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ORIGINAL RESEARCH
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Value of Research and Value of Development in Early Assessments of New Medical Technologies

Valesca P. Retèl, PhD[1], Janneke P.C. Grutters, PhD[2], Wim H. van Harten, MD, PhD[1,3], Manuela A. Joore, PhD[2,4,]*

[1]*Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, The Netherlands;* [2]*Department of Health, Organization, Policy and Economics, CAPHRI School for Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands;* [3]*School of Governance and Management, University of Twente, MB-HTSR Enschede, The Netherlands;* [4]*Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, The Netherlands*

ABSTRACT

Objectives: In early stages of development of new medical technologies, there are conceptually separate but related societal decisions to be made concerning adoption, further development (i.e., technical improvement), and research (i.e., clinical trials) of new technologies. This article presents a framework to simultaneously support these three decisions from a societal perspective. The framework is applied to the 70-gene signature, a gene-expression profile for breast cancer, deciding which patients should receive adjuvant systemic therapy after surgery. The "original" signature performed on fresh frozen tissue (70G-FFT) could be further developed to a paraffin-based signature (70G-PAR) to reduce test failures. **Methods:** A Markov decision model comparing the "current" guideline Adjuvant Online (AO), 70G-FFT, and 70G-PAR was used to simulate 20-year costs and outcomes in a hypothetical cohort in The Netherlands. The 70G-PAR strategy was based on projected data from a comparable technology. Incremental net monetary benefits were calculated to support the adoption decision. Expected net benefit of development for the population and expected net benefit of sampling were calculated to support the development and research decision. **Results:** The 70G-PAR had the highest net monetary benefit, followed by the 70G-FFT. The population expected net benefit of development amounted to €91 million over 20 years (assuming €250 development costs per patient receiving the test). The expected net benefit of sampling amounted to €61 million for the optimal trial (n = 4000). **Conclusions:** We presented a framework to simultaneously support adoption, development, and research decisions in early stages of medical technology development. In this case, the results indicate that there is value in both further development of 70G-FFT into 70G-PAR and further research.

Keywords: cost-effectiveness analysis, decision modeling, development, early technology assessment, EVPI, EVSI, value of information.

Introduction

In a budget-constrained health care system, regulatory and reimbursement authorities face two separate but related decisions: whether a technology is cost-effective and thus should be adopted, and whether existing uncertainty warrants more research to support this decision [1]. The first decision is answered by choosing the technology with the most favorable expected mean cost-effectiveness. The second decision is informed by the expected cost of uncertainty, determined jointly by the probability that a decision based on existing information will be wrong and the consequences of a wrong decision. In early stages of the development of a new health care technology, often several options concerning the further development of the technology exist. Therefore, a decision could be added: is there value in further development of the new technology? For this decision, it is analyzed whether a further developed version of a technology would be seen as favorable compared with other available technologies. In this analysis, a comparator (the "to-be-developed" technology) is added to the already available comparators usually considered for the adoption decision. Any costs associated with the development of the new technology that would lead to additional costs per patient in the health care system can be incorporated in this analysis. Based on this analysis, regulatory and reimbursement authorities can make recommendations on whether further developed technologies would be favored and become the recommended intervention over and above the other comparators currently in the health care

Conflict of Interest: W.H. van Harten is a nonremunerated, non–stake-holding member of the supervisory board of Agendia BV. All other authors declare no conflicts of interest.

* *Address correspondence to:* Manuela A. Joore, Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, PO Box 5800, 6202 AZ Maastricht, The Netherlands.

E-mail: m.joore@mumc.nl.

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system, and against which price. The analysis provides authorities an understanding of the direction of innovation that could maximize health benefits, given currently available evidence.

An example of an innovative technology in its early stages of development is the 70-gene prognosis signature (MammaPrint™), using microarray analysis for patients with breast cancer [2]. Using the 70-gene signature, the selection of patients who will benefit most from chemotherapy could be more accurate, which reduces unnecessary treatment. The promising results of three retrospective validation studies [3–5] led to a prospective feasibility study (RASTER: MicroarRAy PrognoSTics in Breast CancER) from 2004 until 2006 [6]. This study was followed by a prospective, randomized clinical trial (MINDACT: Microarray In Node-negative Disease may Avoid ChemoTherapy) that started in 2007 [7]. A recent cost-effectiveness analysis showed that the 70-gene signature is cost-effective compared with clinical guidelines, based on the promising retrospective validation results [8]. The analysis was performed from a Dutch health care perspective, based on costs per quality-adjusted life-year (QALY). The incremental cost-effectiveness ratio was €4600/QALY compared with the next best clinical guideline. Given a threshold of €30,000/QALY, the probability of the 70-gene signature being cost-effective compared with usual care was 82%. In this stage, however, the technology was not yet stable and still many opportunities were available to improve the test. Based on the findings of the feasibility study, a specific feature of the test was prioritized for further improvement: the proportion of test failures [6]. As a consequence of failure, no 70-gene signature can be derived. Patients who do not receive a 70-gene signature test result will be treated according to current care [9]. To perform the 70-gene signature, it is essential to collect good-quality breast tumor RNA in fresh frozen tissue (FFT). In most hospitals as a routine, however, tumor samples are directly fixed in formalin and embedded in paraffin blocks. It was observed in clinical studies that the use of FFT leads to more failures compared with using paraffin blocks [6,10]. Also, in a scenario study, 80 breast cancer experts mentioned the necessity to use FFT to obtain the 70-gene signature as an important barrier for the successful use of the 70-gene signature [11]. An opportunity to reduce the proportion of test failures could thus be the further development of the 70-gene signature for use on paraffin blocks. However, in an early phase, it was unclear whether it is valuable to invest in such a development.

Recently, three studies were published focusing on early-stage economic models for medical technologies while acknowledging the uncertainties concerning technology dynamics inherent in such a modeling enterprise [12–14]. Girling et al. [12] presented a method for valuing a new medical technology at the concept stage from the perspective of manufacturers, while Vallejo-Torres et al. [13] and Garrison [14] used an iterative approach of decision analyses by integrating health economic modeling in the product development cycle. To our knowledge, the three integrated proposed decisions (adoption, further research, and further development) have not yet been addressed simultaneously in one study. Furthermore, the application of the government/reimbursement authority perspective for these three decisions has not yet been used. Typically, the costs of reimbursing the intervention will lie with government or third-party payer organizations, the costs of the research to reduce uncertainty on existing interventions could be funded either by government research or by commercial research, while the costs of further development of the technology would usually be investments made by the commercial organization owning the technology, which would in the end be passed on to health service purchasers through the price of a technology. In a health care market, patients (consumers) and doctors (their agents) are not very well placed to assess the value of a new technology, based on a synthesis of all available evidence. Therefore, in our opinion, a health care funder has the responsibility to assess and signal the value of health innovations on behalf of the population [15]. Under the principle of value-based pricing, a societal perspective to assess the value of innovation is appropriate. It informs both the health care funder and the manufacturer on the value of innovation, and thus the maximum budget and price, given a certain threshold per QALY.

The present study adds to the existing knowledge by proposing and applying a framework that simultaneously informs three separate but related decisions: 1) the adoption, 2) further development, and 3) further research of the technology. In this article, we applied the framework to address these three decisions for the "currently" used clinical guideline Adjuvant! Online (AO), the "original" 70-gene signature performed on FFT, and the "to-be-developed" 70-gene signature performed on paraffin blocks.

Methods

Analytical Framework

The analytical framework consists of three decisions (adoption, development, and research). The methodology for answering each of these three questions is described below.

Adoption Decision

The adoption decision depends on the expected net monetary benefit (NMB) of all alternative technologies. Imagine $j = 0$ to T different technologies are considered. These would be numbered $j_0, j_1, \ldots, j_T$. Imagine also that there are uncertain parameters concerning the clinical and economic performance of these technologies, which we denote as a vector θ. And, imagine we have a model that estimates the NMB of treatment j, given particular values of θ such that the NMB = NMB(j, θ) [16]. This, in turn, is based on the estimated health outcomes (H; e.g., QALYs), which is provided by treatment j, for a specific vector of values θ, that is, $H(j, \theta)$ and a cost function $C(j, \theta)$ such that

$$\text{NMB for a specific value of } \theta \text{ is: } \mathrm{NMB}(j,\theta) = \lambda * H(j,\theta) - C(j,\theta) \quad (1)$$

with λ being society's willingness to pay for additional health.

On the basis of the set of technologies, the model, and distributions for the uncertain parameters θ, one can undertake probabilistic sensitivity analysis. This integrates over the uncertain values of θ to estimate the expected NMB of each technology.

$$\text{Expected NMB for treatment strategy } j \text{ is: } E_\theta[\mathrm{NMB}(j,\theta)] \quad (2)$$

And this enables us to estimate the best treatment given current information on the parameters. This best treatment we denote as j^*, which is the particular j that gives the maximum expected net benefit, that is,

$$j^* \text{ is the } j \text{ that gives specific value of } \theta \text{ is: } \max_j\{E_\theta[\mathrm{NMB}(j,\theta)]\} \quad (3)$$

Development Decision

In this article, we argue that further development of one of the technologies (original technology j_{orig} into the technology j_{dev}) is an additional option available to the decision makers. Having this new option changes the decision architecture. First of all, there might be parameters θ_{dev} specific to the developed technology. When added together with the parameters for the existing technologies, these create a new set of uncertain model parameters:

$$\theta_{\mathrm{new}} = (\theta, \theta_{\mathrm{dev}}) \quad (4)$$

Also, we have a new possible strategy for which we will calculate an NMB.

$$\text{NMB of the to–be–developed technology is: } \mathrm{NMB}(j_{\mathrm{dev}},\theta_{\mathrm{new}}) = \lambda * H(j_{\mathrm{dev}},\theta_{\mathrm{new}}) - C(j_{\mathrm{dev}},\theta_{\mathrm{new}}) \quad (5)$$

Incorporated into this NMB are the costs of the to-be-developed technology to society per person receiving the technology, that is, $C(j_{dev}, \theta_{new})$. These costs are, in turn, likely to be a function of the total costs of the development of the technology faced by the manufacturer. These costs will depend on factors such as the nature of the development and may also depend on some of the uncertain parameters θ_{new}. It is reasonable to assume that at least part of these costs will be faced by society (the reimbursement agency) through the price of the developed technology. The proportion of these costs that is faced by society might depend on the relative market size of the jurisdiction, the extent to which the manufacturer needs to recoup development costs, and profit from investments made in this development and others, which may or may not come to fruition. One might conceive of the costs to society per individual recipient of the developed technology j_{dev} as the costs to society of the original treatment j, plus some additional costs of development to be borne by society:

$$C(j_{dev},\theta_{new}) = C(j,\theta_{new}) + C_{DevToSociety}(j_{dev},\theta_{new}) \quad (6)$$

The expected net benefit per individual recipient of the to-be-developed technology j_{dev} given current information is given by

$$E_{\theta new}[NMB(j_{dev},\theta_{new})] = \lambda * H(j_{dev},\theta_{new}) - C(j_{orig},\theta_{new}) - C_{DevToSociety}(j_{dev},\theta_{new}) \quad (7)$$

If the expected NMB of the to-be-developed technology j_{dev} is greater than the expected NMB of the best technology (i.e., if $E_{\theta new}[NMB(j_{dev}, \theta_{new})] > E_{\theta new}[NMB(j^*, \theta_{new})]$), then one would consider j_{dev} to be the most cost-effective of the options available at this time. This implies that there is value to society in developing the technology. The increment between the expected NMB of the to-be-developed technology j_{dev} and the expected NMB of the best technology j^* can be perceived as the expected net benefit of development (ENBD) per individual recipient of the to-be-developed technology j_{dev}:

$$ENBD = E_{\theta new}[NMB(j_{dev},\theta_{new})] - E_{\theta new}[NMB(j^*,\theta_{new})] \quad (8)$$

The population-level ENBD is given by multiplying the ENBD by the number of people affected by the decision over the lifetime of the technology (P):

$$\text{Population ENBD} = P * (E_{\theta new}[NMB(j_{dev},\theta_{new})] - E_{\theta new}[NMB(j^*,\theta_{new})]) \quad (9)$$

Research Decision

On the basis of the model for the adoption and development decision, we can imagine obtaining further information to reduce uncertainty in some or all of the uncertain parameters θ_{new}.

If we imagine having complete certainty on all the parameters, then we would be able to choose the treatment strategy that gives the maximum net benefit without any uncertainty being involved. The expected NMB of knowing the true underlying value of θ_{new} is $E_\theta[\max_j\{NMB(j, \theta_{new})\}]$. Therefore, the expected additional value of knowing the true values of θ_{new}, or the expected value of perfect information (EVPI) [17,18], is

$$EVPI = E_\theta[\max_j\{NMB(j,\theta_{new})\}] - E_\theta[NMB(j^*,\theta_{new})] \quad (10)$$

The population-level EVPI is given by multiplying the EVPI by the number of people affected by the decision over the lifetime of the technology (P):

$$\text{Population EVPI} = P * (E_\theta[\max_j\{NMB(j,\theta_{new})\}] - E_\theta[NMB(j^*,\theta_{new})]) \quad (11)$$

In practice, research is likely to result in information on only some of the parameters. Therefore, one would like to calculate the expected value of perfect parameter information (EVPPI). Imagine obtaining perfectly certain information on only some parameters, splitting θ_{new} into two components $\theta_{new} = (\varphi, \psi)$, and obtaining perfect information only on the subset φ.

$$\text{Partial EVPI}(\varphi), \text{ i.e., EVPPI} = E_\varphi[\max_j\{E_{\psi|\varphi}[NMB(j,\varphi,\psi)]\}] - E_\theta[NMB(j^*,\theta_{new})] \quad (12)$$

We can also imagine obtaining sample information, that is data X collected in a particular sample size for a particular follow time, etc. This sample information may, for instance, provide reduced uncertainty in the parameters θ such that the posterior probability distributions for θ given X exhibit, for example, smaller credible intervals for the parameters θ. Then, we can compute the expected additional value of this sample information to the decision making as [19,20]:

$$EVSI(X) = E_X[\max_j\{E_{\theta|X}[NMB(j,\theta|X)]\}] - E_\theta[NMB(j^*,\theta_{new})] \quad (13)$$

At the population level, this is

$$\text{Population EVSI}(X) = P * (E_X[\max_j\{E_{\theta|X}[NMB(j,\theta|X)]\}] - E_\theta[NMB(j^*,\theta_{new})]) \quad (14)$$

Obtaining sample information, that is, data collection, is likely to be associated with costs for the decision maker. Let us refer to these costs as $C(X)$. The net value of the data X to the decision maker, the expected net benefit of sampling (ENBS) [21], is as follows:

$$ENBS(X) = P * (E_X[\max_j\{E_{\theta|X}[NMB(j,\theta_{new}|X)]\}] - E_\theta[NMB(j^*,\theta_{new})]) - C(X) \quad (15)$$

Case Description

In early node-negative estrogen-receptor–positive breast cancer patients after local therapy (surgery with or without radiotherapy), prognostic tests are used to distinguish between patients with a high and a low risk of developing metastases. High-risk patients receive hormonal therapy and chemotherapy, while low-risk patients receive only hormonal therapy. In standard care, a prognostic test based on clinicopathological criteria, the clinical guideline AO software, is used [9]. Recently, genetic tests such as the 70-gene signature that could be used instead of the clinicopathological criteria have become available [3–5]. The original 70-gene signature is performed on fresh frozen tissue samples (70G-FFT). The majority of the hospitals, however, are used to preparing and storing the tissue after surgery on paraffin blocks. They are not used to working with FFT samples. Research has shown that the use of FFT samples is associated with failures of the 70G-FFT [6]. This has led to the question whether there would be value to society in developing a 70-gene signature based on paraffin blocks (70G-PAR). Previously, a probabilistic Markov decision model was developed to assess the effects (QALYs), costs, and cost-effectiveness of the use of the 70G-FFT instead of the AO alone in patients with early, node-negative, estrogen-receptor–positive breast cancer [8]. In each strategy, on the basis of the sensitivity and specificity of the prognostic test, patients were classified as having a true low, true high, false low, or false high risk of developing metastasis. The sensitivity and specificity of each prognostic test were calculated from a database consisting of three previously reported validation studies [3–5]. From this database, a total of 305 untreated, node-negative and estrogen-receptor–positive tumor samples were selected and classified by the 70-gene signature and the clinical pathological guidelines as low or high risk of developing distant metastasis in 10 years. After local therapy, the high-risk patients received hormonal therapy and chemotherapy, while low-risk patients received only hormonal therapy.

Model Description

The model simulated the course of events in a hypothetical cohort of patients aged 50 years. The calculations were performed

per year, with a time horizon of 20 years. For each sample size, for 600 possible trial results the Monte Carlo simulation with 5000 iterations was run to calculate the corresponding EVSI. Subsequently, the 600 EVSI estimates were averaged to obtain an expected EVSI for that sample size. Future costs and effects were discounted to their present value by a rate of 4% and 1.5% per year, respectively, according to Dutch guidelines [22]. We programmed the model in Microsoft Excel (Microsoft, Redmond, WA).

For the purpose of the current study, an additional alternative was added to the above-described decision model: the developed technology 70G-PAR. It was assumed that this, not yet available, technology would resemble the original 70-gene signature (70G-FFT), except for the proportion of failures and the costs. Therefore, two new uncertain model parameters were incorporated into the model: a failure parameter and a parameter to reflect the additional cost of development of 70G-PAR to society per individual recipient of the test. The failure parameter reflects a technical failure in the process of the preparation of the tumor sample for the 70-gene signature. These failures may take place during surgery, at the pathology department, during transport of the sample, or during the performance of the test itself. In the case of a technical failure, the 70-gene signature cannot be determined and treatment will be based on the currently used clinical guideline (AO). The accuracy of the developed technology (70G-PAR) is equal to the accuracy of the original technology (70G-FFT). 70G-PAR, however, is likely to have fewer failures. As a result, the 70-gene signature result will be available for more patients. The failure rate of the 70G-FFT was based on the RASTER study. Observed failures (N = 158) in this study included less than 50% tumor cells in the sample (75), tumor too small for biopsy (39), insufficient RNA quality (14), 28 samples already prepared in formalin, 1 sample stored too long in RNA later, and 1 sample lost in mail [6]. Based on these data, the mean 70G-FFT failure rate was estimated to be 27%. This was modeled as a beta distribution with a standard error of 2% (α 158; β 427) [8]. The mean failure rate of the 70G-PAR was set equal to the observed failure rate of the 21-gene assay (8%), which is a paraffin-based gene expression profile for the same patient group [10]. The failure rate of the 70G-PAR was modeled by using a beta pert distribution (the beta pert distribution emphasizes the "most likely" value over the minimum and maximum estimates) with a range from 0% to 27%. The upper limit of the range was based on the assumption that the failure rate of 70G PAR will not be worse than that of the 70G FFT. It was assumed that no failures occurred in the AO strategy. In the case of failure in the preparation of the tumor sample for either the 70G-FFT or the 70G-PAR, the 70-gene kit is not (entirely) used, and only 10% part of the costs of the 70-gene kit are made [6]. Therefore, the costs in the case of a failure of both 70-gene signatures were assumed to be 10% of the total costs of the test. The mean costs per patient of the 70G-PAR were assumed to amount to the costs of the 70G-FFT, increased with the additional cost of development of 70G-PAR to society per patient receiving the test. For these additional costs of the 70G-PAR, a central estimate of €250 per patient receiving the test was used. This is based on the costs of comparable arrays on paraffin blocks. However, because we are not certain that this will be the same for the 70-gene signature, this uncertainty was incorporated by using a uniform distribution between €0 and €500. For details of the model, see Retèl et al. [8].

Model Analyses

Adoption decision

To obtain the expected NMB for the AO and the 70G-FFT, we performed a probabilistic sensitivity analysis with 5000 iterations [23]. We calculated the NMBs on the basis of a societal willingness to pay (λ) of €30,000/QALY. This resembles the £20,000 to 30,000/QALY threshold used by the National Institute for Health and

Table 1 – Parameter input and results.

	AO	70G-FFT	AO	70G-FFT	70G-PAR
Input					
Sensitivity	0.57	0.74	0.57	0.74	0.74
Specificity	0.54	0.58	0.54	0.58	0.58
Unit cost	€0	€2,675	€0	€2,675	€2,675
Development cost*					€300
Failure	0	0.27	0	0.27	0.08
€ Chemotherapy	€8,596	€8,596	€8,596	€8,596	€8,596
Results					
% Chemo	48%	46%	48%	46%	46%
€	€27,188	€28,080	€27,188	€28,080	€28,490
QALY	12.75	12.92	12.75	12.92	12.96
NMB†	€355,364	€359,520	€355,364	€359,520	€360,384
ENBD				€864‡	
Population ENBD				€91 million	
EVPI	€528			€702	
Population EVPI	€56 million			€74 million	
EVPPI				€644	
Population EVPPI				€65 million	
ENBS	€61 million				

AO, Adjuvant Online; ENBD, expected net benefit of development; ENBS, expected net benefit of sampling; EVPI, expected value of perfect information; EVPPI, expected value of perfect parameter information; NMB, net monetary benefit; QALYs, quality-adjusted life-years; 70G-FFT, 70-gene-fresh frozen tissue; 70G-PAR, 70-gene signature based on paraffin blocks.

* This are the additional costs of development of the 70G-PAR per recipient of the test borne by society.

† Based on a threshold of €30,000 and original costs and QALYs before rounding.

‡ Based on the comparison of the NMBs of 70G-PAR and the best alternative (70G-FFT).

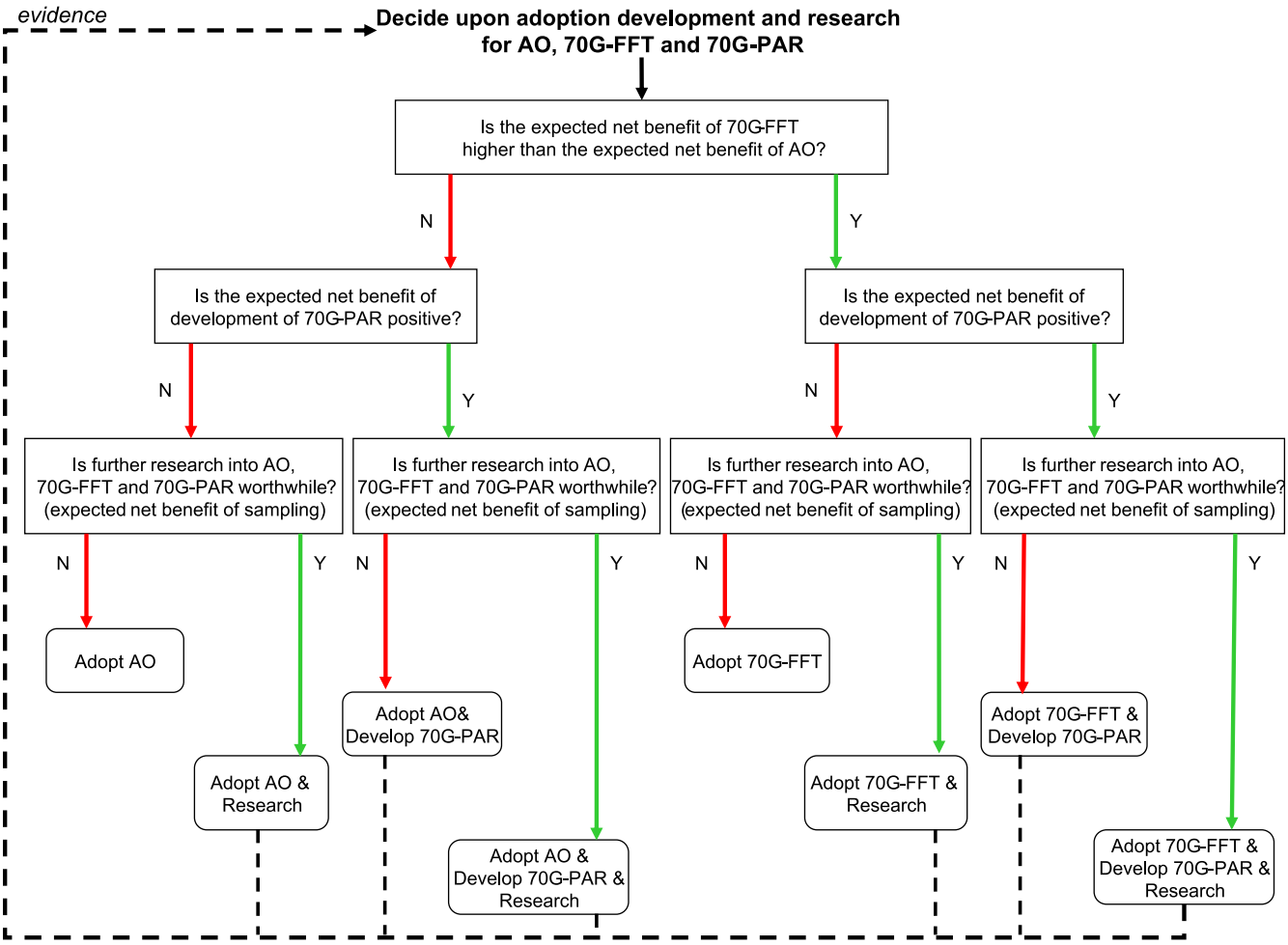

Fig. 1 – Analytical framework.

Care Excellence in the United Kingdom [24,25]. To show decision uncertainty, cost-effectiveness acceptability curves (CEACs) were constructed. We performed a one-way sensitivity analysis on discount rate, using the rate advised by the National Institute for Health and Care Excellence (3.5% for effects and costs) [26].

Development decision

The expected NMB of the 70G-PAR was calculated, and CEACs were constructed to show uncertainty in deciding on which of the three technologies was cost-effective: AO, 70G-FFT, or 70G-PAR. Subsequently, the ENBD, the incremental NMB of 70G-PAR versus the best technology, was calculated. We conducted a one-way sensitivity analysis for a range of fixed values (€0, €100, €200, €300, €400, and €500) of the development costs of 70G-PAR per recipient of the test that are borne by society. Also, we calculated the probability that the ENBD was positive for each of these values. Finally, the population ENBD was calculated by multiplying the ENBD per patient by the number of people affected by the decision over the lifetime of the technology (P). P was estimated to be 105,442 on the basis of an annual incidence of 12,500 early breast cancer patients in The Netherlands [27], a lifetime of the technology of 10 years, and a discount rate of 1.5%.

Research decision

First, the EVPI was calculated on the basis of 50,000 simulations (10 × 5000 simulations) for the two decision architectures: AO versus 70G-FFT, and AO versus 70G-FFT versus 70G-PAR. Subsequently, the EVPPI based on the latter decision architecture was calculated for the following groups of parameters: test accuracy (sensitivity and specificity), costs, utilities, and failure rates. EVPPI calculations were based on 2000 outer loops and 200 inner loops. For the group of parameters with the highest EVPPI, we computed the expected additional value of sample information to the decision making.

Results

Adoption Decision

The total expected costs per patient over 20 years were €28,080 for the 70G-FFT and €27,188 for the AO. The 70G-FFT yielded 12.92 QALYs, and the AO yielded 12.75 QALYs. The expected NMB amounted to €359,520 for the 70G-FFT and €355,364 for the AO (see Table 1). Because it had the highest expected NMB, 70G-FFT was found to be cost-effective. The CEAC shows that the 70G-FFT had the highest probability of being cost-effective if willingness to pay exceeds €5,000/QALY (see Fig. 2A). The one-way sensitivity analysis regarding discount rates of 3.5% resulted in a smaller difference in expected NMB (€3210 instead of €4156).

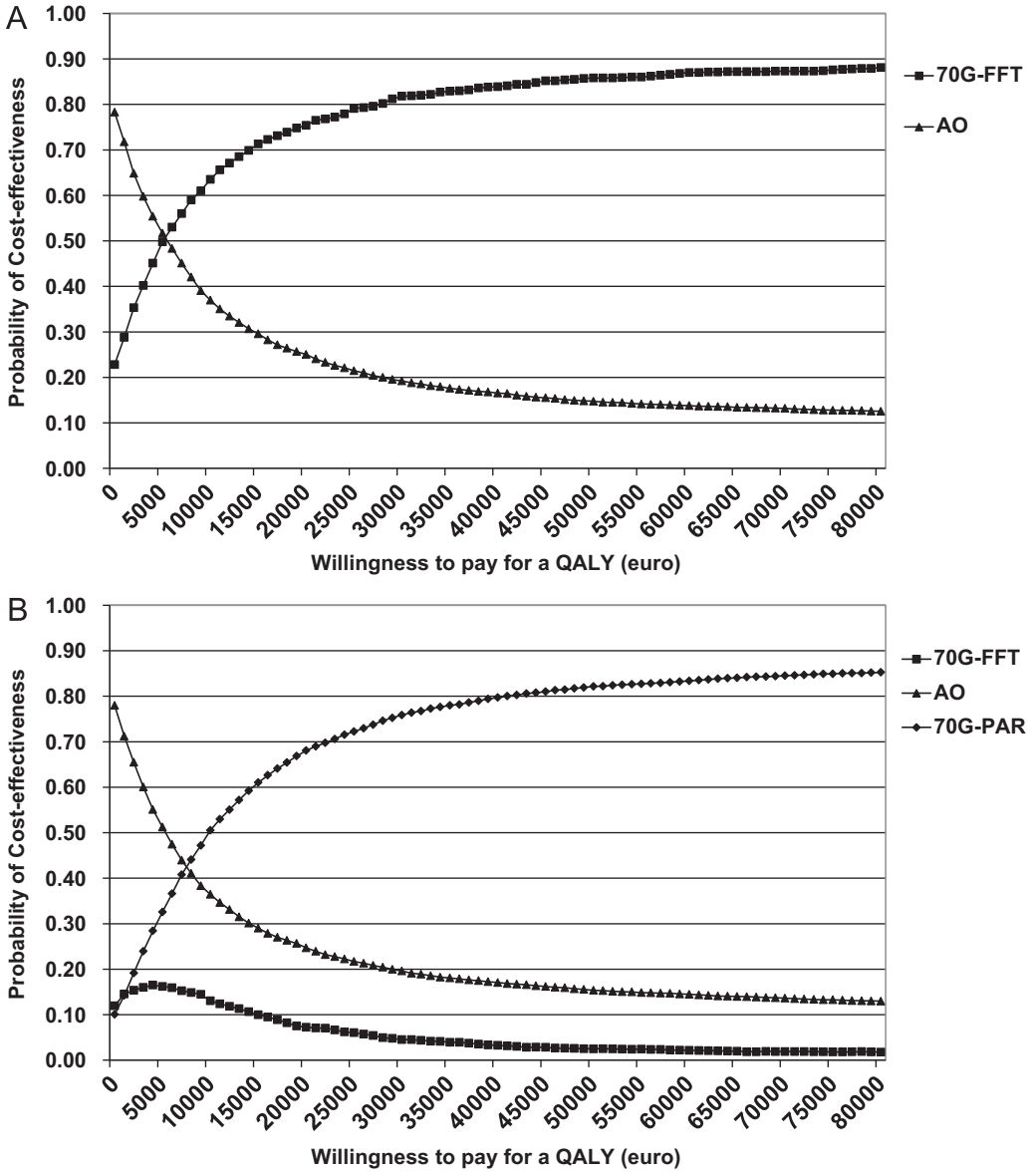

Fig. 2 – (A) Cost-effectiveness acceptability curve (CEAC) of the 70-gene signature versus AO. (B) CEAC of the 70-gene signature FFT versus 70-gene signature PAR versus AO. AO, Adjuvant Online; FFT, fresh frozen tissue; PAR, paraffin blocks.

Development Decision

For the 70G-PAR, the total expected costs were €28,490 and the total expected QALYs were 12.96. The expected NMB of the 70G-PAR amounted to €360,384. Because 70G-PAR had the highest expected NMB, it was found to be cost-effective (Fig. 1B). The CEAC comparing all three technologies shows that the 70G-PAR has the highest probability of being cost-effective if willingness to pay exceeds €8,000/QALY (see Fig. 2B). The probability of 70G-PAR being cost-effective at a threshold of €30,000/QALY was 76%. The ENBD amounted to €864 (Table 1). The ENBD multiplied by the population gives us the population ENBD of €91million.

The results of the sensitivity analysis on the value of the development costs of 70G-PAR per recipient of the test that are borne by society are shown in Figure 3. If the development costs are €0, the ENBD amounted to €1103, and the population ENBD to €116 million. This implies that the maximum budget for development is 116 million. If the development costs increase to €500 per patient, the ENBD amounted to €606, and the population ENBD to €64 million. At a threshold of €30,000/QALY, the probability that the ENBD was positive ranged from 0.82 (€0 development costs) to 0.68 (€500 development costs) (Fig. 3).

Research Decision

The population EVPI for the decision between the currently available technologies AO and 70G-FFT amounted to €56 million (Fig. 4B). The population EVPI in the decision architecture comparing all three technologies amounted to €74 million (Fig. 4A). In the latter context, the EVPPI for test accuracy (sensitivity and specificity of AO, 70G-FFT, and 70G-PAR) was €65 million. For the other groups of parameters, including the probability of failure of the 70G-FFT and 70G-PAR and the development costs of 70G-PAR, the EVPPI was negligible (calculations took around 1200 min on a Core i5 computer). Therefore, it was deemed most valuable to obtain sample information regarding the accuracy of the

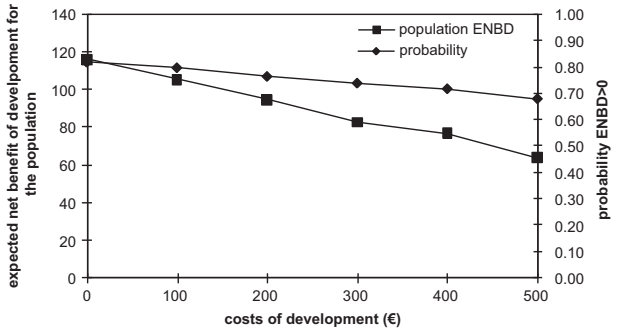

Fig. 3 – Expected net benefit of development (ENBD) for the population and associated uncertainty for a range of costs of development for society.

technologies. For this purpose, we envisioned a trial resembling the ongoing MINDACT trial [28]. In this trial, patients received both AO and the 70-gene signature. (Because the accuracy of the 70-gene signature is not dependent on whether the test is performed on FFT [70G-FFT in the case] or on a paraffin block ([70G-PAR in the case)], it is not relevant which of the versions of the 70-gene signature will be used in this possible future trial. Of course, in the on going MINDACT trial, the 70G-FFT was used, because the 70G-PAR was not yet available.) Subsequently, patients with a discordant test result (low-risk AO vs. high-risk 70-gene signature, or high-risk AO vs. low-risk 70-gene signature) were randomized to be treated according to either the AO or the 70-gene signature test result. The trial costs were estimated to be €1000 per patient [28]. Figure 5 shows that the optimal sample size of this trial was around n = 4000, with an EVSI of €65 million. The total trial costs amount to 4 million, resulting in an ENBS of €61 million.

A summary of the results is depicted in the framework shown in Figure 1.

Discussion

This article presented a framework to simultaneously address decisions with regard to the adoption, further development, and further research of a new, still dynamic, technology in an early stage of diffusion. The framework was applied to the 70-gene signature, a gene expression profile for patients with breast cancer.

The results show that in this case, the to-be-developed technology, 70G-PAR, has the highest probability of being cost-effective compared with the original technology, 70G-FFT, and current care (AO), if the willingness to pay for one additional QALY exceeds €8,000. The expected net benefit of development for the population is positive and amounts to €91 million. The value of development is sensitive for changes in the development costs per recipient of the test to society of the 70G-PAR. The net value of further research, envisioned as a study on the accuracy of the 70-gene signature, amounts to €61 million (65 million minus trial costs of 4 million). The results indicate that there is both value in the further development of the 70G-FFT into a paraffin based test, the 70G-PAR, and value in further research into the accuracy of the 70-gene signature.

The suggested framework draws on probabilistic decision analytical modeling, which can be considered standard practice to inform adoption and research allocation decisions regarding available technologies. To be able to add a still-to-be-developed technology to a decision model, adaptations are likely to be necessary. In the case we presented, the 70G-PAR, a still-to-be-developed paraffin-based test, is thought to yield an advantage to the original 70G-FFT in terms of failures. At the same time, the 70G-PAR may also be associated with additional costs to society. These two aspects of the to-be-developed technology could be incorporated into a previously used decision model to investigate the original 70G-FFT compared with current care relatively easy. Of course, in other cases adapting the model to incorporate a still-to-be-developed technology may require the addition or alteration of other aspects of the model (such as improved efficacy, or fewer side effects). Also, in other cases, the necessary adaptations to the model may be more complicated than the ones shown in this article. In addition, in other cases, it may be more complicated to anticipate the possible advantages and disadvantages of a possible future development of a technology.

Furthermore, in the case of the 70-gene signature, we modeled only one direction of development, because for this case this was the most realistic option. In reality, however, several directions for further development may be indicated instead of just one. The identification of directions of development may be based on quantifiable diffusion scenarios [11].

With regard to the necessary input data to model the developed technology, in our case, evidence was available to obtain a central estimate and an estimate of the uncertainty in the added parameters (failure rate and development costs). For other cases, however, evidence may be lacking, forcing researchers to use expert opinion. Recently, Bojke et al. [29] described a method to obtain expert elicitation and use this by parameterizing the information, including the existing uncertainty, directly into the model.

In case both research and development are valuable, we need to decide on the order in which these activities should take place. For example, it may be better to wait for additional evidence before we start further development. Waiting could be an interesting option because it may prevent wasting a considerable amount of money, if the developed technology turns out not to be cost-effective. However, waiting may result in health benefits forgone, if the developed technology yields the highest health benefit. An argument to start development before conducting further research is that development may also reduce uncertainty. For example, it is possible that the cost of development becomes more certain during development than it is a priori. To inform the decision whether we should wait to further develop a technology until more evidence is available, a trade-off should be made between the costs and benefits of the different options: research and development, first research, first development. A useful technique to assist in making such trade-offs is real options analysis (ROA) [30]. ROA stems from the financial literature, but was recently introduced as an addition to the value of information framework [31]. Its advantage is that it not only considers whether the benefits of (developing) a technology outweigh its costs (as in cost-effectiveness analyses) but also recognizes the option to postpone the adoption or development of the technology. It can then assist the trade-off between adopting a new technology and waiting for more evidence. If the analyses in the proposed framework show that both further development and further research are valuable, ROA can be used in a similar way to assist the trade-off between conducting both simultaneously, and postponing either development or research. Because it requires an additional set of parameters and assumptions, ROA was beyond the scope of the present article. We acknowledge, however, its potential value for the proposed framework, and emphasize that it is an important area for further research.

Previously, publications focused on the evaluation of technologies early in the product life cycle [12–14]. They focused on the dynamic nature of the technology under investigation, indicating

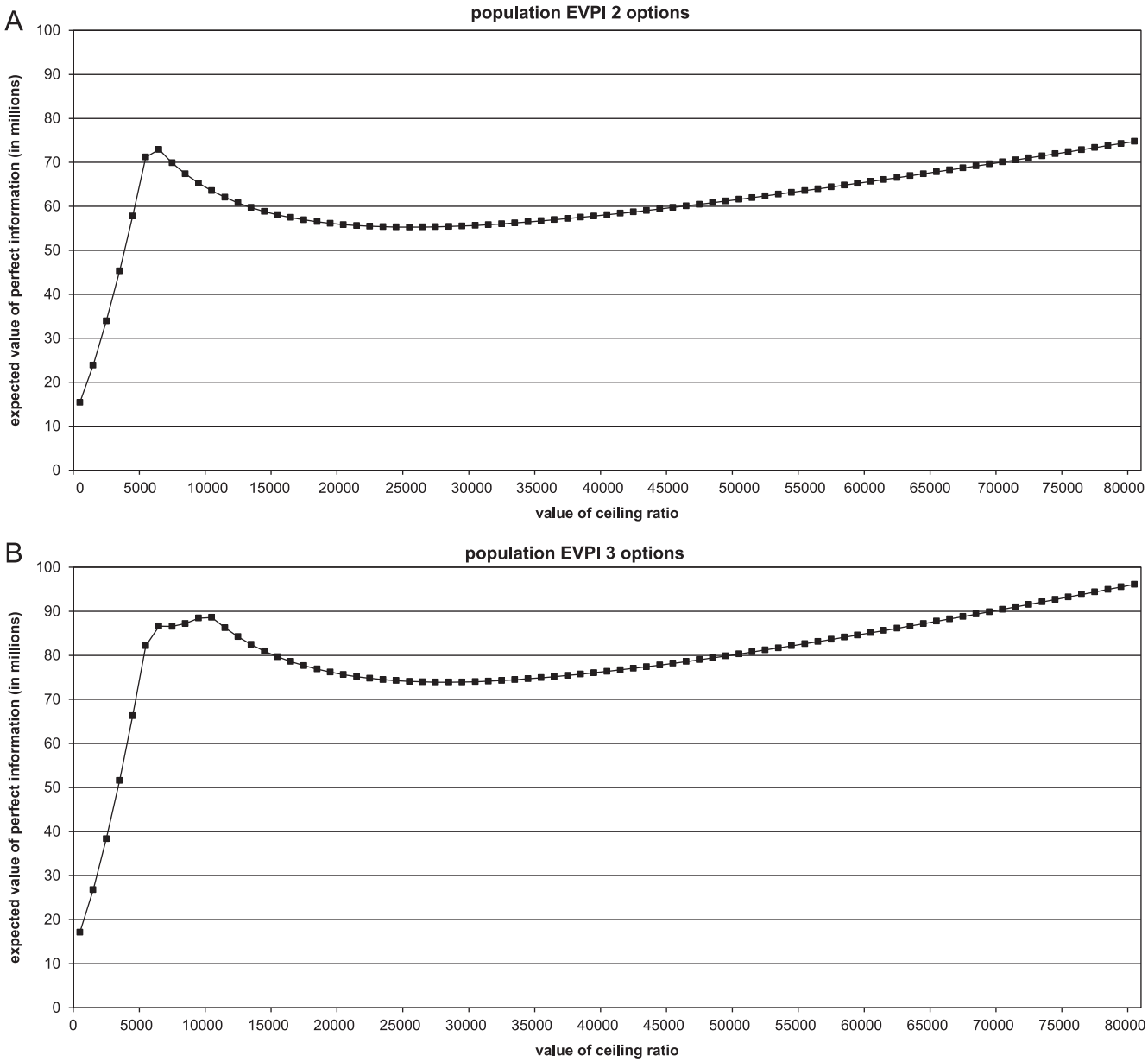

Fig. 4 – (A) Expected value of perfect information (EVPI) curve of the 70-gene signature versus AO. (B) EVPI curve of the 70-gene signature FFT versus 70-gene signature PAR versus AO. AO, Adjuvant Online; FFT, fresh frozen tissue; PAR, paraffin blocks.

the need for iterative assessments. Garrison [14] is highlighting the linkage between the concept of economic value in cancer care and the incentives for innovation. In this study, the key point is that value is also a dynamic and moving target, which is often not taken into account. Our framework gives an example of a technology in its early stages, where the type of tumor sample used has been questioned, as a result of the identification of barriers for more successful use of the technology in clinical practice. An evaluation of barriers for successful implementation, the calculation of the expected net benefit of the further development of a technology that could possibly overcome these barriers, as well as the calculation of the value of further research should ideally be an iterative process. This process could start all over again if new information becomes available, as a result of the development of the technology, evidence from research, or both. Girling et al. [12] developed a framework for valuing new medical devices at the concept stage that balances benefit to the health care provider against commercial costs. They conclude that quantifiable uncertainty that can be resolved before the device is brought into the market will generally enhance early-stage valuations of the device, and this remains true even when some components of uncertainty cannot be fully described. Both articles adopt a perspective from the manufacturer and focus on technology development alone. None of these studies simultaneously addresses the value of research and the value of development from a societal perspective. In the societal perspective, the effects and costs are considered regardless of who experiences the benefits or pays the costs. Our study was performed from a societal perspective. In our opinion, a health care funder has the responsibility to assess and signal the value of health innovations on behalf of the population. Under the principle of value-based pricing, a

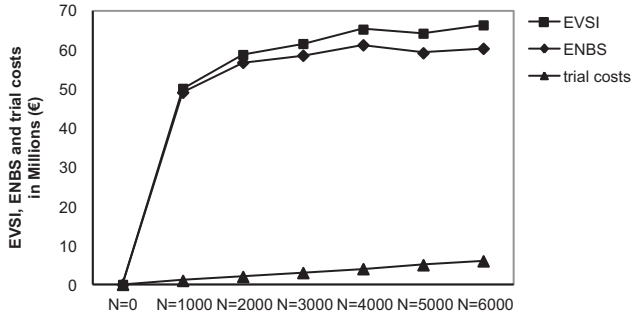

Fig. 5 – Expected value of sampling information (EVSI), expected net benefit of sampling (ENBS), and trial costs for a range of sample sizes.

societal perspective informs both the health care funder and the manufacturer on the value of innovation, and thus the maximum budget and price, given a certain threshold per QALY. Obviously, it is the manufacturer's decision whether or not to actually incorporate the additional development costs into the price of the technology.

The framework presented in this article can be used to inform three conceptually separate but related questions: 1) what is the value of adoption? 2) what is the value of further development? and 3) what is the value of research? This framework can support investment decisions for further development or research in early stages in the development of health care technologies.

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