition probability 20 year	0.0005	0.06%	0.63, 1377.88	Beta	Expert opinion
Utilities						
High dose alkylating chemotherapy		0.610	29.00%	0.61, 0.084	Normal[b]	[15]
Standard chemotherapy		0.620	3.93%	0.62, 0.002	Normal	[16]
Relapse[a]		0.732	1.63%	0.732, 0.0003	Normal	[16]
Disease free survival		0.779	3.06%	0.778, 0.001	Normal	[16]

SE = standard error.
[a] Calculated as an average of the utility of local relapse and the utility of distant relapse.
[b] Truncated normal distribution bounded between 0 and 1.

Outcomes

Model outcomes are: 1) the incremental costs; 2) the incremental number of respondents; 3) the incremental number of Quality Adjusted Life Years (QALYs); and 4) the incremental cost-effectiveness ratio (ICER). Incremental cost-effectiveness was assessed against a Willingness-to-Pay threshold (WTP) of €80.000 per QALY, as recommended in the Dutch pharmacoeconomics guidelines [22].

Sensitivity analyses

Probabilistic sensitivity analysis (PSA) was performed in order to quantify the decision uncertainty around the base case scenario by assigning distributions to all stochastic input parameters (see Tables 1 and 2). A beta distribution was assigned to clinical effectiveness parameters and transition probabilities, a normal distribution to utilities, and a log-normal distribution to costs. For costs parameters, we assumed 25% variance of the mean when empirical

Table 2
Baseline costs included in the Markov model.

Input parameters			Unit costs	Unit measure	Mean resource use	Mean cost	SE	Distribution parameters (ln scale)	Source
BRCA1-like MLPA test		Direct medical costs							
		MLPA Kit	€9	Per sample[a]	24[b]	€219	–	–	[33]
		Other lab material	€62	Per 7 samples	3.4	€212	–	–	NKI-AVL
		Technician	€25	Per hour	5.5	€137	–	–	[34]
		Molecular biologist	€40	Per hour	1	€40	–	–	[34]
		Administration	€15	Per run	1	€15	–	–	NKI-AVL
		Depreciation costs	€40	Per run	1	€40	–	–	NKI-AVL
		Direct non-medical costs	€3	Day	0	€0	–	–	[10]
		Loss of productivity costs	€251	Day	0	€0	–	–	[10]
		Total per run (n = 18)	–	–	–	€664	–	–	–
		Total per sample	–	–	–	*€37*	*10%*[c]	*(3.61, 0.01)*	–
Standard chemotherapy (5* FEC)		Direct medical costs	–	–	–	€3.556	–	–	–
		Fluorouracil	€176	1800 mg	2.2	€390	–	–	[35]
		Epirubicine	€147	100 mg	7.2	€1.062	–	–	[35]
		Cyclophosphamide	€45	1080 mg	3.7	€167	–	–	[35]
		Day care	€279	Day	5	€1.393	–	–	[10]
		Oncologist visit	€109	Visit	5	€544	–	–	[35]
		Direct non-medical costs	€3	Day	5	€15	–	–	[10]
		Loss of productivity costs	€251	Day	25	€6.272	–		[10]
		Total	–	–	–	*€9.844*	*25%*	*(9.19, 0.69)*	–
High dose alkylating chemotherapy (4*FEC +1CTC)	4*FEC	Direct medical costs	–	–	–	€59.901	–	–	–
		Fluorouracil	€176	1800 mg	1.8	€312	–	–	[35]
		Epirubicine	€147	100 mg	5.8	€850	–	–	[35]
		Cyclophosphamide	€45	1080 mg	3	€134	–	–	[35]
		Day care	€279	Day	4	€1.114	–	–	[10]
		Oncologist visit	€109	Visit	4	€435	–	–	[35]
	1*CTC	Cyclophosphamide	€45	1080 mg	8.9	€401	–	–	[35]
		Carboplatin	€117	150 mg	17.1	€1.996	–	–	[35]
		Thiotepa	€1.021	1000 mg	0.8	€784	–	–	[18]
		Day care	€279	Day	1	€279	–	–	[10]
		PBPCT[d] harvesting	€13.440	Per patient	1	€13.440	–	–	[9]
		PBPCT	€24.682	Per patient	1	€24.682	–	–	[9]
		Post PBPCT[e]	€15.476	Per patient	1	€15.476	–	–	[9]
	Other	Direct non-medical costs[f]	€3	Day	6	€18	–	–	[10]
		Loss of productivity costs[g]	€251	Day	62	€15.555	–	–	[10]
		Total	–	–	–	*€75.472*	*25%*	*(11.23, 1.07)*	–
Septicemia		Direct medical costs	€27.330	Episode	1	€27.330	–	–	[36]
		Direct non-medical costs	€3	Day	1	€3	–	–	[10]
		Loss of productivity costs	€251	Day	20	€5.018	–	–	[10]
		Total	–	–	–	*€32.351*	*25%*	*(10.38, 0.91)*	–
Heart failure		Direct medical costs	€31.528	Episode	1	€31.528	–	–	[38]
		Direct non-medical costs	€3	Day	1	€3	–	–	[10]
		Loss of productivity costs	€251	Day	6	€1.505	–	–	[38]
		Total	–	–	–	*€33.036*	*25%*	*(10.41, 0.91)*	–
Disease free state[h]		Direct medical costs	–	–	–	€2.872	–	–	[39]
		In & out -patient	€2.793	Episode	1	€2.793	20%	*(7.93, 0.03)*	[39]
		Drugs	€79	Episode	1	€79	25%	*(4.37, 0.01)*	[39]
		Loss of productivity costs[i]	€251	Day	9.4	€2.352	25%	*(7.76, 0.44)*	[39]
		Total	–	–	–	*€5.225*	–	–	–
Relapse state[h]		Local relapse	–	–	–	€22.987	–	–	[39]
		Direct medical costs	–	–	–	€14.833	–	–	[39]
		In & out -patient	€12.497	Episode	1	€12.497	14%	*(9.43, 0.01)*	[39]
		Drugs	€2.336	Episode	1	€2.336	25%	*(7.76, 0.44)*	[39]
		Loss of productivity costs[i]	€251	Day	32.5	€8.154	25%	*(9.01, 0.66)*	[39]
		Distant relapse	–	–	–	€23.313	–	–	[39]
		Direct medical costs	–	–	–	€17.417	–	–	[39]
		In & out -patient	€11.645	Episode	1	€11.645	11%	*(9.36, 0.01)*	[39]
		Drugs	€5.772	Episode	1	€5.772	25%	*(8.66, 0.60)*	[39]
		Loss of productivity costs[i]	€251	Day	23.5	€5.896	25%	*(8.68, 0.60)*	[39]
		Total	–	–	–	*€23.150*	–	–	–
Breast cancer death state[h]		Direct medical costs	€8.296	Episode	1	€8.296	25%	*(9.02 0.66)*	[39]
		Loss of productivity costs[j]	€251	Day	23.5	€5.896	25%	*(8.68, 0.60)*	[39]
		Total	–	–	–	*€14.192*	–	–	–

SE = standard error.
[a] Each BRCA1-like MLPA test requires both patient and control samples, each of them costing €9 of MLPA kit (enzymes and reagents).
[b] 6 control samples are added in each run. With an optimal sample size of 18 samples, this results in 24 samples.
[c] Using the assumption of 25% variance of the mean reported value in a logarithmic scale resulted in a negative value, thus we used 10% instead.
[d] Abbreviation for peripheral blood progenitor cell transplant.
[e] Follow up period were the patient is controlled until recovery of blood activity.
[f] Includes one trip to the hospital for each FEC cycle, and one trip to the hospital for PBPCT (admission and discharge).
[g] We assumed patients did not work during chemotherapy (n = 20), during PBPCT procedures (n = 21) and during the post- PBPCT program (n = 20).
[h] Source did not report traveling expenses, and thus, they were not added.
[i] Indirect costs were calculated by using resource use of Lidgren et al [39] and the friction method as recommended by the Dutch guidelines.
[j] Loss of productivity was assumed to be the same as in the distant relapse health state.

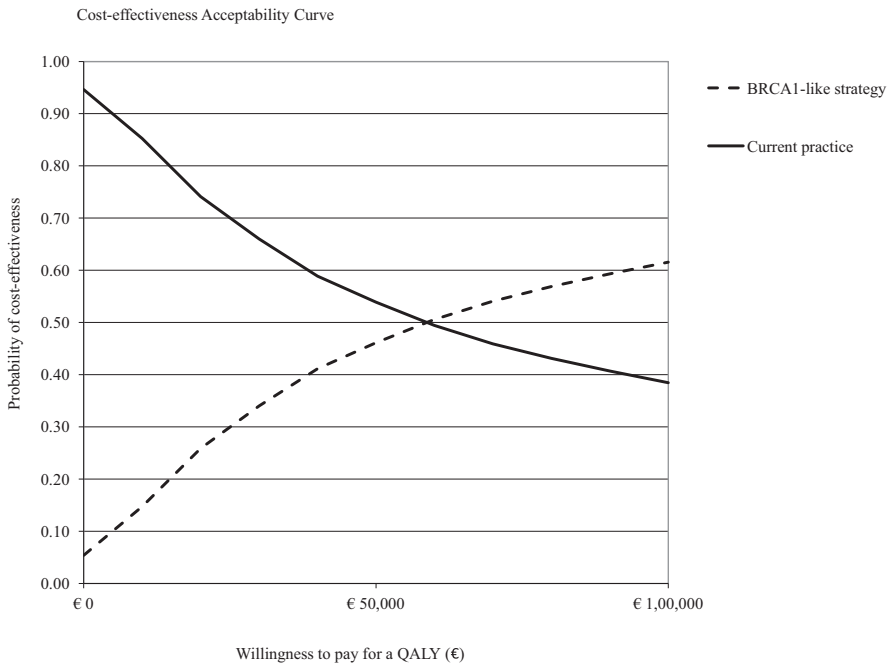

Fig. 2. Cost effectiveness acceptability curves. The BRCA1-like strategy has a 62% probability to be cost-effective when compared to current practice.

estimates of variance were not available. We run the analysis by using Monte Carlo simulation with 10.000 random samples from the pre-defined distributions. Cost-effectiveness acceptability curves (CEACs) were derived from these, to show the decision uncertainty surrounding the expected incremental cost-effectiveness. CEACs are presented at a range (€0 – €100.000) of WTP values for one additional QALY. Furthermore, we plotted the net benefit probability map (NBPM) [23] which shows the evolution of net health benefit over time.

Subsequently, a threshold SA was used to estimate 1) the minimum required prevalence, 2) the minimum required PPV, and 3) the combination, for the BRCA1-like strategy to be cost-effective. The values were initially varied in 20% intervals from 0 to a 100%. Finally, we narrowed the intervals until we found the prevalence (with one decimal place) were the ICER was €80.000/QALY. Furthermore, one-way SA was performed to all parameters, by varying them within one standard deviation of error, or a 25% of their base case value if this information was missing.

Results

Outcomes

Based on our PSA, the BRCA1-like strategy would cost an additional €76.369 per patient while increasing QALYs by 0.93 and the number of respondents by 25%, over a 20-year time horizon. Over this time-horizon, this strategy is expected to have an ICER of €81.981, which is not considered cost-effective. Yet decision uncertainty surrounding the ICER is substantial, with a 62% probability that the BRCA1-testing strategy is cost-effective (Fig. 2). The NBPM illustrates that the BRCA1-like strategy becomes cost-effective only after 20-years (Fig. 3).

Sensitivity analysis

The threshold SA demonstrated that the PPV, but not the prevalence, drives the ICER changes. Only when the PPV and prevalence values are well above 60% the strategy becomes cost-effective (Fig. 4). The minimum prevalence and PPV values at which BRCA1-like testing is expected to be just about cost-effective are 58.5% and 73.0% respectively.

The one-way SA on the remaining model parameters indicated that the effectiveness parameters, the costs of HDAC and the utility of HDAC had the strongest impact on the ICER (Fig. 5) and can change the expectation of cost-effectiveness.

Discussion

This study explored the costs and benefits of BRCA1-like testing followed by targeted treatment with HDAC in TNBC, in order to inform clinicians and developers of BRCA1-like tests on the requirements for this test to potentially become a cost-effective alternative to current clinical practice.

Our base case analysis indicates that the BRCA1-like strategy likely increases the number of respondents by 25% and the number of QALYs by 0.93 over a time horizon of 20-years. However, as indicated by the NBPM, these health benefits are only expected to outweigh the additional €76.369 costs per patient after 20-years, as the costs for testing and HDAC are made in the short term, and the health and financial benefits are recouped in the longer term. Furthermore, decision uncertainty around the ICER remains, and the BRCA1-like strategy is expected to be cost-effective at 20-years with a 62% probability. Threshold SA demonstrated that the PPV, but not the prevalence, drives the ICER, and the lower bounds for these two parameters for the strategy to be cost-effective are 58.5% (prevalence) and 73.0% (PPV). Furthermore, we observed that the effectiveness parameters, the costs of HDAC and the utility of HDAC parameters can affect the cost-effectiveness of the BRCA1-like strategy.

To the best of our knowledge, this is the first exploratory analysis of the potential cost-effectiveness of BRCA1-like testing to target HDAC treatment in TNBC. The results can therefore not yet be compared to other cost-effectiveness estimations. However, key-factors that drive economic value of stratified medicine have been described before and our findings are largely in line with those. Notably, as Trusheim et al. [24], we observed that the therapeutic

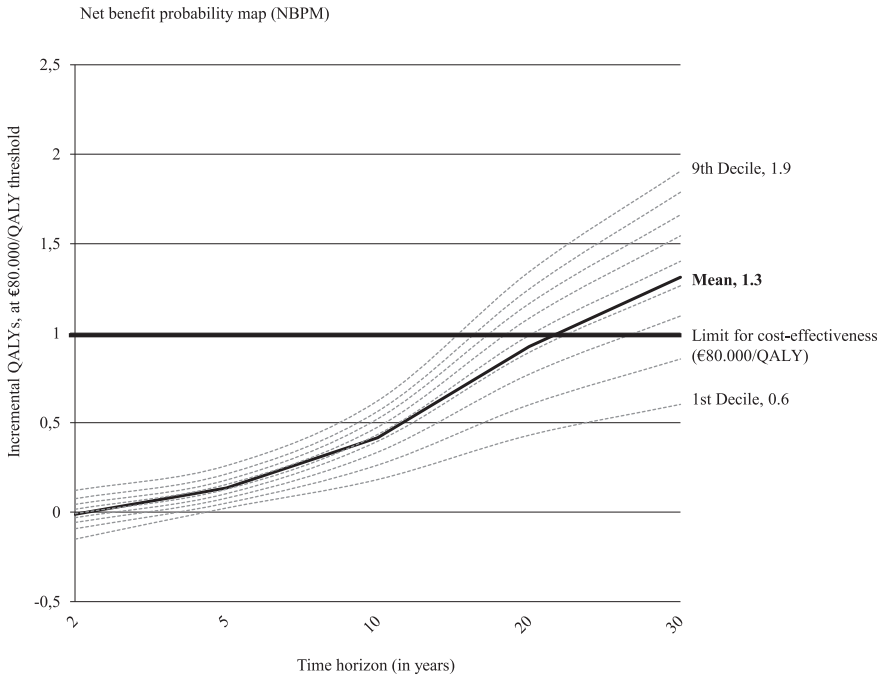

Fig. 3. Net benefit probability map. The BRCA1-like strategy becomes cost-effective only after 20 years, when the cost-effectiveness threshold is met.

effect within the biomarker positive population, the prevalence of the predictive biomarker and the clinical performance of the test drive stratified medicine's economic value. Specifically, we observed that with good therapeutic effect (tps of respondents) and clinical performance of the test (PPV) (note that in our model therapeutic effect in respondents was always good), the BRCA1-like strategy is expected to be cost-effective at a minimum required prevalence (in our study 58.5%). Furthermore, with low test performance, even if prevalence and therapeutic effect are perfect, no good economic value can be derived (Fig. 4).

Given that test performance is crucial for attaining economic value, it is important to realize that several tests for BRCA1-like detection are available [5]. Each test uses different aberrations to characterize the profile, which means that they may yield different

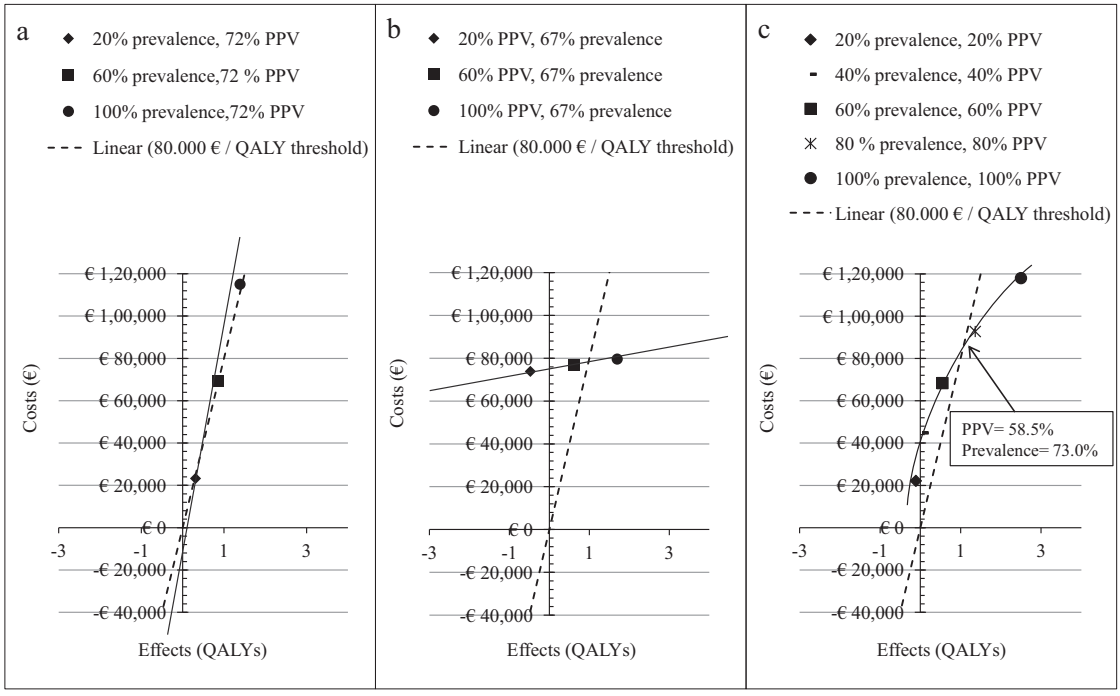

Fig. 4. Threshold sensitivity analysis (SA). a) one-way sensitivity analysis to the prevalence; b) one way SA to the PPV, and c) two-way SA to the PPV and the prevalence. The baseline values for the PPV (72%) and prevalence (67%) were derived from the 10.000 Monte Carlo simulations. The dots falling on the right side of the €80.000 per QALY threshold line are cost-effective results and those falling in the left side of the line are non-cost-effective results. The minimum prevalence and PPV values at which BRCA1-like testing is expected to be just about cost-effective are 58.5% and 73.0% respectively.

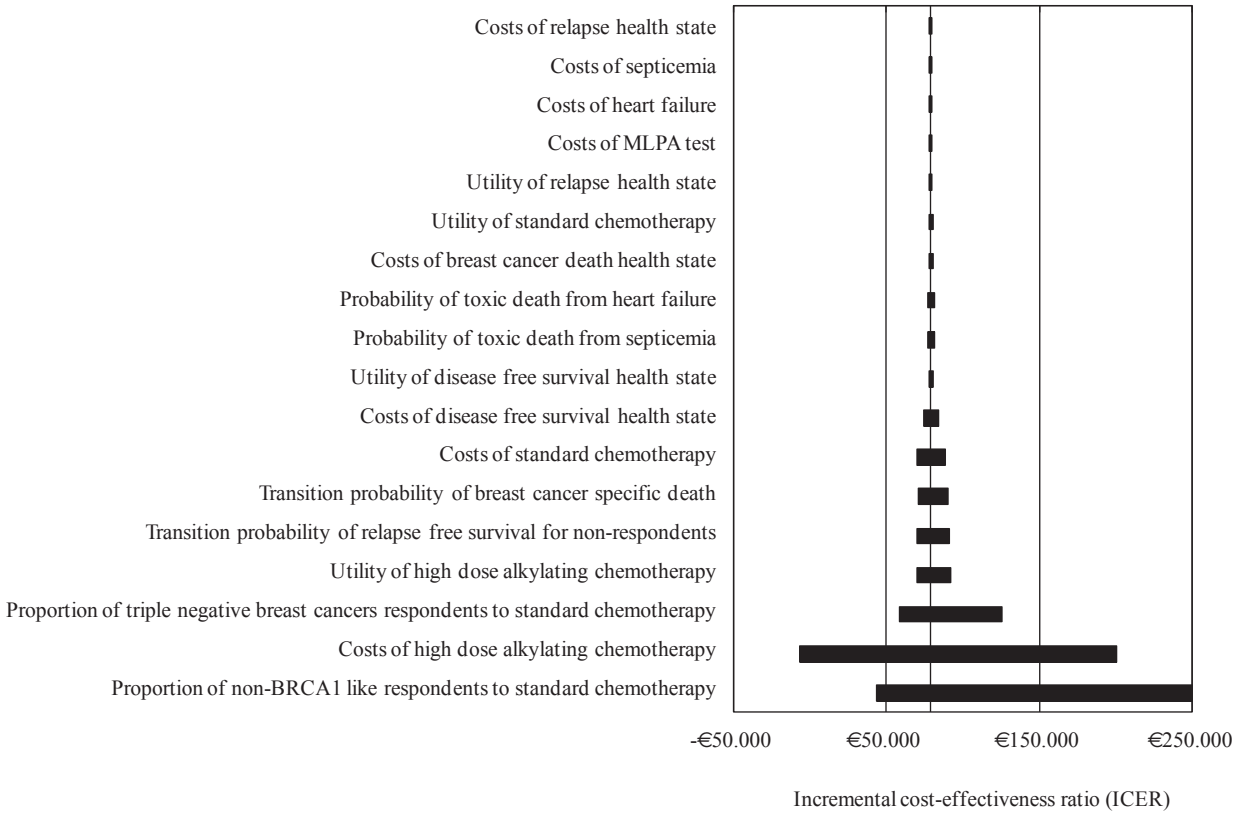

Fig. 5. Tornado plot of one-way sensitivity analyses. The main drivers of the ICER are the effectiveness parameters, the costs of high dose alkylating chemotherapy and the utility of high dose alkylating chemotherapy.

results in terms of clinical effectiveness for specific applications. To our knowledge, the only tests used as predictors of sensitivity to HDAC in TNBC are the aCGH [6,25] and the MLPA [8,26], whose performance data we used in our PSA. Both tests are presently being validated, and from the few available data of these studies (internal NKI-AVL data) it seems that the PPVs for both tests are close to the lower bound of 73.0%.

From a policymaker's perspective, we highlight two important points. First, although incorporating HDAC treatment for TNBC is costly, if based on a BRCA1-like predictive test, the overall strategy costs can be justified by its long-term health benefits. This is of particular relevance to countries such as the United States, in which there is hesitance to cover HD chemotherapy [27,28]. Emergence of clinical and cost-effectiveness data on tests that can better target the usage of such costly treatment, may provide evidence to support coverage for those patients likely to respond. Risk sharing agreements and other reimbursement models might be needed to incentivize this appropriately for both the developers, the care providers and health insurers [29]. However, to support this scenario, further studies on this topic should be performed especially under a United States perspective. Second, although the adoption of a BRCA1-like test requires equipment and expertise to PBPCT, in the majority of Dutch centers that qualify, this would imply practice changes, but no monetary investments would be needed.

Our analysis indicated that the cost-effectiveness of the BRCA1-like strategy is affected by effectiveness parameters and costs. We therefore expect that further analysis of our model with data from other studies using different HDAC regimens and different doses (i.e., the recently published cohort by Schouten et al. [7]) could result in different outcomes.

There are two important limitations of our study. First, we used assumptions for survival based on the TNBC subset of Vollebergh et al. [6]. Second, calculations of per test costs assumed optimal sample turnaround time, i.e. 18 samples per 10 days. Given the prevalence of TNBC in the BC population (2.797/year in the Netherlands [2]), this may be an optimistic assumption. That said, one-way SA reveals that test costs have little influence on the ICER.

Since we present an exploratory cost-effectiveness study performed in early stages of test development, we recommend subsequent cost-effectiveness analyses [30–32] to be performed once new data becomes available from clinical studies. For instance, from the on-going prospective validation study of the BRCA-1like MLPA test (NCT01057069). This study aims at providing evidence on the effectiveness of the BRCA1-like MLPA test to personalize HDAC (using the same regimen as the one used in this study) in TNBC. It can thus contribute information on transition probabilities, on BRCA1-like prevalence, MLPA test' PPV and costs.

Conflict of interest statement

The authors declare that they do not have a conflict of interest.

Disclosures

The authors declare that they had no writing assistance.

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Ethical approval

State approval for this study was not required.

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Annex

Testing costs

The costs of BRCA1-like testing were calculated based on the multiplex ligation-dependent probe amplification (MLPA) test, used in the NKI as part of prospective validation study (TNM study; NCT01057069). This test is suitable for clinical routine practice as it is robust, user-friendly, rapid and commercially available [15]. Costs of testing included (1) technician and laboratory costs to perform the test (material and overheads), (2) molecular biologist costs to interpret the results and generate reports, and (3) administration and depreciation costs. The costs of running the tests were calculated with the optimal test batching of 18 samples per 10 days. The purchasing costs for the MLPA kit were obtained from the MRC-Holland (Amsterdam, the Netherlands) website (SALSA MLPA P376 BRCA1ness probemix [26]). Other laboratory costs, administration and depreciation costs were derived from the financial department of the NKI-AVL, and the personnel costs from the collective labor agreement for Dutch hospitals [35].

Chemotherapy related costs

Medical direct costs of chemotherapy consisted of drug costs, day care costs and medical visit costs. We did not include the costs of radiotherapy because they were assumed equal under both regimens. The costs of chemotherapy were derived from and based on Dutch prices [12,36]. The costs associated to peripheral blood progenitor cell transplant (PBPCT) procedures and subsequent follow up (in the HDAC arm) were derived from the Dutch Healthcare Authority's tariffs [11]. For both regimens we made two assumptions: (1) patients did not work during chemotherapy and (2) visits to the oncologist were scheduled during the chemotherapy days. Therefore, direct non-medical and productivity costs in the conventional regimen included the traveling costs on the days of chemotherapy and the 25 days missed at work. The direct non-medical and productivity costs in the HDAC regimen included one day of traveling costs for admission to the hospital, and productivity losses for 20 days of 4*FEC, 21 days hospitalized for 1*CTC/PBPCT and 21 days post-transplant were the patient is controlled until recovery of blood activity. The costs associated with toxic deaths under the HDAC regimen were obtained from literature [37–39].

Health states costs

The costs of the health states disease free survival (DFS) and relapse (R) were based on Lidgren et al. [39]. Cost of relapse was calculated as an average of local and distant relapse costs. The costs of death were excluded, unless it was consequence of treatment toxicity or breast cancer. In those situations we accounted for the specific costs to treat the toxicity (mentioned in the previous section) and for the palliative treatment.

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