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

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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

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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.

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