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

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Chapter 7

General discussion
As a public-private translational research project, the aim of Center for Translational Molecular Medicine (CTMM) PREdiction and early diagnosis of DIabetes and diabetes-related Cardiovascular Complications (PREDICCt) project was not to merely generate new fundamental knowledge on molecular diagnostics for type-2 diabetes mellitus (DM2), but rather to develop clinical innovations that positively impact society by increasing length and quality of life. This aim should be taken into account in the many decisions that have to be made from the initial investment until final market access of new technologies. Our project set out to conduct analyses to support this decision-making. We aimed to provide insight into the likely impact of the PREDICCt project on length and quality of life and costs, both of improved diagnostic and prognostic capabilities in general, as well as specific biomarker candidates. Our first finding was that, at the time of the start of this project, such research was rare and appropriate methods were lacking. As a result, we developed new methods for the early economic evaluation of biomarkers in translational research projects where we saw the need for them. In large parts, these methods built upon existing methods of health technology assessment and economic evaluation of medical technologies. By applying the newly developed methods to assess the work done within the PREDICCt project, we were able to provide insights on the potential clinical and economic impact of this work as the project went along. This chapter starts with a summary and discussion of the results of our work per research objective. Additionally, we discuss the general limitations related to our work. Finally, the chapter closes with an overview of the lessons learned during our research for several involved stakeholders.

POTENTIAL CLINICAL AND ECONOMIC IMPACT OF THE CTMM PREDICCT PROJECT

In its business plan, CTMM formulated ambitious objectives. In the area of health, it aimed to increase life expectancy and improve the quality of life of the Dutch population. More specifically, the aim was to reduce mortality rates
of the most prevalent cancer types by 10% to 30% by 2019. It also formulated the specific objective to realize an annual 1 billion savings in Dutch health care costs by 2019. Apart from objectives in the health and healthcare system areas, CTMM aimed to create a positive impact on the Dutch economy by strengthening the health technology sector. Lastly, it aimed to strengthen the Dutch academic institutions in the field of molecular medicine.

Our primary research objective was to assess the clinical and economic value of the biomarkers and biomarker-based technologies that were developed within the CTMM PREDICt project. The first analysis performed was to support the investment decision of the remaining project funds. At the start of the project a strategic reserve was made which was to be allocated halfway the project, with the aim to further strengthen the most promising research lines. At the time of our first analysis, the project had not resulted in tangible research output in the form of candidate biomarkers or biomarker-based products. We therefore set out to prioritize research endeavors based on their overall potential to achieve the societal objectives of the PREDICt project, as stated in the project’s business plan. As the core aim of the PREDICt project was to enhance the possibilities for prevention of DM2 and associated complications, we sought to prioritize between four different prevention strategies; primary prevention, secondary prevention, tertiary prevention of macrovascular complications, and tertiary prevention of microvascular complications (Chapter 2). Our analyses indicated that developing a biomarker technology applied to the general population to identify those with undiagnosed DM2 in order to initiate treatment sooner (i.e., secondary prevention) was the option that was least likely to contribute to achieving the goals set forth by CTMM. This was to a large extent due to the limited effects of earlier treatment of screen-detected diabetes on downstream healthcare costs and gain in quality-adjusted survival. Additionally, as DM2 is defined based on blood glucose tests, it is highly unlikely that a new biomarker-based technology will be used as the sole diagnostic test to identify patients for secondary prevention. A blood glucose test remains necessary
as long as DM2 is defined on that measure. As a result, novel biomarker technologies can only be used as a low cost or minimally invasive tool to select patients for blood glucose testing. Numerous very inexpensive and reasonably accurate anthropometric risk scores are already available for this purpose. It is unlikely that a novel biomarker-based technology can present a cost-effective improvement over these risk scores. The attractiveness of the other strategies depends strongly on the decision makers preferences. If a large impact on downstream medical costs and quality-adjusted survival is prioritized, primary prevention is the best alternative. In case having an innovation developed and implemented in clinical care within the stated 10-year time span is prioritized, then the focus should be put on developing biomarker technologies for tertiary prevention. Primary prevention has the possibility to reduce the health and cost burden of both diabetes and all complications together, while tertiary prevention can only reduce the burden of complications. On the other hand, implementing a biomarker-based innovation in primary prevention requires the initiation of a new screening program in the general population, whereas the target population for tertiary prevention is already in contact with healthcare providers. No meaningful difference was found between the attractiveness of tertiary prevention of microvascular or macrovascular complications. At the time we conducted our analysis, secondary prevention was still pursued within the PREDICCt project. Based on our findings, the remaining resources were predominantly allocated to research efforts in the field of tertiary prevention.

The PREDICCt project delivered, amongst others, a set of biomarkers to increase the accuracy of macrovascular risk prediction in DM2 patients. We sought to identify a clinical application for these biomarkers and estimate their commercial headroom (Chapter 3). We found that the most likely and quite possibly the only application of these biomarkers is to identify DM2 patients with a low cardiovascular risk, and, subsequently, refrain from prescribing the standard statin treatment. Currently, all DM2 patients are classified in the highest cardiovascular risk category, and consequently, statins are indicated
for all DM2 patients. This strategy does not account for the wide variety of cardiovascular risk in the DM2 population. Our analysis indicated that withholding statins to DM2 patients with a low cardiovascular risk (10-year risk below 10%) will lead to one additional cardiovascular disease (CVD) event in every 75 patients. The maximum headroom of the biomarkers in this application was €119.09 in case the willingness to accept for one additional CVD case was €0, which is almost certainly not a realistic case. The headroom reduced to €0 when the willingness to accept for one additional CVD case exceeded €15,614. Thus, it is reasonable to assume that there is no commercial headroom for the PREDICCT biomarkers in this application. Investments in the further development of these biomarkers are therefore not advisable.

In addition to the analysis of biomarkers for the tertiary prevention of macrovascular complications, we also assessed the potential commercial headroom of biomarkers to be applied within the primary prevention of DM2 (Chapter 4). As the PREDICCT project did not provide such markers for evaluation, we based our analysis on biomarkers recently presented in literature. We assessed the commercial headroom of a set of four biomarkers added to 11 classical risk factors to predict clinically incident diabetes, and estimated this to be €75. This result is in line with the findings presented in chapter 2, namely that there is a larger commercial headroom to be expected in the primary prevention of DM2 than in the tertiary prevention of macrovascular complications. Whether this commercial headroom is large enough to warrant investments in discovery research to find such biomarkers depends on many factors, mainly the cost required for the research and development of these biomarkers, as well as the production cost of the eventual biomarker-based technology.

We further explored the potential for novel biomarkers in the primary prevention of DM2. To that end, we optimized a current design of a stepwise screening program for prediabetes on costs and cases detected (Chapter 5). Our previous finding that there likely is a commercial headroom for novel
biomarkers in primary prevention programs was confirmed. Increasing the accuracy of the risk prediction tool used in stepwise screening lead to lower costs per case detected, as well as a higher detection rate. However, we also found that other aspects of the screening program, such as patient response rates and costs of screening instruments, had a larger impact on these outcomes than improved accuracy. We found that when the costs for the first steps of screening were reduced through communicating by email, the subsequent reduction in costs per case detected was of the same magnitude as when the accuracy of the risk prediction tool was increased from an area under the curve of 74.3% to an area under the curve of 90%. This represents an improvement in accuracy far greater than thus far demonstrated by DM2 risk prediction biomarkers, quite possibly an unrealistic improvement.7,8

By far the largest improvements in cost per case detected and the detection rates were achieved when patient response rates improved. This has a positive impact on both outcomes and is the only way to increase the total detection rate of the screening program. We thus conclude that even though there is a commercial headroom for novel biomarkers in the primary prevention of DM2, it is unlikely that developing novel biomarkers is an efficient strategy to improve screening programs. Our work did not include a comparison of the return on investment of research on novel biomarkers versus strategies to increase patient response rates. However, taking into account the enormous research effort required to develop and market biomarker base technologies, it is unlikely that returns on investments in that area will exceed those that may be achieved in effective public health strategies.

The yield and efficiency of screening for prediabetes is certainly not the only obstacle that stands in the way of implementing this primary prevention strategy. When screening for patients with prediabetes, some patients with previously undiagnosed DM2 will inevitably be identified and subsequently treated. There is currently no robust evidence that the standard DM2 treatment is cost-effective in screen-detected DM2 patients. Standard treating protocols have been developed for the treatment of clinically detected
DM2 patients, who invariably have a higher risk for complications than screen-detected DM2 patients. No treatment guidelines for screen-detected DM2 patients have been developed yet. Even though the treatment of prediabetes patients is likely to be cost-saving, it is uncertain whether these savings are large enough to compensate for the additional cost of treating the previously undiagnosed DM2 patients. Previous studies on the cost-effectiveness of prediabetes screening were based on data from two to three decades ago. Since then, the lead-time of DM2 has decreased due to increased awareness and the standard of care for DM2 patients has seen drastic improvements. As a result, the previous studies likely present an overestimation of the health effects of prediabetes screening, and thereby a too favorable cost-effectiveness estimate. We used more recent estimates of the lead-time of DM2 and treatment effects and found that treating patients identified through a prediabetes screening program is not likely to be cost-effective (chapter 6). Even when more favorable assumptions are made regarding the health effects of treating screen-detected DM2, the incremental cost-effectiveness ratio for treating patients identified through prediabetes screening is only just below the willingness to pay threshold. However, because the costs of the screening program itself were not included in this analysis, it is unlikely that the screening program and subsequent treatment of identified patients combined will remain cost-effective.

Besides the search for novel biomarkers, the PREDICCt project also included the continued development of a number of prototype devices that were in different stages of development at the start of the project. We conducted an early economic evaluation of one such technology, the DiagnOptics Diab-spot. The results of this work are however not presented in this thesis as they cannot be published in scientific journals due to the confidentiality of the data and outcomes. DiagnOptics has eventually discontinued the development of the Diab-spot.
Conclusion of our assessment of the potential clinical and economic impact of the CTMM PREDICCt project

The CTMM consortium had set itself very ambitious objectives. Our analysis of the research strategy and output indicates that these objectives have not been achieved within the stated time horizon. We found that there is potential to achieve the defined objectives when research output would result in improvements in primary and tertiary prevention of DM2. However, the actual research output in the form of novel biomarkers for tertiary prevention is unlikely to provide significant clinical or economic value. Novel biomarkers to be used in primary prevention were not available to us for assessment. However, we have concluded that investments in public health innovations are more likely to contribute to the consortium’s objectives than investments in biomarker research. Our work only assessed the output of the PREDICCt project, and then only part thereof. The objectives stipulated at the beginning of this chapter were formulated for CTMM as a whole. We can thus not state with full certainty that the objectives have not been met through the results of other consortia. However, we have little indication that the PREDICCt project is an outlier within CTMM with respect to its contribution to the overall CTMM goals. As the output of the PREDICCt project has thus far not been shown to lead to a reduction in mortality or savings in healthcare costs, we are inclined to conclude that the objectives of CTMM to reduce mortality by 20% and reduce annual healthcare costs by 1 billion Euro have not been realized.

NOVEL METHODS FOR THE EARLY ECONOMIC EVALUATION OF TRANSLATIONAL RESEARCH AND BIOMARKERS

Our second research objective was to further the methodology available for the early economic evaluation of translational biomedical research. Our methods are building upon existing methods from early HTA and other disciplines. Below, we discuss the methodological advancements on three
areas of health economic evaluation presented in this thesis: priority setting for translational research, early economic evaluation of biomarkers, and the evaluation of stepwise screening programs.

**Priority setting and resource allocation in biomedical translational research**

We have demonstrated the applicability of multi-criteria decision analysis (MCDA) in priority setting in biomedical translational research projects (chapter 2). MCDA has previously been applied in the context of biomedical innovation, as well as government-sponsored technology development programs in other fields. The work in this thesis demonstrates for the first time how it can be used to take societal and commercial aims into account when allocating funds in a translational research project.

Translational research aims to address societal objectives, rather than to develop fundamental knowledge. The societal objectives of translational research must be taken into account during the many decisions that have to be taken at the start and during a translational research project. Due to the very complex nature of healthcare provision, successful biomedical innovations have to satisfy numerous different and often conflicting requirements. This calls for the incorporation of expertise from a large variety of disciplines in the research and development process. In such a complex setting it is unlikely that decision makers are able to adequately assess and weigh all information relevant to the decision. This can easily lead to an inefficient allocation of resources (i.e., investment in projects that have a lower probability than others in achieving the formulated societal objectives). In addition, the investment of large amounts of public funds calls for transparent and reproducible decision-making. For these reasons, decision-making approaches based on heuristics are not adequate in initiating and guiding large translational research projects and are expected to lead to suboptimal outcomes. Thus, formal decision-making frameworks such as MCDA are preferred.
Given its complexity, it is astounding that research priority setting and resource allocation for translational biomedical research is most often done without formal decision-making frameworks. For example, within the Horizon 2020 program of the European Commission, the translation of abstract societal objectives (e.g., improve longevity and quality of life of the European population) into calls for research proposals is not transparent and no analysis is presented to demonstrate that the formulated research topics have a reasonably high potential to achieve those objectives. In the process of selecting which research proposals to fund, reviewers score the proposals on a set of subjective criteria, (e.g., the extent that the proposed work is beyond the state of the art, and demonstrates innovation potential) and subsequently aim to reach consensus. Again, no empirical data is used to estimate the potential impact of proposals. Considering the vast amounts of public funds that are distributed through programs like Horizon 2020 (€77 billion) and CTMM (€321 million), it is surprising that so little effort is being put in ensuring that the funds are allocated in a way that provides the largest chance of achieving the societal objectives. We believe that the method we applied in the context of CTMM can be adapted to be applied to other programs, such as Horizon 2020.

Compared to the current practice, more time and effort are likely required in order to use MCDA for priority setting and resource allocation. It may therefore not be a suitable approach for smaller funding programs where this investment cannot be justified. However, for programs the size of Horizon 2020 and CTMM, the additional investment required to implement formal decision-making is very small compared to the funding budget and can be easily justified from the perspective of due diligence towards the public. In the case of CTMM PREDICCT, the total budget was €18.4 million. Conducting an MCDA assessment for priority setting would cost less than €75,000 and for around €200,000 a full package of priority setting and early HTA assessments could be done to optimize resource allocation at the start and during the first half of the project. This is just over 1% of the total budget.
General discussion

One important added value of the MCDA methods as we have applied it in the case study in chapter 2 over most existing early HTA methods, is that it can prioritize between alternative conceptual approaches, rather than specific clinical applications. Most early HTA methods are based on the incremental assessment that is central to HTA. This requires the specification of a target population and comparator intervention, or in the case of diagnostics or prognostics, a clinical decision to be informed. During the priority setting phase at the start of translational research projects, it is often not viable to define a potential application in such detail and compare alternatives. However, it is a phase in which it is crucial for decision-making to be guided by the societal objectives of the project. The MCDA method allows the use of available information on the general clinical effectiveness and cost-effectiveness of the standard of care in different alternative areas of application on a more general level to be incorporated. The information on clinical and cost-effectiveness gathered as part of the MCDA process can serve as input for early HTA methods. In that way, the MCDA method can be the start of an efficient iterative appraisal process alongside a translational research project.

The early health economic evaluation of biomarkers

In Chapter 3 and Chapter 4, we have demonstrated how early HTA methods can be adapted and applied to the early health economic assessment of novel biomarkers. Frameworks for the development of biomarker-based technologies place economic evaluation at the end of a number of assessment steps that must be passed. This makes sense from a regulatory perspective, where assessments can be done sequentially, and only those candidates that pass an assessment go on to the next. However, such a sequential assessment framework has limited value for developers and investors. They have to make an estimate of the commercial potential of a biomarker candidate at each of the decision gates in their R&D process. As a technology must fulfill all criteria to be a commercial success, all criteria have to be considered in each
decision. Not determining the potential of a technology under development to fulfill some criteria until very far in the development process is a very risky and potentially costly strategy if a technology under development fails that assessment. An assessment of the strength of the association between the presence of a biomarker and a target disease currently marks the endpoint of biomarker discovery research. This may present a logical time point for a decision gate in translational research. However, methods to provide an early insight into the potential clinical impact and commercial potential of biomarker candidates at this early phase of development have been lacking.

To assess biomarker candidates on their association with a disease or predictive power, only a disease of interest has to be specified. To assess biomarker candidates on clinical impact and economic or commercial value requires a definition of how the eventual biomarker-based technology will be used in clinical practice. This requires a definition of the target population that goes beyond the disease (e.g., age, prior lines of treatment), as well as specification of the clinical decision the biomarker-based test intends to inform (i.e., what is done as a result of different possible outcomes of the test in terms of treatment or other interventions). Such a clinical application definition is often lacking for diagnostic or prognostic tests in development. That in itself poses a problem for well-supported decision-making in the early phases of technological development. It is possible that in an early phase of development a test still has the potential to be applied in many different clinical settings. Assessing the value in all clinical settings is not always a viable option. However, the aim in this phase of development is most often not to obtain an estimate of the total value of an innovation in all possible applications, but rather to demonstrate that clinical applications exist in which the technology is likely to have a large enough value to merit the continuation of development. To that end, specifying the most likely application or the application where the most value can be expected intuitively is sufficient. In case investors want more certainty that the continued development of a biomarker candidate is warranted, an estimate of the total post-market cash
flow can be obtained from the commercial headroom estimate and target population size of one or several defined applications. It can then be decided if this total post-market cash flow presents an acceptable risk-adjusted return on the investments required to bring the biomarker-based technology to market.

One key advantage of the method we demonstrated in Chapter 3 is that it can be done relatively quickly and does not require much data beyond what is available from association studies. This means that such analyses can be done relatively inexpensively and are suitable to be performed for a number of different applications. This is an important quality for such an analysis, as predictive and prognostic tests are more often developed by smaller companies with limited R&D budgets instead of larger pharmaceutical companies. The method can be used to obtain a quantitative substantiation of a value story and enables the identification of inadequate product concepts, thereby reducing the waste of R&D resources. It fits in an efficient ‘fail fast fail cheap’ approach. A limitation of this method, however, is that there is a considerable amount of uncertainty in the outcomes. The method will have limited value in cases where the point estimate of the outcome is ambiguous, i.e., when it does not indicate either a very large or a nonexistent commercial headroom.

Early modeling methods, such as demonstrated in chapter 4 could also be applied at the same phase of development. They have the potential to provide more detailed insights and allow for more flexibility in assessing different scenarios compared to the methods demonstrated in chapter 3. However, early health economic modeling requires much more data and is methodologically more complex. As a result, it is more resource intensive. It is rarely feasible to assess multiple biomarker candidates - each with multiple possible clinical indications - using early health economic modeling unless all these candidates can be assessed using the same health economic model. Apart from the time and resource demands of early modeling, this method also often runs into
the problem of data availability when it is used to analyzed biomarkers or other diagnostic technologies. In order to accurately model the effects of changing the cut-off of the test, detailed data is required from which the relation between the risk level in a population and the effects of treatment in this population can be inferred. Such data is often not available.

**The assessment of stepwise screening programs**

Like all healthcare interventions, screening for prediabetes should be assessed on its cost-effectiveness. However, the complex mechanism by which different design aspects of the stepwise screening program have an impact on the downstream costs and health effects of the subsequent intervention make such an analysis difficult to perform. Conducting a randomized controlled trial of prediabetes screening would be able to answer these questions, but such a study is very unlikely ever to be conducted due to ethical objections. Modeling studies are also hampered by this complexity and the lack of data to model such effects accurately. One way to simplify the economic evaluation of screening is to employ an investment perspective. In this perspective, screening is seen as an upfront investment that will later result in benefits in terms of improved health, lower healthcare expenditures, or both. It is then the objective to design a screening program in such a way that it most efficiently identifies those individuals that benefit from the treatment following identification. In this perspective, the total uptake and cost per identified patient are relevant as they indicate, respectively, the total effectiveness and efficiency of the screening program. Until now, few studies on the design of screening programs have employed this approach. In chapter 5 we demonstrate how a stepwise screening program can be assessed in this manner. This method enables the assessment of the effects of changing many different design parameters of a stepwise screening program in isolation or in combination. Besides optimizing the design of the screening program, it also indicates where further improvements in aspects of the screening program yield the most benefit. This enables setting research priorities
General discussion

over the entire scope of disciplines involved, from the development of more accurate (biomarker-based) screening instruments to public communication strategies aimed at improving participation.

Limitations

The methods we use in this thesis are built on the principles of HTA. This means that they stem from a societal decision context that expects policymakers to aim to provide the largest possible health benefits from the public resources allocated to healthcare provision. The relevance of this decision context for investors and developers depends both on their intrinsic motivation and extrinsic incentives. Investors and developers may have an intrinsic motivation to develop technologies that result in the largest possible health benefit. To some extent, this is to be expected from investors and developers in public-private translational research consortia. External incentives are formed by market regulators and technology purchasers who limit market access and demand for technologies that do not provide good value for money. The extent to which these internal and external incentives are applicable differ per country, type of technology, and project. For example, the market for medical technology is in most countries much less regulated than the market for pharmaceuticals, also in terms of the requirements on the cost-effectiveness of innovations. On the other hand, pharmaceutical companies demonstrate time and time again that their main objective is profit maximization (i.e. ‘creating shareholder value’). Additionally, we observe that regulators and purchasers are not able to keep expensive new products off the market, which likely leads to the displacement of more efficient forms of treatment and prevention. Investors and developers that aim to maximize profit in poorly regulated markets with no regard for the possible harm their actions might cause due to the displacement of more efficient technologies will find little value in our methods. Those that aim to improve the health outcomes of the population will.
Chapter 7

IMPLICATIONS FOR POLICY AND FURTHER RESEARCH

Initiators and funding programs of translational research projects

Agencies investing in translational research who are serious about addressing societal issues would be well advised to use formal decision-making methods when making funding decisions (as discussed extensively above). We have shown that formal decision-making methods can be applied in this setting and that they can identify suboptimal investment options. However, the commitment to optimally allocating resources should go beyond the methods used to inform decisions. In many research funding agencies (biomedical) fundamental scientists are over-represented in the committees that decide on the allocation of research funds (see CTTM for example[26]). This can be expected to impact funding decisions. First, it is likely that fundamental scientists are better able to determine the scientific merit, value, and feasibility of a research proposal, rather than its societal value. To some extent, this limit in expertise can be addressed using formal decision methods, when applied correctly. However, it is also likely that an over-representation of fundamental scientists leads to a conflict of interest. This can be very direct, e.g., when a researcher submits a proposal to a funding agency at which he or she is also a referee. It can also be indirect, such as when fundamental biomedical research as a profession is competing with other research professions for the same resources (e.g., public health researchers, health policy researchers, or health economists). Thus, translational funding agencies (like CTMM and H2020) should include input from experts from all areas relevant to medical innovation in the committees that decide on resource allocation. Apart from fundamental biomedical research, this also would include medical experts, (bio-)statisticians, epidemiologists, health economists, patient advocates, insurance companies/ national payers, manufacturers, hospital management, regulatory agencies, and many others. Obviously, a funding
committee comprised of all these experts can become impractical due to the number of participants and different viewpoints. This, again, is where formal decision methods such as MCDA can help by having a working committee of decision method experts who are impartial to the funding decision collect and synthesize expertise from all these experts to inform the allocation decision.

**Personalized medicine and biomarkers**

The vast majority of biomarker discovery research is fundamental research aimed at obtaining a better understanding of the molecular pathology underlying a disease. Unfortunately, such research has often been presented to investors, funding agencies, and the general public as translational research. This often involves the claim that a biomarker can be used in treatment stratification or risk prediction in a manner that has clinical value (see for example Van der Leeuw et al. 27). For such a claim to be more than just a strategy to make fundamental research seem more clinically and societally relevant than it actually is, a plausible value hypothesis has to be formulated a priori. This fundamental premise of this value hypothesis differs between prognostic and predictive biomarkers.

For predictive biomarkers to be of value, there has to be an indication that there is heterogeneity in the underlying (molecular) pathology or pharmacokinetics in the target population. Sometimes multiple different pathological mechanisms are considered one and the same disease because they present the same symptoms, and the underlying pathologies have yet to be discovered. 28 In these cases, it is possible that differentiating treatment to each pathological mechanism provides better health outcomes. Developing a biomarker that is able to distinguish these different pathological mechanisms and thereby enabling this differentiated treatment can, in that case, have value. Pharmacogenetics has revealed that genetic differences can to some extent explain heterogeneity in treatment response. 29 These genetic differences impact on pharmacokinetics as they are related to liver enzymes.
involved in the metabolism of certain pharmaceuticals. Biomarkers that can identify those patients that are not able to metabolize a drug can have value by avoiding resource waste on ineffective treatments.

In the case of prognostic biomarkers, the value hypothesis is that the distribution of disease risk in the population is very broad or possibly bimodal. In cases where there is a group with a very high risk and one with a very low risk, the classification of patients in these risk categories allows for more appropriate prevention or screening strategies. The value of risk stratification is reduced as the variation of risk in the population becomes smaller. As the health effects of preventive approaches are directly related to the level of risk, there is little value to be gained by stratifying on risk when there is little difference in risk within the population.

When it is not possible to formulate a value hypothesis grounded in current knowledge on the pathology and risk of the disease or pharmacokinetics, biomarker discovery research cannot be considered to be translational. This is the case for a large share of biomarkers published in literature. In case a value hypothesis is formulated, it can serve as a starting point for all methods we have described in this thesis from MCDA to early health economic modeling.

**Type 2 diabetes prevention and screening**

The incidence of DM2 is expected to continue to increase over the coming decades. Given that prognosis it is understandable that policymakers and researchers are looking into ways of preventing or reducing the burden of disease from DM2, either through primary or tertiary prevention. In this thesis, we have attempted to provide an early assessment of the potential of primary and tertiary prevention strategies to address the health and economic burden of DM2 through their impact on the incidence of DM2 or DM2 related complications. However, both primary and tertiary DM2 prevention strategies have an impact which extends beyond their effect on DM2 and related
complications. These interventions should therefore be assessed within this broader context. Primary prevention of DM2 has to be seen within the context of the prevention of metabolic syndrome, that is, overweight or obesity and a sedentary lifestyle. The main prevention tool, lifestyle intervention, is directly aimed at addressing these factors. The target population of such interventions should be defined on risk for developing metabolic syndrome, not only the risk for DM2. The design, implementation, and evaluation of such interventions should be done within this appropriate target population, rather than patients with a high risk for DM2. The idea that the prevention of DM2 must be regarded within the larger scope of the metabolic syndrome had been addressed before the CTMM PREDICCT project had started. Not following this broader approach limited the possible societal impact of the project.

Similarly, tertiary prevention of cardiovascular complications has to be regarded within a broader context of cardiovascular risk management. Over the past years, we have seen an increase in the integration of guidelines for DM2 treatment and cardiovascular risk management. For example, the American Diabetes Association and American Heart Association have published a joint guideline. In this perspective, DM2 is regarded as one of many risk factors for numerous cardiovascular diseases. It should always be considered in conjunction with other risk factors of the metabolic syndrome. This shift in perspective has not yet fully precipitated into the research and development of new prevention strategies in this field. New tertiary DM2 prevention strategies should be regarded as interventions addressing cardiovascular risk factors, and their health and economic impact should be assessed as such.

Assessing innovations for the prevention of DM2 and related complications from the narrow (at risk for) DM2 patient population perspective may lead to underestimating the health and economic effects of these interventions. This narrow perspective can also distort the relative potential of different innovations, when some alternatives only realize an impact in the DM2
patient population, whereas others additionally have a large effect in non-DM2 patients. This may lead to suboptimal decisions when prioritizing research lines or allocating research funding. Assessing multiple research alternatives must therefore always be done from the broader metabolic syndrome or cardiovascular risk management perspective.

The debate whether screening for undiagnosed DM2 is effective, whether or not in combination with prediabetes, still endures in the scientific community. The arguments for and against have not changed much over the past five years. This is in no small part due to the fact that no randomized controlled trial of screening versus no screening has been conducted, and is not likely to be ever conducted. It remains uncertain whether screening and early treatment of DM2 result in improved health outcomes. Circumstantial evidence indicates that population screening (i.e., screening every individual within a certain age group) is not likely to provide any benefits over current care. This is due to the increased awareness of DM2 in the general practice and the subsequent opportunistic screening (i.e., testing for DM2 when it is suspected based on symptoms). As awareness with general practitioners and the general public on DM2 and its risk factors increases further, and as inexpensive point of care tests for HbA1c enable opportunistic general practice, it becomes increasingly less likely that population screening will be a cost-effective use of public health resources. Further research and technological innovation aimed at addressing the expected increasing burden of DM2 should therefore be focused elsewhere.

Further early HTA research

The work presented in this thesis has strengthened the available methodology to assess and guide translational research from beginning to end. That is to say, from investment decision to market access and implementation. We mainly contributed to the first phase of this path, from investment decision to the phase of (pre-)clinical testing. The latter phase, from clinical testing
to market access (i.e., classical HTA) was already better developed and has seen continued development over the past years.\(^{34,39-41}\) The methodology for early HTA will no doubt continue to be developed over the coming years, as questions about the efficiency and sustainability of health care systems will further come to the forefront.

The methods presented in this thesis have been developed within the context of a translational public-private consortium. We are however convinced that these methods are also relevant for private investors and developers of biomedical technologies. Private developers and public-private consortia differ on several important aspects, such as their investment horizon, willingness or ability to take risk, cost of capital, access to necessary expertise, and ultimately their objectives. Further research should be done to optimize the methods presented in this thesis for their application to support the decision-making of private developers of biomedical technologies, taking into account the conditions unique to private development in smaller enterprises. Subsequently, it should be confirmed empirically that these methods provide value for the investment and R&D decision-making in those companies. After all, a scientific field that is committed to maximizing the value created by the healthcare system should be equally committed to maximizing the value of their methods to achieve that goal.
REFERENCES


General discussion