Department of Mathematics and Systems Analysis

Model-based efficiency analyses of healthcare delivery

Yrjänä Hynninen

Aalto University

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Model-based efficiency analyses of healthcare delivery

Yrjänä Hynninen

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Abstract

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Abstract

In the years to come, healthcare organizations are challenged to deliver care to more patients, of higher quality, and with scarce financial and human resources. To improve the value of healthcare delivery, allocating resources efficiently is paramount. In support of allocation decisions, there is an increasing amount and variety of patient-related information available from, for example, clinical tests and biomarkers. This information provides substantial possibilities of improving healthcare but, nevertheless, its full exploitation requires advanced methods.

This Dissertation develops and applies mathematical models to support the efficient use and allocation of resources in healthcare. The models help assess the efficiency of healthcare systems and thus identify best practices for learning. Furthermore, the models can be used to identify efficient testing and intervention strategies. These models can support, for instance, the benchmarking of healthcare systems, clinicians' decision making, policy making, and decisions on the acquisition or price setting of testing or treatment technologies.

The Dissertation provides evidence in support of the claim that systematic methods of efficiency and decision analysis help improve the practices of healthcare. For example, the Dissertation demonstrates that the use of decision-analytic modeling and optimization methods is useful when identifying such prevention, detection, and treatment actions which are, on the one hand, targeted based on patients' personal information, and, on the other hand, efficient on the population-level examination. Also, making the impact of value judgments explicit related to healthcare resource allocation decisions is important and possible with advanced models and methods.

Keywords Healthcare, decision analysis, efficiency analysis, cost-benefit analysis, cost-effectiveness analysis, bayesian analysis, testing strategies, resource allocation

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Tiivistelmä

Tulevaisuudessa terveydenhuoltopalvelujen tarve ja laatuvaatimukset kasvavat paljon. Siksi on ensiarvoisen tärkeää parantaa terveydenhuollon tehokkuutta suuntaamalla resurssit tarkoituksenmukaisesti. Kohdentamispäätösten tueksi on saatavissa aiempaa paljon enemmän kliinisten testien ja biomarkkereiden tarjoamaa potilaskohtaista tietoa. Tämä tietopohjan vahvistuminen tarjoaa huomattavia mahdollisuuksia terveydenhuollon kehittämiseksi, kunhan tieto pystytään jalostamaan kehittyneillä menetelmillä päätöksenteon tueksi.

Väitöskirjassa kehitetään ja sovelletaan matemaattisia malleja, jotka tukevat terveydenhuollon resurssien tehokasta käyttöä ja kohdentamista. Malleilla voidaan analysoida terveydenhuoltojärjestelmien tehokkuutta ja täten tunnistaa parhaita käytäntöjä, joista voidaan oppia ja joita kannattaa ottaa laajemmin käyttöön. Samoin ne auttavat suunnittelemaan kustannustehokkaita testaus- ja hoitostrategioita. Malleihin tukeutumalla voidaan parantaa esimerkiksi terveydenhuoltojärjestelmien vertailu- ja kehittämisprosesseja, tukea kliinikoiden päätöksentekoa ja tuottaa perusteita testaus- ja hoitoteknologioiden hankintaa ja hinnoittelua koskeville ratkaisuille.

Väitöskirjan tulosten valossa tehokkuus- ja päätösanalyysimenetelmät antavat pohjaa terveydenhuollon käytäntöjen systemaattiselle kehittämiselle. Potilaskohtaiseen tietoon perustuvat päätösanalyyttiset optimointimallit auttavat valitsemaan sellaisia ennaltaehkäisy-, havaitsemis- ja hoitotoimia, jotka ovat tehokkaita myös väestötasolla. Malleissa voidaan käsitellä eksplisiittisesti myös kysymyksiä siitä, mitä erilaiset terveysvaikutuksia koskevat arvostukset tarkoittavat muun muassa resurssien kohdentamisen kannalta.

Avainsanat Terveydenhuolto, päätösanalyysi, tehokkuusanalyysi, kustannushyötyanalyysi, kustannusvaikuttavuusanalyysi, bayesilainen analyysi, testausstrategiat, resurssien allokointi

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Publications

This Dissertation consists of a summary article and the following papers.

I Schang, L., Hynninen, Y., Morton, A., Salo, A. Developing robust composite measures of healthcare quality – Ranking intervals and dominance relations for Scottish Health Boards. *Social Science & Medicine*, Vol. 162, pp. 59-67, 2016.

II Hynninen, Y., Vilkkumaa, E., Salo, A. Optimization of sequential testing for medical diagnostics. *Manuscript*, 29+4 pages, 2018.

III Hynninen, Y., Linna, M., Vilkkumaa, E. Value of genetic testing in the prevention of cardiovascular events. *Manuscript*, 19+6 pages, 2018.

IV Hynninen, Y., Vilkkumaa, E., Salo, A. Optimal allocation of resources for utilitarian and egalitarian healthcare objectives. *Manuscript*, 32+2 pages, 2018.

Contributions of the author

I Schang is the primary author. Hynninen implemented the computational algorithms, carried out the computations for the numerical analyses, and took the lead in writing section 3.1. He also contributed to the planning of the study and to the interpretation of the results.

II Hynninen is the primary author. Hynninen and Vilkkumaa formulated the model and developed algorithms based on Salo's initial idea. Hynninen implemented the computational algorithms and carried out the computational analyses. Hynninen drafted the paper. Vilkkumaa participated in writing the final version of the paper. Vilkkumaa and Salo contributed on the positioning, structure, and scope of the text.

III Hynninen is the primary author. Linna proposed the topic and participated in the design of the study and to the interpretation of the results. Hynninen and Linna jointly collected the data. Hynninen implemented the computational algorithms and carried out the computations for the numerical analyses. Hynninen took the lead in writing the paper. Linna and Vilkkumaa participated in writing the final version of the paper and contributed on the positioning, structure, and scope of the text.

IV Hynninen is the primary author. Hynninen took the lead role in establishing the research topic with inputs from Vilkkumaa and Salo. Hynninen formulated the model, developed and implemented algorithms, and carried out the computations for the numerical analyses. Hynninen drafted the paper. Vilkkumaa participated in writing the final version of the paper. Vilkkumaa and Salo contributed on the positioning, structure, and scope of the text.

Preface

For me, this dissertation is a product of collaboration. During the years of my doctoral studies I have received so much help, guidance, cheering, warmth, and compassion by the surrounding people that I feel touched and privileged. I am deeply grateful for all the support. The experiences and encounters of this journey have had a great effect on me and they color the version that I am today and who I will be.

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This journey has given me lessons about myself and life in general: Have courage to let others close, to admit the inevitable weak moments and to ask for help. Discover the strengths of yourself and others, lift them to the light and unite them with mutual respect in order to create something meaningful and exceptional.

Helsinki, February 22, 2018,

Yrjänä Hynninen

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1. Introduction

There is an acute need for and considerable potential in developing systems that deliver the best healthcare for the limited resources that are available. Demand for and expenditures on healthcare increase steadily, as a result of ageing populations, technological developments, and increased medical knowledge (WHO, 2010; OECD, 2015). At the same time, there is also substantial potential for improvement: World Health Organization estimates that globally, $20 - 40\%$ of the healthcare resources could be saved by utilizing the available resources more efficiently (WHO, 2010).

The overarching goal of healthcare delivery is argued to be achieving high value for patients (e.g., Gray, 2012; Porter, 2010; Porter & Teisberg, 2006). Porter (2010) defines value as health outcomes achieved per money spent, where the health outcomes are multidimensional and include, for example, the effectiveness, quality, and timing of care, treatment appropriateness, and the effect on the equality of population.

This Dissertation focuses on two essential elements of improving healthcare and its value. The first element is that of identifying which healthcare systems (i.e., organizations, processes, or programs under scrutiny) perform the best and therefore can be learned from. The multidimensionality of the value of healthcare creates challenges of (i) comparing the performance in a comprehensive and robust way, (ii) presenting the results clearly and intuitively, (iii) assessing to what extent the objectives of healthcare systems related to health outcomes, treatment appropriateness, and other dimensions have been met, and (iv) facilitating communication with the public. Earlier methods vary from estimating the relative performance separately for each objective (e.g., Hauck & Street, 2006) to obtaining a composite measure of performance by setting weights which reflect the relative importance to different indicators (e.g., Smith, 2002).

The second element of improving the value of healthcare considered in this

Dissertation is the design of efficient healthcare delivery strategies. In the context with many alternative clinical tests and treatments, the delivery strategy answers the questions of (i) whom to test, (ii) which tests to carry out and in which order, and (iii) which treatments to carry out based on the test results. Efficiency measures whether healthcare resources are being used to maximize the health outcomes (e.g., Palmer & Torgerson, 1999). The amount and diversity of diagnostic and prognostic information from, for instance, different biomarkers, clinical tests, and activity gadgets grows continuously. This provides substantial possibilities for more accurate estimates about the patient's health, individual preferences, and interventions' effectiveness. Nevertheless, the optimal utilization of diagnostic and prognostic information is not unambiguous, because the tests and biomarkers are rarely totally reliable and entail costs. From the perspective of evaluating the value of diagnostic information, earlier methods in the literature are not entirely aligned with decision support needs: a decision maker (DM) needs to know not only whether information is accurate, but whether it is clinically helpful, possibly in combination with other tests and treatments (Steyerberg et al., 2012; Vickers, 2008).

The scarcity of healthcare resources complicates the design of optimal healthcare delivery strategies and leads to the question of value judgment. When resources are limited, it is impossible to provide everyone with every test or treatment they might need or want. In these situations, a decision maker faces the problem that each unit of resources spent on interventions (for instance, treating a patient or carrying out diagnostic tests) means that somewhere or sometime, resources will be unavailable for some other healthcare purpose (Hunink et al., 2001). This phenomenon lifts the objectives of healthcare delivery strategy from the single-patient-level to the population-level, or to population medicine as Gray (2013) labels it. On the population-level, a decision maker may need to choose, based on her values, the objective of, for example, maximizing the total health outcome of a population or reducing health inequalities, which, in general, result in different optimal resource allocations and healthcare delivery strategies.

Methods of operations research can support decision makers of healthcare in the problem domains described above. Operations research is a scientific approach to decision making which uses techniques such as mathematical modeling and optimization and seeks to determine how best to design and operate a system, usually under conditions requiring the allocation of scarce resources (Winston & Goldberg, 2004). In the last decades, the breadth and volume of operations research applied to healthcare has expanded hugely. To highlight

the suitability of operations research for the problems considered in this Dissertation, we quote Gray (2012): “the choice of which set of cost-effective interventions to invest in within programmes and the allocation of resources across programmes in order to achieve good value health care is a complex, multi-layered problem ripe for operations research”.

1.1 Objectives and scope

This Dissertation develops and applies models for supporting efficiency analysis and decision making in healthcare. These models take into account (i) the multidimensionality of healthcare value and system performance and (ii) the efficient use of resources in order to maximize the appropriate objectives. The models support decision makers and healthcare professionals in realizing the best possible use of available resources. In particular, this Dissertation addresses the following research questions (RQ), which are linked to Papers [I]-[IV] as shown in Table 1.1:

RQ1: What methodological aspects should one consider when attempting to assess the performance of healthcare systems and delivery in a robust and comprehensive way?

RQ2: What kind of framework should one use for designing sequential testing strategies with the aim of expending resources efficiently?

RQ3: What kind of framework should one use for designing healthcare delivery strategies under limited resources with respect to population-level objectives?

RQ4: What is the influence of different population-level objectives of healthcare systems on the healthcare delivery strategies and population-level health outcomes and costs?

Table 1.1. Scope of Papers [I]-[IV]

	[I]	[II]	[III]	[IV]
RQ1	X			
RQ2		X	X	
RQ3				X
RQ4				X

1.2 Research methods and dissertation structure

The modeling approach in Paper [I] builds on ratio-based efficiency analysis (REA) (Salo & Punkka, 2011) which uses mathematical programming methods such as linear programming and mixed integer programming (Bertsimas & Tsitsiklis, 1997) to assess which decision-making units are more efficient than others in converting inputs to outputs. Papers [II], [III], and [IV] use (i) decision trees and Bayesian methods to model uncertainties about the patients' probability of having the disease and the tests' results (see e.g., Hunink et al., 2014; Gelman et al., 2014; Sox et al., 2013), and (ii) dynamic programming to solve the optimal path through the decision tree (e.g., Bertsekas, 1995). Moreover, mixed integer linear programming (MILP) and multi-objective optimization (MOO; e.g., Miettinen, 1998) are used in Paper [IV] to identify the optimal resource allocation at a population-level. In Papers [II] and [III], the efficiency of healthcare delivery is assessed through the framework of cost-benefit analysis (Drummond et al., 2005), whereas in Paper [IV], the framework of cost-effectiveness analysis (Gold et al., 1996) is used.

The rest of this summary article is structured as follows. Section 2 discusses the methodological foundations of the main topics in this Dissertation. Section 3 presents the key contributions of Papers [I]-[IV]. Section 4 discusses the implications of these contributions and suggests avenues for future research.

2. Methodological foundations

2.1 Efficiency analysis

Evaluating and comparing the efficiency of decision making units (DMUs; i.e., systems, organizations, processes etc.) usually involves several criteria. Many of these criteria can be considered either as inputs a DMU consumes or as outputs it produces. In the context of healthcare, the inputs can include, for example, the use of resources and the outputs, for example, the various health outcomes. The efficiency of the DMU is then considered to be the ratio between (i) the value of outputs it produces and (ii) the value of inputs it consumes (e.g., Charnes et al., 1978). Efficiency analysis, a subfield of economics and operations research, provides models to evaluate the overall value and performance with regard to multiple criteria.

In the healthcare literature, there have been calls for the development of composite measures of performance (WHO, 2000; Carinci et al., 2015). Composite measures, as a part of efficiency analysis, summarize the information contained in diverse indicators in a single index and thus simplify the comparison of DMUs (Smith, 2002). Rather than having to identify a trend across a range of separate indicators, a single number may be easier to interpret and thus provides a rounded evaluation of performance. Traditionally in the literature, composite measures of performance have been obtained as weighted averages of criterion-specific performances, where the weights reflect the relative importance of the criteria. Nevertheless, the determination of weights is unlikely to be straightforward because, for example, experts may not agree on what is actually important for the attainment of overall objectives. This difficulty of determining relative importance of the criteria is considerable also because composite measures are highly sensitive to the choice of weights (Jacobs et al., 2005; Nardo et al., 2005; Reeves et al., 2007).

To overcome the challenge of determining appropriate point estimates for criterion-specific weights, data-driven weighting systems are frequently used. Data envelopment analysis (DEA; Charnes et al., 1978), for example, is a widely used method of efficiency analysis in which the weights are derived from the data so as to maximize each DMU's efficiency measure. In DEA, the DMUs' efficiencies are characterized by evaluating them with the output and input weights that are most favorable to them, in the sense that their efficiency ratio divided by that of the most efficient DMU is maximized over the set of output and input weights. As a result, the efficient DMUs are assigned an efficiency score of one, and inefficient DMUs' efficiency scores are between zero and one. Some of the shortcomings of DEA are that (i) the efficiency scores do not discriminate between efficient DMUs, and (ii) the efficiency score is based on one combination of weights, which is typically different for each DMU and also depends on what other DMUs are included in the comparison.

The shortcomings of DEA are addressed in the ratio-based efficiency analysis (REA) methodology (Salo & Punkka, 2011) which resembles the DEA method in that it models DMUs' efficiencies with their efficiency ratios. However, it differs from DEA methods in that it derives results not only based on a single set of weights for each DMU, but for all feasible output and input weights, which fulfill possible statements about the relative importance of different inputs and outputs. REA extends conventional efficiency scores by computing efficiency bounds, which indicate how efficient a DMU can be within a benchmark group of DMUs for all feasible output and input weights. To our knowledge, REA has not been applied to healthcare before the research of this Dissertation.

2.2 Cost-effectiveness analysis and cost-benefit analysis

When healthcare resources are limited, the costs of medical care need to be taken into account in addition to health-related outcomes. Clinicians and policy makers must identify inefficient healthcare systems, management strategies, and interventions and improve them. In healthcare, the most established methods for characterizing efficiency are cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA).

Cost-effectiveness analysis (e.g., Gold et al., 1996) is a method for comparing the relative value of different interventions and clinical strategies by their relative costs and clinical effects. Effects refer to health outcomes, such as cases of a disease prevented, years of life gained, or quality-adjusted life-years (QALYs) in which the outcome, in terms of length of life, is adjusted to reflect the quality

of life (e.g., Sox et al., 2013). The costs and effects of decision alternatives, such as healthcare interventions or strategies, are often presented in a ratio of incremental cost to incremental effect. This incremental cost-effectiveness ratio (ICER) serves as a basis for decision rules of resource allocation between alternative interventions or programs (see, e.g., Johannesson & Weinstein, 1993; Karlsson & Johannesson, 1996). CEA can be used to inform DMs about how to apply new or existing tests, therapies, and preventive and public health interventions so that they represent a judicious use of resources (Sanders et al., 2016).

Cost-benefit analysis (e.g., Drummond et al., 2005) estimates the net benefit of an intervention or strategy as the incremental health outcomes of the program minus the incremental cost, with all health outcomes and costs measured in the same units (either monetary units (Claxton & Posnett, 1996) or health-related units (Stinnett & Mullahy, 1998)). Health outcomes and costs are converted to same units using a coefficient which often represents the threshold of societal willingness-to-pay per an additional unit of health outcome gained. As a decision rule, it is recommended that the interventions which have a positive net benefit should be carried out. In CBA, the efficiency between health outcomes and costs is implicitly considered in the converting coefficient: the less monetary value is assigned to an additional unit of health outcome gained, the more efficient an intervention must be to provide a positive net benefit.

Both CEA and CBA are known to have methodological challenges. First, CEA lacks a criterion for cost-effectiveness: it is not possible to say if an intervention or strategy is cost-effective; it is only possible to compare the cost-effectiveness of alternatives. Artificial threshold values have been used in the decision making, at least in the literature, but those are highly contested (e.g., Eichler et al., 2004; Neumann et al., 2014). CBA, in a sense, provides a clearer decision rule but again, the coefficient value for converting health outcomes to monetary units is highly contested. In Finland, there are no explicit threshold or coefficient values which are commonly used. Elsewhere, values such as $50000 per QALY gained (in the US) or £20000 or £30000 per QALY gained (in the UK) have been used (Cleemput et al., 2008). Second, CEA and CBA are typically used to compare a small subset of predetermined intervention strategies without exhaustively considering all possible strategies, whereby the recommended strategy is likely to be suboptimal (Severens et al., 2001). Third, equity considerations are largely neglected in CEA and CBA studies (Johri & Norheim, 2012; Sassi et al., 2001; Ubel et al., 1996; Weatherly et al., 2009). A normal assumption in the studies is that the value of a health outcome is the same no

matter who receives it. Yet, the distribution of health gains between population sub-groups takes on particular importance in public health, given that there is evidence to suggest that tackling inequalities is considered more preferable by the majority of the population (Cuadras-Morató et al., 2001; Dolan & Cookson, 2000; Nord et al., 1995; Yaari & Bar-Hillel, 1984).

2.3 Decision tree modeling

In medical decision making, there is typically uncertainty about the patient's state of health and thus also in the effects of possible interventions. There are both personal and societal costs of not treating a patient with a disease, on the one hand, and the costs and other undesirable consequences of providing unnecessary treatments, on the other. Often, there are many diagnostic and prognostic tests which can be carried out to acquire information about the patient's state of health and thus to assist decision making. However, tests consume resources and are not totally reliable. From these premises, it is important to determine which tests are optimal and in which order they should be carried out, and given the preceding test results, when it is the time to stop testing and choose a treatment action.

Decision analysis, a field of operations research helps address the above question of medical decision making. In decision analysis, one identifies possible actions and consequences, and selects the action with the best expected consequence, in recognition of relevant risk preferences. Often this process is aided by constructing a decision tree. The principle of the decision tree is first to identify every possible decision, then to identify every possible consequence of each decision, and finally to assign a probability and a benefit to each consequence (e.g., Hunink et al., 2014; Sox et al., 2013).

In the case of a treatment decision, the probability of each treatment outcome can be seen to depend on the prior probability of having the particular disease. In the case of additional testing, these probabilities of having the disease are also dependent on the results of the additional tests. Such models can benefit from Bayesian analysis, where prior belief about the patient's state of health (e.g., the probability of having the disease) is updated according to the information obtained from test results (e.g., Gelman et al., 2014). For fundamental works on this topic in the medical decision making literature, see, e.g., Doubilet (1983); Hershey et al. (1986); Pauker & Kassirer (1980).

2.4 Multi-objective optimization

Almost all real-world optimization problems in healthcare involve multiple, often conflicting objectives. In most decision problems in practice, these multiple objectives or multiple criteria are apparent, such as maximizing diverse health benefits and minimizing costs in healthcare. In the past, such problems have been mostly converted and solved as a single-objective optimization problems. One such approach is cost-benefit analysis, in which the health outcomes and costs are first converted to the same units and then the formed net benefit is maximized. However, because of the contradictions and possible incommensurability of the objectives and criteria, sometimes it is neither possible nor desirable to convert and consider the problem as a single-objective problem.

Multi-objective optimization (MOO; e.g., Miettinen, 1998) provides formal methods for quantitative analysis of decisions with multiple objectives. In MOO, much of the computational effort lies in finding all Pareto optimal solutions, defined as solutions for which there are no other solution which would be as good on all criteria and better on at least one criterion. Once a set of such Pareto optimal solutions has been found, a DM can then use higher-level qualitative considerations to make a choice. Classical MOO methods include, for example, (i) the weighted-sum method which scalarizes a set of objectives into a single objective by pre-multiplying each objective with a DM-supplied weight, and (ii) ϵ-constraint method in which the problem is reformulated such that just one of the objectives is kept and the other objectives are restricted within DM-specific values.

In healthcare, multi-objective optimization is called for, e.g., supporting decision making in priority setting of health interventions (Baltussen & Niessen, 2006). Other examples of healthcare applications are the studies of Cardoen et al. (2009); Harewood (2002); Li et al. (2009); Oddoye et al. (2007); Petrovic et al. (2011).

3. Contributions of the papers

Table 3.1 summarizes the contributions of Papers [I]-[IV]. Specifically, Paper [I] applies ratio-based efficiency analysis (REA; Salo & Punkka, 2011) to the comparison of the quality of Scottish Health Boards. In Paper [II], a decision-analytic model for identifying optimal testing sequences is developed. Paper [III] applies this model to the identification of the optimal use of genetic testing in the prevention of cardiovascular events and assesses the cost-benefit of various testing strategies. Paper [IV] extends the decision-analytic model of Paper [II] to identify optimal population-level allocation of scarce healthcare resources.

3.1 Paper [I]

Paper [I] explores a robust approach to ranking organisations based on a composite indicator of performance in a context of ambiguity about choices of weight sets and choices of appropriate denominator variable. The study adopts a novel ratio-based efficiency analysis (REA; Salo & Punkka, 2011) technique. The main benefit of REA is its ability to use the full set of feasible weights and to take into account multiple denominator variables which in this study represent various probable definitions of the "population at risk". This avoids the need to settle on a single, potentially controversial set of weights and on a single, possibly biased denominator population. The results, displayed as ranking intervals and dominance relations, allow one to identify organizations whose rank cannot be, for example, worse than 3rd or better than 8th. Using data from the Scottish HEAT target system, the study demonstrates the applicability of REA to comparative performance assessment in healthcare.

The significance of the study is that it introduces an intuitive, information-rich, and robust method for comparing the performance of healthcare systems. By using ranking intervals and dominance relations, REA offers an alternative

Table 3.1. Contributions of the papers

Paper	Research objectives	Methodology	Main contribution
[I]	Explore a robust approach for health system performance comparison and ranking	REA methodology	REA considers incomplete information and provides robust composite measures in the form of ranking intervals and dominance relations
[II]	Develop a model for optimizing sequential testing strategies with multiple tests and testing stages	Decision tree, Bayesian analysis, dynamic programming, cost-benefit analysis	Decision-analytic model to determine which tests and in which order to carry out for various segments of population
[III]	Assess the value and optimal use of genetic testing in the prevention of cardiovascular events	Decision tree, Bayesian analysis, dynamic programming, cost-benefit analysis	Optimal use and targeting of genetic testing and its cost-benefit
[IV]	Develop a model to allocate limited resources optimally between testing and treatment and between different patient segments	Decision tree, Bayesian analysis, dynamic programming, linear programming, cost-effectiveness analysis, multi-objective optimization	Optimal priority setting of population and allocation of limited resources. Cost of equity.

for the traditional approach of assigning single performance rankings, which may be questionable from a policy and management perspective. Since REA is able to make the uncertainty on rankings explicit and visualize it, Paper [I] suggests that REA can help improve the transparency and reliability of performance rankings and thus usefully complement the existing techniques of healthcare decision makers.

3.2 Paper [II]

In Paper [II], we develop a decision-analytic model for the optimization of sequential testing strategies. It extends the classical framework of selecting and interpreting diagnostic tests (Doubilet, 1983; Hershey et al., 1986; Pauker & Kassirer, 1980) to take into account a larger number of tests, test results, and testing stages. In the context of multiple available tests, testing stages, and treatments, a testing strategy is defined to determine: (i) which tests should be carried out and in which order? (ii) when is it optimal to stop testing and decide on a treatment action? (iii) how to segment the population of patients for different clinical pathways? The problem of determining an optimal testing strategy is modeled as a decision tree in which the probability of a patient having a disease is updated based on the test results using Bayesian methods. The model applies the approach of cost-benefit analysis, whereby the health outcomes and costs of decisions are converted to same units, called net benefit. Testing strategies are then optimized by maximizing the expected net benefit of a testing and treatment sequence. We also develop a dynamic programming algorithm which can be used to determine the optimal testing strategies in a computationally efficient way for all prior probabilities about the patient's state of health.

The study is important because it provides a generic framework for optimizing and assessing the value of the joint use of tests. Previous methods in the literature have mainly focused on single tests even though in reality, tests are most often used in combinations and sequences. The capability to analyze and optimize testing strategies is particularly important in the future healthcare, given that the number of available tests and the resulting amount of information about the patients' state of health increase continuously. The model helps understand, for example, for whom and at which stage it is justified to use approximate, inexpensive tests, on the one hand, or expensive, state-of-art tests, on the other hand. The assessment of the additional value of a test can also support both acquirement and price setting decisions about novel testing tech-

nologies.

3.3 Paper [III]

In the case study of Paper [III] the model developed in Paper [II] is applied to support the value assessment of genetic testing in the prevention of the cardiovascular disease (CVD) events. The model is used for optimizing the targeting and sequencing of genetic testing alongside traditional risk factors. Specifically, testing strategies are optimized by maximizing the net benefit (CBA approach) on a single-patient level. Paper [III] extends the model of Paper [II] such that the outcomes of the optimal strategies can be presented (i) at a population-level in addition to a single-patient-level, and (ii) separately in aggregated health outcomes and costs. A further noteworthy feature of the study is its exceptionally wide data which is combined from national healthcare registers, the Finnish Institute for Molecular Medicine, and published literature.

To our knowledge, this paper is the first to optimize the targeting of a genetic test to different patient segments in the prevention of CVD events. Even in the more comprehensive earlier analyses in the literature, the focus has been mainly on predetermined strategies in which, for instance, patient segments to be tested have been fixed in advance. The comparison between optimized and predetermined, non-optimized strategies indicates that the optimization provides substantial benefits.

3.4 Paper [IV]

Paper [IV] contributes to the literature of healthcare resource allocation and priority setting. Building on the models of Papers [II] and [III], Paper [IV] develops a model to optimize resource allocation between sequential testing and treatment and between various patient groups. The earlier models are extended to take into account (i) limited healthcare resources and (ii) population-level objectives in the optimization of testing and treatment strategies. The models of Papers [II] and [III] optimize the strategies by maximizing the single patient's net benefit in the context of unlimited resources whereas the model of Paper [IV] takes into consideration that, typically, (i) not everyone can be provided with every effective test or treatment one might need or want, and (ii) the objectives of healthcare policies are often related to the population-level outcomes rather than patient-level outcomes. Under these assumptions, the

model optimizes the testing and treatment strategies and provides the optimal priority setting, i.e., the allocation of resources between testing and treatment and between patient groups. The health outcomes and costs are considered separately throughout the optimization process by utilizing methods of multi-objective optimization (MOO). This approach allows us to identify Pareto optimal strategies while avoiding the use of the somewhat artificial coefficient (e.g., the societal willingness-to-pay threshold) which is needed in the earlier models to convert the health outcomes and costs to same units.

The model of Paper [IV] can be used to understand the impacts of different population-level objectives on testing and treatment strategies. The study compares two population-level objectives: (i) maximizing the total health outcome of a population (utilitarian) and (ii) maximizing the health outcome of those worst off (egalitarian). The utilitarian objective is dominant in standard economic evaluations of public healthcare interventions whereas the egalitarian objective (i.e., the reduction of inequalities) is considered more acceptable by most people and is a primary goal of many public healthcare interventions and programs. The model estimates the impact of the objective on the population-level costs and health outcomes. It also estimates the cost of equity, defined as the opportunity cost in terms of health outcome forgone for the sake of equity. The results support decisions about healthcare policies and help determine a reasonable level of investment on the care of a particular disease.

4. Discussion and avenues for future research

This Dissertation develops and applies new mathematical models to support efficient use and allocation of resources in healthcare. The overarching goal of these models is to assess and improve the value of healthcare systems and delivery. The models serve to support real decision and policy making by acknowledging the multiple dimensions of healthcare processes, most notably by accounting for both costs and health outcomes alike. The models help understand (i) which healthcare systems appear most efficient and can thus serve as benchmarks and (ii) which testing and intervention strategies are efficient. Moreover, the computational algorithms developed in this Dissertation provide reasonable computational efficiency for applying the Dissertation's methods in practice.

The ratio-based efficiency analysis (REA) explored in Paper [I] offers a tool for the robust comparison and ranking of healthcare systems. The REA technique is able to incorporate the full set of feasible weights and different choices of denominator variables when forming the ratio of multiple outputs and inputs. The results include ranking intervals and dominance relations which can help to avoid the forced assignment of a single, potentially controversial ranking based on a composite measure of performance to each organisation under examination.

The purpose of and the level on which comparison methods are carried out need to be chosen carefully. Methods for comparison and ranking, such as REA, can be used for various purposes and on various levels of operations. Traditionally, such methods have often been used for the comparison of healthcare performance between countries or large units such as hospitals (e.g., Linna et al., 2006, 2010). Even though such an administration-level analysis provides a "big picture", it alone may not provide enough practical support for local healthcare managers for decisions, as varying patterns of clinical practice can obscure the analysis at the higher level. For instance, it has been observed that in local

healthcare management, many decision makers prefer to work with local and disaggregated data consisting of separate indicators on different processes, because local management processes can be too different to be consistently compared on geographical level (Schang et al., 2014). Thus, in order to reveal and identify the reasons for differences, it is reasonable (i) to carry out the comparative, composite-indicator-based analyses such as REA on many different levels (e.g., geographical, administrative, provider), and (ii) to complement the analyses with other techniques, such as separate indicators or simulation-based methods.

Papers [II], [III], and [IV] propose and apply models to support the design of optimal testing and treatment strategies, i.e., the sequence of tests and a treatment for various patient groups. One of the strengths of the models is that they integrate the testing and treatment decisions. The domains of testing and treatment are often considered separately in the literature even though they are not independent: both testing and treatment have an impact on patient's health outcomes and costs. For example, an optimal policy for the screening of a disease is likely to be highly dependent on the treatment options of the disease. Another strength lies in the versatility and applicability of the models: they provide a generic framework which can be applied to different contexts, even beyond healthcare in the testing and maintenance of technical systems, for instance.

The models developed in Papers [II], [III], and [IV] are topical in the current healthcare as the amount, variety, and possibilities of information increase continuously. The number of new state-of-art clinical tests and biomarkers grows constantly (e.g., genetic testing (Abraham et al., 2016) and metabolomic testing (Würtz et al., 2015) for estimating cardiovascular event risk), rapid diagnostic tests provide information faster and with less costs (for instance, in managing Ebola epidemics (Nouvellet et al., 2015)), and various activity meters and other gadgets monitor many people's physical activity non-stop. In view of this abundance of information, questions arise: How to interpret information and what decisions to do based on data? What is the value of tests and the information they provide? How can the tests be used jointly in the best possible way?

In addition to relevant mathematical models, addressing these questions requires platforms which gather and combine the data from various sources and from large groups of people: test results on the same patient cohorts, national healthcare register data on healthcare visits, costs, and health outcomes during follow-up periods, quality of life surveys etc. For this purpose, among others, the Finnish government decided in 2016 to invest 17 million euros in a

new national center which integrates all genome, biobank and healthcare utilization registers (Government Communications Department, 2016). The data collected by this center would make it possible to acquire more accurate risk estimates for individual patients which, in turn, would deliver more accurate cost-effectiveness analyses about new tests.

The rapid development of new biomarkers and other health-related data enables personalized medicine which creates new possibilities and challenges for modeling healthcare systems. Personalized medicine emphasizes the customization of healthcare interventions for individual patients using each person's unique clinical, genetic, genomic, and environmental information (see, e.g., Ginsburg & Willard, 2009). Ginsburg & Willard (2009) state, for example, that "the overarching goal of personalized medicine is to optimize medical care and outcomes for each individual, to include treatments, medication types and dosages, and/or prevention strategies [which] may differ from person to person resulting in an unprecedented customization of patient care". From the viewpoint of modeling, this increases the number of possible prevention, testing, and treatment strategies that need to be evaluated, preferably in an integrated way taking into account the whole continuum from health to disease. Here, mathematical modeling and optimization techniques can be powerful tools, although significant methodological and computational challenges remain in determining the solutions for large-scale and multi-group instances (Denton et al., 2011).

This Dissertation opens up several avenues for future research. First, empirical case studies are needed to test and validate the methodological developments of Papers [II], [III], and [IV] in practice. Second, extending and applying the models to the context of comorbidity should be considered. The approach developed in Paper [II] can be used to model multiple diseases and their joint detection and treatment. However, there are challenges related to the availability of suitable data and the computational efficiency. Third, considering the time dynamic of diseases' progression provides an interesting challenge for the scheduling of screening. Often tests and biomarkers are used to screen patients repetitively in order to detect a disease at its early stages or to estimate the risk of having a disease in following years. In this context, key questions include: (i) at what age should one start and end screening and (ii) how often should one carry out a screening test. Fourth, if the aim is to provide even more generic framework, the models of this Dissertation could be extended to integrate all prevention, detection, and treatment decisions. This means modeling, for instance, multiple and sequential preventions and other treatments and the means to measure their effectiveness. Model-wise, this would further

increase the number of decisions to be evaluated which may cause computational challenges. Finally, as the context of healthcare is continuously changing, there is a need for robust optimization results. For instance, the uncertainty and variation related to parameters about costs and health outcomes of interventions imply that methods are needed to help assess how sensitive the proposed strategies are to these parameters. This incomplete information about the model parameters can, to some extent, be captured by allowing parameters to be set-valued (e.g., Liesiö & Salo, 2012; Weber, 1987). Applying such models to healthcare is a potential avenue for future research and requires further work.

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