Eyes on the prize: early economic evaluation to guide translational research

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DOI:
10.33612/diss.100467716

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 1

General introduction
THE CHANGING CONSTRAINTS FOR HEALTHCARE INNOVATION

We may have reached a point in healthcare where we are able to do more than we can or are willing to afford. As a consequence of the ongoing technological development in healthcare, the number of diseases, syndromes, and conditions for which no form of intervention is available, has become very limited. In the not too distant past, the arrival of a new healthcare technology almost always represented new treatment possibilities for patients that could not be treated before or a drastic improvement to what was previously possible. This has created a persistent positive attitude towards healthcare innovations among doctors, patients, and the general public that lasts until the present day. Nowadays, however, new technologies that enter the market often present only a minor benefit over existing ones, if at all. This is especially true for the major disease fields such as cardiovascular disease and cancer, which, due to their potential large target market, receive the most interest from researchers, funding agencies, pharmaceutical companies, and device manufacturers. Independent of the magnitude of their added clinical benefit, new technologies almost always come at a higher cost than available ones. The welcoming attitude towards new technologies is therefore a substantial driver of the increase in healthcare costs that has been observed in most developed countries during the past decades.

The rising healthcare costs are increasingly seen as a problem and a threat to the sustainability of healthcare systems. As a response, governments are increasingly initiating cost containment actions. These often take the form of budget cuts, caps, or maximum growth agreements. This means that when new, expensive medical technologies are incorporated in the care practice, spending on other modes of care provision has to be reduced. This is known as displacement. The health benefits foregone because of the displacement of existing modes of health care provision are known as the opportunity cost of the new technology. When the new intervention that is funded produces less
health than the displaced care, the amount of health in the total population is reduced. Therefore, new technologies such as the expensive cancer medicines that have been introduced on the market over the past years do not only pose a threat to financial sustainability, but in fact also to population health.

In order to prevent a reduction in population health through displacement, only those new technologies that produce more health for a given amount of financial resources should be introduced in the health care system. This requires a thorough assessment of the impact of a new technology on resource use and health effects, which can be obtained using Health Technology Assessment (HTA).

HEALTH TECHNOLOGY ASSESSMENT

HTA is a multidisciplinary method of evidence synthesis that considers evidence on safety, clinical effectiveness, and cost of health technologies. The term technology should be interpreted in the broadest possible way. It refers to all proceedings and means used in healthcare, including pharmaceuticals, diagnostic tests, and medical devices, but also treatment protocols or the choice between immediate action and watchful waiting. In a broader application, HTA can include social, ethical, and legal aspects of the use of health technologies. Which aspects are included in an HTA depends on the purpose of the evaluation, i.e., the decision it aims to inform. In practice, costs and health effects are the dominant aspects in HTAs, as their purpose is most often to inform decisions on the reimbursement and adoption of new medical technologies. The evidence synthesized in an HTA often comes from epidemiological studies or clinical trials (evidence on health effects), and costing studies or other economic evaluations (evidence on costs). An HTA is always an incremental analysis, meaning that it will compare two or more competing alternatives. Most often these are a new intervention and the current way patients are treated (referred to as care as usual or current care). The dominant outcome measure used in HTA is the ratio of additional
cost per unit of health effect gained. The latter can be a disease-specific effect (such as the number of exacerbations in COPD), but it is more often a general effect (life years or quality-adjusted life years). This outcome ratio is referred to as an incremental cost-effectiveness ratio. Using a general effect measure allows comparing interventions for different diseases and is therefore almost always demanded by regulatory authorities for decisions on adoption and reimbursement. A reference cost-effectiveness threshold based on the overall production efficiency of the healthcare system can be used to determine whether the new technology will produce more health than the displaced care modalities. Governments and market regulators increasingly use such insights produced by HTAs in their decision to adopt and reimburse new technologies.

THE RELEVANCE OF HTA TO RESEARCHERS, DEVELOPERS, AND INVESTORS

When the cost-effectiveness of a new intervention is one of the criteria that determine its adoption and reimbursement, it becomes a factor critical to commercial success. Therefore, in order to make sound decisions on whether a new concept is worth developing or investing in, developers and investors must assess the potential of a new technology to be a cost-effective intervention. Likewise, when selecting from multiple targets, prototypes, or development portfolios, an estimate of potential cost-effectiveness of the alternatives is an important decision criterion. HTA performed in this setting – before or during development – is referred to as early HTA.

Public investors in research have an obligation to maximize the societal benefit of their investments. For them, an assessment of potential cost-effectiveness is critical to fulfilling that obligation. Public or public-private funders of translational research such as the Center for Translational Molecular Medicine (CTMM) or the European Commission (Horizon 2020) allocate large sums to address an abstract societal goal (such as the reduction
of burden from diabetes). In practice, there are often many ways in which such an abstract goal could be reached, not all of which have the same expected impact or likelihood to succeed. Their responsibility towards society obliges public investors to select those research proposals that have the highest expected societal benefit. Early HTA can be used to make an early assessment of the potential impact of translational research projects on quality of life and healthcare costs.

**The difference between early HTA and mainstream HTA**

Early and mainstream HTA differ on two main aspects. First, the aim of the analysis and research questions are different. Mainstream HTA is most often used to support adoption or reimbursement decisions. Early HTA, on the other hand, is used to inform decisions on investment, portfolio management, and price setting, among other strategic business decisions. Second, the available evidence at the time of analysis is different. For mainstream HTA, the intervention is clearly defined, and there is almost always trial or other experimental data on the impact of the intervention on costs and effects. In early HTA, the intervention is not well defined. Rather, the research question of an early HTA could be to identify the most promising form of the intervention. Also, data on the impact of an intervention is seldom available. This, however, does not mean that no useful analysis can be performed. Valuable insights can be obtained by collecting information on the current care setting of the intended target population, such as epidemiological data and the costs and health effects of the current intervention. Synthesis of such evidence in a model enables the testing of the central premise of the mechanism by which a novel intervention might improve health and cost outcomes. This compels the formulation of a clear definition of a set of key characteristics of the new intervention, such as a precise definition of the patients who should receive the intervention and how and by whom the intervention should be provided, a process that is informative and thus valuable in itself.
Because early and mainstream HTA have different objectives, they have different outputs. The central outcome of a mainstream HTA is most often the aforementioned incremental cost-effectiveness ratio. Due to the large uncertainty in the input data in an early HTA, this outcome is not the most informative. Instead, indicating boundaries or tipping points of key parameters are more informative as they can be used as input during research and development processes.

As a scientific sub-field, early HTA is still very young, with most papers being published during the past ten years.\textsuperscript{9,10} Many of the methods for early HTA are still in concept or pilot phase.\textsuperscript{11} Their application by investors and developers for investment decisions, portfolio management, and R&D decisions is still very limited. A strong catalyst for the development of early HTA methods is the demand for the incorporation of early HTA in research projects by several large public-private partnerships and international funding agencies.

THE CTMM PREDICTT PROJECT

The Center for Translational Molecular Medicine (CTMM) was a large Dutch public-private partnership, consisting of several partners from academia (25\% of funding), industry (25\% of funding), and government (50\% of funding). The rationale was that translational research could be done more effectively if experts from these partners cooperated in all phases of development. Historically, translational research is meant to bridge the so-called bench-bedside gap.\textsuperscript{12} This gap is perceived to exist between the vast amount of knowledge on the biomedical processes underlying disease produced by fundamental research on one hand, and the slow progress in clinical care which is supposed to benefit from this knowledge on the other. Many different definitions of and approaches to translational research exist.\textsuperscript{12} Within CTMM, the goal was to develop novel techniques based on insights from molecular medicine to improve diagnostic and treatment capabilities in the most prominent disease areas in western society, i.e., cardiovascular disease,
oncology, degenerative disease, and auto-immune disease. These improved capabilities were expected to improve the health outcomes for patients as well as the sustainability of healthcare systems. Due to the translational nature of the CTMM projects, early HTA was considered an important tool to inform strategic decisions and provide early estimations of the potential impact on the set objectives. As a result, an HTA work package was part of every CTMM project. This approach gave a substantial impulse to the development and application of methods for early HTA in translational research.

One of the CTMM research consortia was the PREdiction and early diagnosis of DIabetes and diabetes-related Cardiovascular Complications (PREDICCt) project. This project was initiated with the aim to develop innovative biomarker-based technologies to allow identification of individuals at increased risk of type-2 diabetes mellitus (DM2) and related complications. The research presented in this thesis was conducted as part of the CTMM PREDICCt project.

**Type-2 diabetes**

Diabetes Mellitus is a group of metabolic disorders in which the regulation of blood glucose levels is disrupted. This leads to high blood sugar levels over prolonged time periods. In DM2 this is caused by insulin resistance, whereby cells in the body are less responsive to insulin. Lack of physical exercise and obesity are important factors contributing to the development of DM2. As obesity rates rise around the world, so does the incidence of DM2. The worldwide prevalence is estimated to rise to 642 million people by 2040. The burden of DM2, both for patients as well as society, is for the largest part caused by its complications. Complications are usually categorized into microvascular (damage to small blood vessels) and macrovascular (damage to large blood vessels). The most common microvascular complications are damage to the eyes, kidneys, and nerves (called retinopathy, nephropathy, and neuropathy, respectively). This can lead to blindness, kidney failure, skin
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damage, and amputation of extremities. Macrovascular complications include coronary artery disease, stroke, and peripheral vascular disease. Diabetes patients have a 2 to 4 fold increased risk for coronary heart disease.\textsuperscript{15}

Because of their contribution to the burden of disease, diagnostic and treatment protocols for DM2 are to a large extent focused on the prevention of complications (tertiary prevention). Treatment of DM2 patients is aimed at regulating glucose levels in order to minimize vascular damage. In addition, complication risk is reduced by treating hypertension and dyslipidemia. Also, DM2 patients are regularly screened for the occurrence of complications such as retinopathy.

**Strategies to reduce the burden of disease from DM2**

The rise in prevalence of obesity and DM2 calls for improved strategies to prevent DM2 and its complications in order to avoid a large societal burden. Several strategies are possible, ranging from primary prevention (aiming to reduce the incidence of DM2) to better disease management and early detection of (people at risk for) complications (tertiary prevention). The target population for primary prevention is the general population. Therefore, strategies in primary prevention are generalized to a broad audience (e.g., lifestyle advice). Most often it is proposed to target a subgroup of patients who are at increased risk to develop diabetes for such interventions. A well-established high-risk group are patients with impaired glucose regulation, also known as prediabetes. In this condition, glucose regulation is abnormal, but not yet so severe that it can be classified as diabetes. On the other hand, tertiary prevention has to be more specific to individual patient characteristics, in order to take into account specific disease risk, risk factors, and comorbidities. A challenge in that area is to obtain a detailed profile of individual risk factors in order to provide an effective intervention for that individual. Historically, characteristics such as age, anthropometric measurements (e.g., height, weight, waist circumference), and lifestyle (e.g.,
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smoking, diet) have been used to determine a personal risk profile. More recently, advances in molecular diagnostics have engendered enthusiasm and high expectations on the possibilities for personalized medicine.

PERSONALIZED MEDICINE AND BIOMARKERS

The mapping of the human genome (genomics), the increased insight in the regulation of the transcription of the genome (transcriptomics), and expanding knowledge on the function of proteins in the body (proteomics) have repeatedly challenged conventional definitions of diseases. Increasingly, different pathological mechanisms are identified within what was previously seen as one disease. These differences in pathological mechanisms at a molecular level are hypothesized to be driving differences in disease progression and response to treatment that are observed in patient populations with seemingly the same disease. As such, these discoveries have led to a new paradigm in medical science that foresees improved treatments and outcomes by means of grouping patients based on their risk for disease or response to a therapy. Personalized medicine, precision medicine, and stratified medicine are all labels for this paradigm. Within the paradigm of personalized medicine, many research efforts are aimed at identifying novel biomarkers. A biomarker is a substance, structure, or process that can be measured in or on a person or specimen, which can provide information on the incidence or outcome of a disease. From a clinical perspective, biomarkers can be considered diagnostic tests: they are used to obtain information on the risk or stage of disease or treatment response, in order to optimize the care for a patient. Besides the role of a diagnostic test, biomarkers have many different applications in the disease-therapy continuum (Figure i).
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Figure 1: Possible applications of biomarker-based tests in the disease-treatment continuum. 31

The unfulfilled potential of biomarkers

The hopes that newly discovered biomarkers enable personalized medicine strategies and therefore improved clinical outcomes, fewer side effects, and more cost-effective treatments have spawned a massive effort to identify new biomarkers for a wide variety of diseases. 17–20 Unfortunately, the vast amount of biomarker research fails to live up to the expectations. 20–27 This can be explained in part by the fact that much less effort has been put in translating newly discovered biomarkers into clinical applications than in discovering new biomarker candidates. The translational process from newly discovered biomarker to a diagnostic or prognostic test used in the clinic is a long and complex process requiring substantial financial investments. It
requires several different types of studies generating evidence on diagnostic accuracy, clinical effectiveness, and finally cost-effectiveness. Much like in the sequence of clinical trials used to determine the safety and effectiveness of novel pharmaceuticals, each step presents a hurdle that some candidates will fail to pass.\textsuperscript{21,28,29} Only very few discovered biomarker candidates make it to the clinic (Figure 2).\textsuperscript{30} Therefore, in order to support strategic decision making, each step requires an (updated) assessment to determine which candidates have enough potential to justify the required investments, and to determine their most promising clinical application. Thus far, well described and proven methods to generate evidence inform these decisions are lacking, leading to poor research and investment decisions and a stagnation of biomarkers in the translational process. In the end, this entails both a loss in health potential for patients and society, as well as wasted resources for public and private investors in research. Novel early HTA methods are therefore urgently needed.

\textbf{Figure 2:} The personalized medicine paradigm has resulted in countless biomarker publications, but so far has made little impact in the clinic.\textsuperscript{30}
AIM OF THIS THESIS

Our primary objective was to assess the clinical and economic value of the biomarkers and biomarker-based technologies that were developed within the CTMM PREDICCt project. As we set out to do this, we found that methods to perform such analyses were lacking. As a result, our second objective was to further the methodology for the early economic evaluation of biomarkers so that future R&D and investment decisions can be better informed.

OVERVIEW OF THIS THESIS

The two aims are entwined throughout this thesis, as methods were developed to address specific research needs for the PREDICCt project. Most chapters present a novel method for the early economic evaluation within translational research projects and demonstrate this method by applying it to the PREDICCt project. Chapter 6 is an exemption in that it focuses on a key issue of DM2 screening using established methodology. The chapters in this thesis are ordered in chronological order from the perspective of a translational research project, starting with an abstract societal objective and working towards specific biomarker-based technologies. When a project is selected for funding or when a project commences, a translation of the abstract research objectives into concrete research activities has to be made in the form of priority setting. In chapter 2 we demonstrate how research priority setting can be done using multi-criteria decision analysis. When a specific research target is chosen, biomarkers are identified through their association with the relevant clinical endpoint. Chapter 3 demonstrates how the clinical application of a biomarker candidate can be defined and how the data from an association study can be used to make an early estimate of the clinical and economic impact of a biomarker candidate. Similarly, chapter 4 demonstrates an early estimate of the cost-effectiveness specifically for biomarkers that are to be applied in the context of primary prevention. Continuing further towards the application of a new biomarker-based
technology in primary prevention, **chapter 5** demonstrates a method for the optimization of a 2-step screening program on costs and number of cases detected. The case study presented in this chapter estimates the efficiency of currently available screening techniques and thereby provides a benchmark for potential new biomarkers in this field. Finally, **chapter 6** assesses the effects of different lengths of lead-time of DM2 on the cost-effectiveness of a screening program for patients with impaired glucose regulation.
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