Precision and Uncertainty

Cancer biomarkers and new perspectives on fairness in priority setting decisions in personalized medicine

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Thesis for the degree of Philosophiae Doctor (PhD)
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Preface

This thesis addresses some of the difficult questions surrounding priority setting decisions for new cancer drugs, especially how personalized medicine may offer both new possibilities and new challenges to the current system - a system where fairness is key: A fair distribution of available resources is the central ambition of priority setting in health.

In no health care system are there sufficient resources available to provide all types of beneficial services to all patients, and this warrants the need for fair distribution of health care according to prespecified principles. While very few would argue for an unfair distribution, there is a room to argue for different types of fair distribution, as the concept of fairness can hold different meanings and be operationalized in different ways.

The corona pandemic has made discussions about priority setting an everyday topic. Theoretical priority setting dilemmas only known from books have suddenly become dinner table-discussions, and questions about how personal characteristics like age, comorbidity and social status should inform priority setting decisions has become part of every-day talk. Moreover, it has been evident that fair distribution of benefits and burdens is something many have opinions about, but opinions are not always agreed upon.

As the pandemic ends there is little reason to believe that the cancer drug controversies will be gone. This can be illustrated with various examples: First, everyone has now seen how much government and society are willing to sacrifice to prevent death, even among the very elderly. Second, funding to tackle the consequences of the corona pandemic and prevent future pandemics must be taken from somewhere, and there might be less money for new drugs. Third, and unrelated to the coronavirus pandemic, is that the drive towards personalized medicine is strengthened every year, and it has not lost momentum during the pandemic.

Personalized medicine is by many defined as the concept of tailoring life-saving treatment to the biological characteristics of individual patients in order to promote longer and better lives. This concept is especially prominent in oncology, where the development of personalized diagnostics and treatment already is part of standard care.

A key feature of personalized cancer medicine is its ability to classify patients into smaller groups based on some commonly shared biological characteristic. For example, mutations in the tumor genome or alterations in the intracellular signaling pathways can be identified and targeted with different type of drugs. This development of highly sophisticated methods for diagnosis and treatment requires skills, effort and resources, and is truly a remarkable scientific achievement. Nevertheless, the health effects derived from many of the drugs are modest, and they literarily come with a cost. The prices for new cancer drugs are very high, which makes them difficult to fund in a publicly financed health care system like Norway's. This again makes fair priority setting both important and challenging.

In this context, my aim for this thesis is therefore to describe and discuss how biomarkers and personalized medicine are being incorporated into priority setting decisions for new cancer drugs in Norway and explore how this may challenge concepts of fairness in the priority setting system. This is a broad aim, involving perspectives from medicine, ethics, economics, politics, and society. The methods I apply in this thesis is perhaps a reflection of this, as I include both empirical and theoretical perspectives from different scientific traditions.

The thesis has the following structure: in chapter one I introduce and contextualize precision medicine and health care priority setting, and I link the two concepts together and highlight some of the main challenges for priority setting in precision medicine. In chapter two I present the aims of the thesis. In chapter three I present the materials and methods applied in the studies and discuss important methodological considerations. Chapter four gives a short synopsis of the results from the three studies, and in chapter five I discuss the strengths and limitations of the three studies before analysing my

results in a broader context and against my research aims. A conclusion is provided in chapter six, before I offer some future perspectives on research and policy based on my results and discussion.

Scientific environment

Since I first started my academic work in 2012 I have been part of what was then called the Global Health Priorities Research Group, which is now the Bergen Centre for Ethics and Priority Setting (BCEPS). BCEPS is part of the Ethics and Health Economics Section at the Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen.

In my PhD project I have also been affiliated with Centre for Cancer Biomarkers, a Centre of Excellence at the Faculty of Medicine, University of Bergen.

My work with this thesis has been supervised by Professor Ole Frithjof Norheim, who has been my mentor from the start. Professor Roger Strand, Associate Professor Trygve Ottersen and Professor Lars Andreas Akslen have been co-supervisors.

I have been employed in a four-year PhD Research Fellow position funded by the University of Bergen.

Acknowledgements

Not a single page in this thesis would have existed without the support and supervision from Professor Ole Frithjof Norheim. He has been my supervisor and mentor since I first entered academia almost ten years ago. Therefore, it is only fair that this first acknowledgement is to him. He is both a world-class ethicist and researcher, and a friendly and caring person. His trust, support, and the freedom and confidence he has given me has been crucial for both my academic development and balancing of work and family life. I am fortunate that our collaboration will continue.

Thank you to all my co-supervisors, who have contributed with important and complementary input. To Roger Strand, who has broadened my perspectives, taught me to question established facts and made my work with this thesis truly inspiring and refreshing. To Trygve Ottersen, who has always been helpful, providing detailed feedback on every text I have sent, and demonstrating what is possible to achieve with dedication and hard work. And to Lars Akslen, who has given me useful advice, believed and supported my work, and given me the opportunity to be a part of an excellent research centre.

I am so grateful to all my colleagues at the Bergen Centre for Ethics and Priority Setting and the Section for Ethics and Health Economics. I cannot imagine a better place in academia, with a friendly, supportive, social, and highly skilful and competent environment. Thank you to Bjarne Robberstad, Inger Lise Teig, Ingrid Miljeteig, Kjell Arne Johansson and Kristine Bærøe. And thank you to all former and current PhD fellows, post-docs, research track students and others whom I have had the pleasure to meet and work with. I dare not mention any names in fear of forgetting anyone. But you know who you are.

During my entire academic career I have been at the Department of Global Public Health and Primary Care. Thank you to Head of Department Guri Rørtvedt and to everyone at the administration who has helped me with so many things during these years.

I want to thank everyone at the Centre for Cancer Biomarkers for always supporting my project and ideas. A special thanks to Elisabeth Wik, Eli Synnøve Vidhammer and Geir Olav Løken for good collaboration. I would also like to thank all those who have had a formal or informal affiliation to the ELSA group, and especially to Anne Bremer. You have all made this group a unique meeting point for interesting discussions and new perspectives.

I am very grateful for the unconditional love and support from my family and especially my parents Kari and Jørgen. They have always believed in me, encouraged me to follow my dreams and ambitions, and never questioned the choices I have made.

Finally, I want to thank my wife Margrethe. You are kind, loving, smart, social, hardworking, and have a stronger sense of justice than anyone I have ever met. It was a book in your bookshelf, the spring we first met, that first introduced me to new ideas about fairness and distributive justice. Together we have three beautiful kids who have probably never really understood what I do at work. To Mikkel, Helle and Edith: thank you for never letting me forget what the most important priorities in life are.

Summary

Introduction: Precision oncology aims to tailor diagnostics and treatment to patients' individual biological characteristics, and a central part of this approach is the stratification of patients into smaller groups. This might increase treatment effect, avoid ineffective treatment and harmful side effects, and promote fair priority setting. But precision oncology may also increase uncertainty about the quality of evidence, creating public controversy and challenges for fair priority setting.

Objectives: The primary aim of this thesis was to describe and discuss how biomarkers and personalized medicine are being incorporated into priority setting decisions for new cancer drugs in Norway, and to explore how this may challenge concepts of fairness in the priority setting system. This was done by investigating three secondary aims, all with special attention to biomarkers: I) To describe the Norwegian system for priority setting and drug appraisal, and to analyse if coverage decisions are in accordance with the established criteria for priority setting; II) To study Norwegian cancer doctors' stated preferences for considering individual patient characteristics in a hypothetical priority setting scenario; III) To provide a critical analysis of the current priority setting practice for personalized medicine through a perspective from science and technology studies.

Methods: Three studies were conducted to respond to each of the secondary objectives. Study I and II were empirical, while study III was a theoretical analysis. In study I we used logistic and linear regression analysis to evaluate drug coverage decision for the Norwegian specialized health care sector from 2014 to 2019, using confidential price data. In study II we distributed a survey to Norwegian cancer doctors where we used a conjoint analysis to elicit preferences in a hypothetical priority setting scenario between two cancer patients. In study III we examined and criticized the Norwegian priority setting practice through a Science and Technology perspective.

Results: Study I shows a strong inverse relationship between the incremental cost-effectiveness ratios and the probability of approval, after price negotiations and

severity of disease has been taken into account. This demonstrates how cost-effectiveness, price negotiations and concerns for a fair distribution of health benefits are systematically implemented in the Norwegian drug appraisal system. This was also found for biomarker-accompanied cancer drugs; however, a systematic quantitative evaluation of uncertainty is not possible due to the lack of data.

Study II shows that biomarker status is perceived as relevant for priority setting decisions, alongside more well-known patient characteristics like age, physical function, and comorbidity. Based on these findings we discuss a framework that can help clarify whether biomarker status should be accepted as an ethically acceptable factor for stratifying patients into smaller groups and give them unequal treatment. In this framework a key aspect of reducing uncertainty is to improve biomarker quality.

In study III precision oncology is seen not only as a solution but also a potential contributor to high health care costs and persisting controversy. We argue that a wider perspective on science and society is needed to strengthen the priority setting system. From a co-production perspective, scientific, technological, and societal developments are causally entangled into each other. Alongside refining priority setting principles, one can and ought to raise normative questions about the trajectory of personalized cancer medicine and of how to create a well-functioning public sphere.

Conclusion: Precision oncology and cancer biomarkers appear to be well integrated in the priority setting system, but there are also concerns about how uncertainty increases and how this may challenge priority setting. Acknowledging the interdependence between science and society, this calls for a stronger emphasis on co-production of knowledge and procedural aspects of fairness. This could strengthen the priority setting system and reduce public controversy. A wider participation of stakeholders is essential, and deliberation must address both the production of knowledge and of standards. The former includes organization of trial design, research and development of new drugs, and even the whole political economy of drug development, and the latter the normative foundations of priority setting, its

principles and practices. In such reimagining there is still a role for biomarkers, but their role would be reimagined too.

List of publications

How Norway rations new drugs: The role of cost-effectiveness, price negotiations and severity of disease in coverage decisions. Eirik Joakim Tranvåg, Øystein Ariansen Haaland, Bjarne Robberstad, Ole Frithjof Norheim. (*Manuscript*)

Precision Medicine and the Principle of Equal Treatment: a Conjoint Analysis. Eirik Joakim Tranvåg, Roger Strand, Trygve Ottersen, Ole Frithjof Norheim. (*Accepted for publication in BMC Medical Ethics*)

Rationing of personalized cancer drugs: Rethinking the co-production of evidence and priority setting practices. Eirik Joakim Tranvåg, Roger Strand. (*Submitted as a book chapter for "Precision Oncology and Cancer Biomarkers: Issues at Stake and Matters of Concern", for publication in the Springer Series "Human Perspectives in Health Sciences and Technology"*)

Abbreviations

A4R	Accountability for Reasonableness
AMCE	Average Marginal Component Effect
AS	Absolute Shortfall
CA	Conjoint Analysis
Cas-9	CRISPR associated protein 9
CEO	Cheif Executive Officer
CML	Chronic Myeloid Leukemia
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CTLA4	Cytotoxic T-lymphocyte associated protein 4
DALY	Disability Adjusted Life Years
DCE	Discrete Choice Experiment
dMMR	deficient MisMatch Repair
ECOG	Eastern Cooperative Oncology Group
EMA	European Medical Agency
FDA	Food and Drug Administration
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
MSI-H	Microsatelite Instability High

NGS	Next Genome Sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
PNS	Post-Normal Science
pp	percentage point
PPP	Purchasing Power Parity
PS	Proportional Shortfall
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
STA	Single Technology Assessment
STS	Science and Technology Studies
TLV	Tandvårds- och läkemedelsförmånsverket (The Dental and Pharmaceutical Benefits Agency in Sweden)
UGT1A1	UDP glucuronosyltransferase family 1 member A1
UK	United Kingdom
USD	United States Dollar

Tables and figures

Contents

1. Introduction

This chapter is structured in the following way: In the first section I introduce precision medicine, how it is defined and has developed. I then highlight some key features, namely stratification and the use of biomarkers. In the second section, I present the concept of priority setting, its theoretical foundation including the dominant view on fairness, and the development and status of systematic priority setting in Norway. I will also introduce other theories of fairness in priority setting, theories that may have a complementary perspective on what fair priority setting is. The third and last section of the introduction links precision oncology and priority setting in health together and presents the persistent public controversy that coverage decisions for new cancer drugs in countries like Norway and the UK continue to rise. This will also identify the knowledge gaps that this thesis seeks to address and lay grounds for my research aims.

1.1 Precision medicine

Better treatment effect and less side effects, and at a lower cost - who can say no to that? This is what precision medicine promises and is for sure an honourable goal. Which patient would not like such a treatment? Which doctor would not like to prescribe this to their patient? Which partner, parent or family member would not want their loved one to be given a medication like that? Our society and the health care system should always aim high: to live longer and better lives.

1.1.1 Defining precision medicine and precision oncology

Precision medicine has been described as a new paradigm and the beginning of a new era in cancer medicine - it is by many used synonymously with the term personalized medicine. A proper introduction to the subject therefore requires an attempt to clarify the different terms. I will first discuss the technical definitions of relevant terms before I in the next section briefly examine the origin and development of precision medicine.

It is difficult to make a distinction between precision and personalized medicine (and this is equally valid for oncology too), and it may not be meaningful to try to separate the two. Some, like the American Cancer Society, do not make a distinction at all (1). The US Research Council prefers precision medicine to personalized medicine as they argue that the latter may be misinterpreted "as implying that unique treatments can be designed for each individual." Nevertheless, they still define the two in the same way: "the tailoring of medical treatment to the individual characteristics of each patient" (2).

In one sense, it can be argued that truly good doctors have always tailored diagnostics and treatment to each individual patient, and that personalized medicine has been around for as long as the art of medicine has been practiced. Many therefore prefer the term precision medicine when describing the novel scientific development of the recent decades. The US National Cancer Institute defines precision medicine as "a form of medicine that uses information about a person's own genes or proteins to prevent, diagnose, or treat disease" (3). According to The Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person" (4).

In Norway, precision and personalized medicine are used almost synonymously. In their action plan for research and innovation in the field of personalized medicine the Norwegian Research Council juxtaposes the terms precision medicine, personalized medicine and stratified medicine, and states that the terms are used to describe "prevention, diagnostics and treatment and follow-up adapted to each individual's biological characteristics" (my translation) (5). A similar definition is used by the Norwegian Directorate of Health (6).

I will use oncology to describe the branch of medicine specialized in the diagnosis and treatment of cancer, both solid tumors and haematological cancers. Sometimes I will use cancer medicine or cancer care as synonyms. Prevention of cancer is also a part of oncology, but not exclusively, as prevention typically involves other areas

both within and outside of medicine. Oncology is at the frontier of precision medicine[1] (7), and precision oncology has therefore been established as an expression used for precision medicine in oncology.

Use of the expressions precision and personalized oncology in publications has been analysed by Audrey Tran and colleagues, and they found that the definitions are overlapping and evolving (8). The use of precision oncology has increased more than personalized oncology and is now the most common expression used. Another important finding is that definitions vary, and consequentially someone may have quite different opinions about what precision or personalized oncology are. Commonly used definitions are "Molecularly targeted therapy", "Molecular biomarkers for subclassification of cancer types" and "Omics and next generation sequencing". Others again may perhaps think of gene editing tools like CRISPR-Cas9 or gene therapies using recombinant adeno-associated viruses, like Zolgensma against spinal muscular atrophy or Luxturna against inherited retinal disease.

Since different publications use different terms and definitions, I believe it is wise to have an agnostic approach. Depending on the context and discussion it might be more correct to use one expression over another, as it may give a more precise description. An example is when discussing n=1 trials, where unique treatment for each unique individual is the key point - here the US Research Council's fear of misinterpretation is actually the correct interpretation.

Many may primarily associate personalized and precision oncology with targeted treatments, but the diagnostics play an equally important role. Targeted therapies are treatments that "…uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells" (9), and companion diagnostics are medical devices, like biomarkers, that provide imformation about a corresponding drug (10). To precisely diagnose a condition with genetic or molecular markers may

[1] Precision or personalized medicine is not exclusive to oncology, as notable development also take place for neuromuscular diseases like spinal muscular atrophy and Duchenne muscular dystrophy, and also other diseases like cystic fibrosis and retinitis pigmentosa. Many of the arguments made about precision oncology is equally valid for precision medicine, and vica versa.

not necessarily lead to targeted treatments, and precision diagnostics can be of clinical importance even without targeted therapies. An example is testing of the UGT1A1 gene, where some have a genotype that reduces the clearance of chemotherapy drug irinotecan and therefore experience greater toxicity. The US Food and Drug Administration (FDA) therefore recommend starting treatment at a lower dose for patients with that genotype (11).

As my work is concerned with cancer biomarkers and precise diagnostics, I will primarily use the narrower expression precision oncology and use it in line with the US National Cancer Institute as "information about a person's own genes or proteins to prevent, diagnose, or treat [cancer] disease". However, in parts where I discuss a wider societal perspective on this practice of tailoring cancer diagnostics and treatments to individual characteristics, as I discuss in study III, I will also use the phrase "personalized". As both the challenges and discussions can be relevant to more than just oncology, I will sometimes also use the phrases "precision medicine" and "personalized medicine".

1.1.2 The development of precision oncology

New diagnostics and treatments are the product of decades of cumulative work, and importantly, they are not only products of science, but also politics and society. Therefore, it is not correct to look for any single point in time where precision oncology started. Two proxy measures can be applied, however, to map, not its scientific origins, but when it first surfaced: citation records and drug approvals. Nevertheless, before I introduce these two, a brief look at the wider context is required.

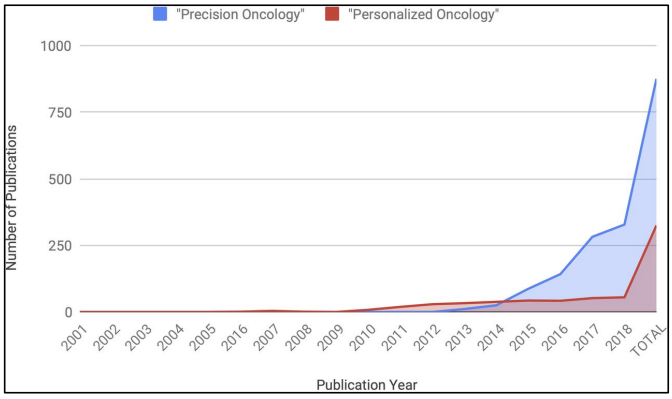
I have already mentioned that personalizing medicine always has been practiced, in the sense that doctors consider the individual characteristics of patients. In the 1950s, pharmacogenetics was established as the first step towards a more biomedical and molecular meaning of the term (12). When the Human Genome Project was started and developed in the 1990s, the vision of precision medicine grew in momentum. It is interesting to note that the leader of the National Humane Genome Institute at that

time, Francis S. Collins, later became the leader of the National Health Institute and a key actor in the development of the precision medicine vision (13,14).

Alessandro Blasimme has nicely described the interaction between science and politics in the development of precision medicine (15). As a Science and Technology (STS) scholar, he examines the "inherent normative drivers that sustain the deployment of novel biomedical paradigms, such as precision medicine" (p.96) and how precision medicine is co-produced from scientific knowledge and social arrangements.

One way of presenting the history of precision oncology is by analysing its citation record. In the retrospective literature analysis by Audrey Tran and colleagues, the use of precision oncology and personalized oncology in Pubmed and Scopus between 2000 and 2018 was quantified and classified. They find that the terms were first used regularly from around 2010 and with increasing frequency from around 2014-2015.

Figure 1: Total number of publications identified with the search term "precision oncology" and "personalized oncology" on PubMed and Scopus, 2000–2018. Figure from Audrey Tran et al. BMJ Open 10.6 (2020): e036357 (8) - reused with permission under CC BY-NC Open access licence.



Another way of pinning precision oncology to the timeline of history is through successful drug developments and approvals. The first and perhaps still the greatest success can be traced back to several decades of research, but the impact it had on

clinical practice was immediate. Imatinib, a targeted therapy for chronic myeloid leukaemia (CML), was given accelerated approval by the US Food and Drug Administration in 2001 (16) based on a phase 1 clinical study that showed an almost 100 % haematological response (17) - a result never seen before in the treatment of CML. A five year follow-up study demonstrated an overall survival of 89 % (18), a dramatic improvement compared to the current standard of care.

Imatinib is a tyrosine kinase inhibitor that deregulates a tyrosine kinase protein that is overactive due to an abnormal switch of positions by parts of chromosome nine and 22. This translocation creates a new gene, the *bcr-abl* fusion, that produces a protein that is part of a cell signalling pathway that causes cells to proliferate at an abnormally high rate, leading to the overproduction of immature white blood cells. The specific chromosome translocation, named the Philadelphia chromosome, can be easily measured[2]. This makes the treatment of CML with imatinib a model for precision oncology: a disease can be accurately diagnosed using a biological marker and a targeted therapy that has an immediate and very strong positive effect on patient survival[3].

Another important early breakthrough was the one concerning the *human epidermal growth factor receptor (HER2)* gene and the development of trastuzumab as a targeted therapy (19). Amplification of this gene leads to overexpression of the encoded protein and a more aggressive breast cancer that has a reduced prognosis, making HER2 both a prognostic and predictive biomarker.

The development of immune checkpoint inhibitors to treat a range of cancers is another and more recent success story, having led to the 2018 Nobel Prize in Physiology or Medicine being awared to two of the research pioneers, Tasuku Honjo and James P. Allison (20). One of the first immune checkpoint inhibitor drugs with a

[2] For more details see Xin An et al. 2010 (138).

[3] This story is unfortunately more of an exception than a rule for precision oncology. Imatinib for treatment of CML is still, after 20 years of research and development, an unprecedented success that no other drug for any other type of cancer has been able to replicate.

large clinical impact was ipilimumab for the treatment of metastatic melanoma. Building on research starting in the 1980s, Madison and colleagues identified and developed an antibody that could bind the T-cell protein CTLA4. T-cells are an important part of the immune system and can recognize non-self structures that can trigger an immune response. However, for the immune response to be full-scale, intracellular brakes in the T-cells, like the CTLA4 protein, must be blocked. The antibody designed by Allison and his co-workers inhibited CTLA4 and could therefore promote a powerful immune response to cancer cells[4]. The first two phase III trials with ipilimumab demonstrated improvements in overall survival, which had not been demonstrated in any other treatment for metastatic melanoma (21,22).

Another landmark drug approval, although without as significant an impact on clinical outcome as imatinib, is the approval of pembrolizumab by the FDA in 2017. This was not the first approval granted to the checkpoint inhibitor pembrolizumab, but it was the first ever drug that was approved on a tissue agnostic indication. Up until then, every cancer drug approval was given on specific tissue indications, meaning it was based on where the cancer originated: Pembrolizumab, for example, had earlier been approved for treatment of cancers in various lung tissues, melanoma, lymphoma and urothelial carcinoma, but this approval of pembrolizumab was not based on any specific tissue indication. Rather, it was approved for "adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors… or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan" (23).

This can be seen as a further advancement in the development of precision oncology. Biological markers (in this case, tumors that are microsatellite instability-high or have a mismatch repair deficiency) that may be present in a range of different histopathological types of tumors, instead of in the tissue of origin, are the indication

[4] A more in-depth introduction to the mechanisms and the development of ipilimumab can be read in a review by Axel Hoos et al. 2010 (139).

for treatment. In August 2020, the FDA granted pembrolizumab a second tissue-agnostic approval, this time with tumor mutational burden as the biomarker (24).

1.1.3 Key features of precision oncology

A typical introduction of precision medicine usually starts by painting a rather sober picture of traditional "one-size-fits-all" medical treatments (or imprecision medicine as it is called by Schork (25)): a drug is given to a large group of patients, who despite their high degree of interindividual heterogeneity, all receive the same treatment. Some of them will respond, most will not, and independent of treatment effect they are all at risk of experiencing side-effects. The total cost is also high, as no one knows who will respond and therefore everyone must receive the treatment.

With this background, precision medicine is introduced: Through (usually) sophisticated technological approaches, patients' own biological characteristics are identified and used to classify patients into smaller groups based on the probability of treatment success (or prognosis or some other feature). Then, different treatments can be given: one drug for those with a high probability of effect, while those who are not likely to respond will not be given the drug. This spares them a treatment that may have severe side-effects. Overall, this is also cost saving as not everyone will be given the treatment.

From this approach it is possible to identify some key features that are needed (and must be successful) for precision medicine to function properly: A) identify biological markers for B) stratification of patients into subgroups, that can then be given C) a (targeted) therapy.

Large resources are invested, and ground-breaking science is being performed to discover biomarkers and develop new therapies for cancer. This thesis is not directly concerned with these achievements. Rather, I am interested in the process of stratification. How are these biological markers, good or bad ones, used to classify patients into groups that may be given unequal treatments? This is not only a technical or medical question; it is also truly an ethical one.

1.1.4 Cancer biomarkers in precision oncology

A common definition of personalized oncology, which I highlighted earlier, is the use of biological markers to classify cancer patients into subgroups. This biological marker may be a genetic sequence, mutation or protein found in the tumor tissue, blood or some other body fluid. The often-cited American National Institute of Health's definition of a biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic process or pharmacological response to a therapeutic intervention" (26). Such a definition is fairly broad, and may suggest that radiological imaging, blood pressure, levels of blood glucose, and even chronological age can be called biomarkers.

Biomarkers are further classified based on their purpose. A prognostic biomarker informs about a patient's prognosis, that is, the natural course of the disease without (further) interventions. This can be used to identify patients that have a higher risk of recurrence or a more severe disease development, suggesting they may benefit from extra treatment. A prognostic marker can also identify patients with a lower risk, which may spare them unnecessary treatment. In localized melanoma, lesion thickness and ulceration are the two most powerful predictors of survival (27). In breast cancer (and in many other types of cancer) histological grade describes how morphologically abnormal the cancer tissue is, a strong prognostic marker for survival (28). Surrogate endpoints used in clinical trials may also be seen as prognostic biomarkers, with measures of tumor growth often used as a proxy for overall survival (29).

A predictive biomarker informs about a patient's potential response to a specific treatment. This may help direct treatment to groups of patients that will benefit more, and also to hold back treatment to patients that would not respond. This is a key feature to fulfil what can be seen as the slogan of precision medicine: "To provide each patient with the right drug at the right dose at the right time" (14). If this is achieved, not only will the benefit of the treatment be higher, but unnecessary side-effects and the overall cost of treatment may be lower as only those likely to respond will be given the drug. Examples of predictive markers are PD-L1 for treatment with

pembrolizumab (30) (which resulted in Tasuku Honjo being awared the 2018 Nobel Prize) and imatinib for treatment of Philadelphia positive CML (18).

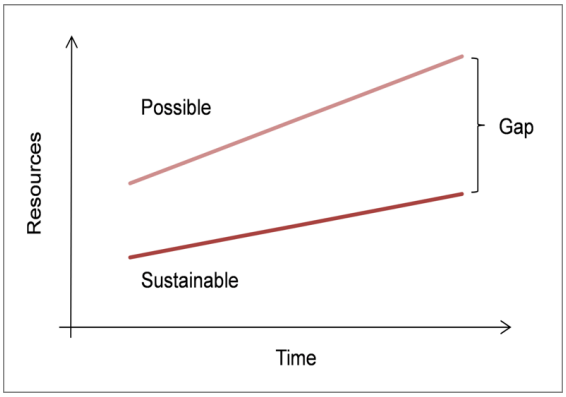
In principle, the attributes of identifying patients with risk of more severe disease or higher likelihood of benefiting from a treatment align well with how many see important principles for priority setting in health care (31), thus making the potential role of cancer biomarkers in priority setting decisions apparent (32). I will return to this in the last section of this chapter but will first introduce the concept of priority setting in health.

1.2 Priority setting in health care

As oncology and medicine progress, new possibilities for diagnostics and treatment are made available. These may be consumed by a growing number of patients, as the incidence of cancer is increasing (33), as are the general public's expectations of what the health care system can offer if one gets cancer; a week rarely passes without some newspaper story about a breakthrough or gamechanger medicine. This notwithstanding, the available resources for health care may not be growing as much as the demand for health care. Even in a wealthy country like Norway, the general budget does not necessarily have the fiscal space to substantively increase funding for health care, particularly not an increase that matches the increasing demand. Long term projections on health expenditure from the Organisation for Economic Co-operation and Development (OECD) suggest a modest increase just above the projected growth in gross domestic product (34).

This discrepancy between the demand for increasing resources and a sustainable financing of health care can be called the health gap. This can be addressed in different ways. Two approaches are to increase funding and invest more, and to get more health out of the money invested. An obvious question for the latter will then be as follows: for which interventions and patients should we invest more money?

Figure 2: The health gap illustrated as the increasing gap between resources possible to spend on health care and the resources sustainable to use. (Made by the author.)



This question can be generalized to all situations where some degree of scarcity, absolute or relative, exists in health care: How should we distribute our resources? Who should be given priority? And how can we ensure that this is done in a fair and ethically acceptable way?

1.2.1 The definition of priority setting

Priority setting can be defined as "who gets what at whose expense" (35). A slightly more detailed definition is the "ranking of services in order of importance" (36). A broader and more general use of priority setting is perhaps "distribution of health care resources" (37), which importantly for the work featured in this thesis also naturally includes drug coverage decisions for new treatments in countries like Norway, Sweden and the UK. As part of all three definitions, decisions must be made based on some order of importance. This is a central part of priority setting, to decide this actual order of importance - what is more important? This question has both substantive and procedural aspects.

Defining priority setting like this means that some patients will be denied interventions that are likely to benefit them - health care is held back, because some service is ranked lower than other services and since, due to scarcity, not all services

can be implemented. This is certainly seen in oncology, where many new drugs with potential benefit, and for some patients sometimes substantial benefit, are not approved for coverage and are therefore not funded by the public.

Before continuing it is helpful to briefly mention other words and expressions that are sometimes used in the priority setting discussion and that may be encountered in the literature. Rationing can be defined as "the withholding of potentially beneficial health care through financial or organisational features of the healthcare system in question" (38). In that sense, rationing is something one does as part or because of the priority setting process, for example, when refusing to approve new drugs for coverage in the public health care system.

The expression resource allocation is perhaps the one that is most synonymous with priority setting, and it is often used interchangeably (39). Other words that may have the same purpose as priority setting, but whose use has not been established in the literature, are financial stewardship, parsimony and prudence (40).

Priority setting decisions are made throughout the health care system, at all levels: at the micro level, meso level and macro level (41). Other names may be applied but follow a similar structure (42). At the micro level, clinical priority setting decisions are being made concerning individual patients: who should be given priority to the only Intensive Care Unit (ICU)-bed available is a classic example. Or what kind drug should be given to a cancer patient. The meso level may involve decisions within hospitals and services, for example, budget decisions about which services to offer. Macro level decisions typically involve national or state budgets or coverage decisions for new drugs in systems like Norway's, which has a national publicly financed single-payer system.

1.2.2 What is fair priority setting?

A broad (but not complete) agreement has been reached, building on population health ethics and principles from distributive justice, that fair priority setting should be guided by two principles: maximizing health benefits, and a fair distribution of

those health benefits (43–47). Results from empirical studies also supports this (48,49).

Maximizing health

The principle of maximizing health benefits has a strong intuitive appeal: if resources are scarce, one should try to obtain as much health as possible from whatever resources are available (50). The principle builds on utilitarian normative theory, which argues that "the morally right action is the action that produces the most good" (51). A strength of this theory is that it sees every individual as equal, and every benefit equally valuable, regardless of who receives it. In health care priority setting, maximizing health means that an intervention that provides more health should be given priority over an intervention that provides less health, if the resources required are similar. The principle is operationalized as types of cost-effectiveness estimates[5].

One shortcoming of the health maximizing principle is that it is agnostic about the distribution of benefits. Priority setting decisions solely motivated by maximizing health can increase inequality in access to health or in health outcomes for individuals and groups in society. If some groups of patients are more difficult to reach, for example, due to geographical or socioeconomic reasons, it may be less cost-effective to treat them compared to other groups, and they may be given lower priority. Therefore, most accounts for fair priority setting include concerns for a fair distribution.

Fair distribution of health

The importance of a fair distribution can be justified from a range of ethical theories. An egalitarian can, in a very general term, be described as someone who attaches some value to equality in itself (52 p. 7). This is perhaps a too wide definition, as

[5] Cost-effectiveness is here used as a general and perhaps unprecise term used to indicate that some sort of cost, in a wide sense, is weighed against some kind of outcome. Cost-effectiveness analysis, cost-benefit analysis and cost-utility analysis all have distinct features and important differences in health economics. See Drummon et al. 2015, chapter 1 (140).

most (if not all) of us attach some value to equality. Egalitarians[6] are concerned with relative levels, with how someone compares with others. In that sense, inequality (in health) is bad because someone is worse off than others. In contrast, a prioritarian is concerned for people's absolute levels instead of their relative levels (53). This means that in health, those who are worse off have a stronger claim to some benefit, independent of how they compare to others. In practice, in health care priority setting, egalitarians and prioritarians would have many of the same views regarding who is worse off.

Being worse off in terms of health has important similarities with concepts like need and severity, which have strong support in clinical medicine and medical ethics. It is common to argue that those with stronger needs and more severe disease have a stronger claim for medical services, a claim that may not be captured in cost-effectiveness analysis. A classic example of this shortcoming is the priority list of interventions made by the Oregon Health Service Commission in 1990 (54): interventions that were to be covered by Medicaid were ranked solely on the basis of their cost-effectiveness, making dental caps for pulp exposure a higher priority than appendectomies for acute appendicitis. Heavily criticized, the list was soon modified, based on a number of other considerations.

A pluralistic view on fair priority setting as a combination of the principles maximizing health and fair distribution of outcomes, where the latter incorporates concerns for both equality and severity, has been established in a range of policy documents over the last years (46,55–57). These are also the two principles Barasa and colleagues identified as central to the consequentialist approach to priority setting, an approach whose aim can be said to be "the development of a set of rational rules to guide priority setting decisions and promote fair outcomes" (58).

Fair process in priority setting decision

[6] Egalitarian theory may be specified in a number of ways, for example, as instrumental or non-instrumental, pure or pluralistic, teleological or deontological. But this pertains to matters outside the scope of this thesis.

Fairness may also concern how a priority setting decision is made, and not only what the consequences are. In contrast to these consequentialist approaches, where priority setting decisions are judged (primarily) by their outcomes, procedural measures for priority setting are not concerned about the outcomes per se but aim to promote fairness in the priority setting process. There may be legitimate disagreement over which principles to apply and how they should be interpreted and weighed. If agreement about the outcomes of priority setting is hard to achieve, one can at least aim for agreement about a fair process. In health care priority setting, Norman Daniels and James Sabins' Accountability for Reasonableness (A4R) framework is the most commonly applied (58). In A4R, four conditions are suggested for ensuring a fair and legitimate priority setting process (59): 1) Priority setting decisions and their rationale must be publicly available; 2) arguments and rationale used in decision-making must be relevant; 3) it must be possible to appeal and revise decisions as new arguments and evidence are available; and 4) mechanisms must be in place to enforce the three first conditions.

Aspects of procedural fairness are incorporated into many of the official policy documents for priority setting, for example in Norway (47,57) and the UK (56,60). However, there are reasons to question how current practices of confidentiality and redaction in public documents prevent procedural fairness (61,62).

The principle of equal treatment

In addition to the principles of health maximization, fair distribution and a fair process, there is much consensus over two more fundamental and underlying principles for priority setting in health (31): Priority setting should be impartial or unbiased, and the principle of equal treatment should be respected. The principle of equal treatment implies that equal patients should be treated equally[7]. But who are to be considered as equal?

[7] A principle that can be attributed to Aristotle (141 page 242).

According to the principle of equal treatment, patients that are equal in all ethically relevant aspects should be treated equally. Moreover, patients that are unequal in some ethically relevant aspects may be treated unequally. Patients that are of a different gender, religion or sexual orientation should therefore be seen as equals, and be given equal treatment, while individual information about prognosis and expected benefit make patients unequal, and may be a reason for providing unequal treatment (63). This ethical rationale for providing unequal treatment to different groups of patients is a key feature in the priority setting system and is also something that is fundamentally challenged by precision medicine and the practice of stratification.

1.2.3 Other perspectives on fairness

Although endorsed by many, these consequential and procedural measures mentioned above are not the only possible strategies towards fairness in priority setting. In this section I will briefly discuss some other approaches that are well-known in ethical theory but not commonly applied in priority setting practice. My aim at this point is not to give an extensive introduction to these views, nor is it to argue that they are in total better suited than the current priority setting theories. Instead, I will return to this matter in my discussion. Importantly, some of these approaches are not mutually exclusive, hence combining them may be feasible.

First, one can reasonably disagree over how much extra priority one should give to the worse off (64). By giving the distribution of outcomes some weight, health benefits that could be gained by maximizing health outcomes are sometimes sacrificed in order to provide a fairer distribution of those benefits.

Concerns for equality may also have different perspectives than equality of outcome. Equal access is an important value in most health care systems, where equality in access to diagnostics and treatment are considered valuable irrespective of the outcome (65). Also, equality is not always related to outcomes. One can argue that in some cases equality is best achieved by giving everyone an equal chance to priority through a coin toss or lottery (66). Modification of such a method can be to create weighted lotteries, where one’s probability of winning is proportional the degree of

how worse off one is, or one where probabilities are proportional to the outcomes. The latter was suggested by Dan Brock as a compromise between the choice between fair chances and best outcomes (39).

These notions about fairness presented above are still concerned about outcomes and consequences, but fairness can be independent of both the sum and distribution of outcome. In contrast to these consequentialist views stands the broad category of non-consequentialism. Non-consequentialism, according to Frances Kamm, denies that what is morally right or wrong is solely determined by its consequences (67 p. 76).[8]

Many see the impartialness of utilitarianism as a strength. Some, however, will argue that proximity, or special obligations between persons, is something valuable that gives rise to moral reason (68). Similar grounds of reason may be found in care ethics and professional ethics: there is a special moral connection between the patient and the health care provider, a connection that exists because of the proximity and responsibility. While most see this view as a beneficial supplement to the more accepted priority setting principles, some go further in their critique. Vegard Bruun Wyller rejects the concept of "fair rationing at the bedside" completely, arguing that the caregiver should not worry about distributive justice and fair rationing at all and only focus on the patient in front of her (69).

Related to, and also integrated into, professional ethics is virtue ethics. Here personal traits like motives, moral character and the underlying question of what sort of person you want to be are central (70). For health care workers this relates to what kind of nurse or doctor you want to be. Trustworthy, honest and caring may be desirable virtues.

Another perspective is presented by Leonard Fleck (71). He argues that priority setting in health needs a pluralistic account of health care justice, because no single

[8] This is perhaps a rather wide definition for some, but it is well-suited to introduce some alternative views on what may be seen as relevant for fair priority setting.

normative theory can "address well some range of practical moral problems that are better addressed by a competitor theory" (p.125). He also uses the concept of non-ideal justice[9] to illustrate that some moral problems are too complex, involve too much uncertainty and are too open for conflicting moral judgements, so that no dominant, reasonable moral judgement may be accepted by all reasonable moral agents. This domain, he argues, is the domain of rational democratic deliberation.

This concrete account of rational democratic deliberation for use in health care priority setting builds on earlier accounts of deliberation and participation as concepts of fairness, like the work of Sherry Arnstein in the 1960s (72). It also links to concepts of procedural fairness, like the accountability for reasonableness framework highlighted earlier by Daniels and Sabin.

1.2.4 The Norwegian system for priority setting

Norway has for many decades worked systematically to develop a framework for priority setting in health. Several official reports and governmental white papers have been developed, starting with the report from the first Norwegian priority setting committee in 1987 (73). In this report, the committee was asked to discuss several principles for priority setting: severity of disease, equal opportunities for treatment, waiting time, aspects of health economics, and personal responsibility for health. All five were considered important for the committee, but severity of disease was recommended as the main criterion for priority setting.

Motivated by an increasingly older and more ill population, and a medical and scientific development offering more possibilities for diagnostics and treatment, a new committee was appointed in 1996. This second official priority setting committee recommended three criteria: severity of disease (as in the first report), expected utility, and cost-effectiveness (74). Recommendations from the report had important impacts on several Norwegian official policies: it provided a base for the Patient's Right Act (75), national guidelines for priority setting, and the establishment

[9] I will return to this concept later in the thesis, as I believe it is well-suited to describe many priority setting decisions for new cancer drugs.

of an official council for priority setting in Norway. This council had an important role as a venue for open and inclusive discussion about difficult priority setting cases, before it was dissolved in 2017.

The second official priority setting report from 1997 was thorough and also very influential. But problems with an increasing health gap continued, and public controversy about priority setting continued. In 2013, before the parliamentary elections, the decision whether the immunotherapy drug ipilimumab should be offered to patients in the public health care system was heavily debated. The initial decision was no, but after an intense media coverage the current minister of health bypassed the official system and ordered ipilimumab treatment to be part of a new clinical study. This decision was criticized by many (76,77), and the need for a new and perhaps more specific set of criteria to guide priority setting decisions were signalled. Two important products emerged: a new official priority setting committee and a new system for evaluating new health technologies.

The third committee was appointed, and it delivered their report "Open and fair - priority setting in the health service" in November 2014 (47). An intense debate followed, and especially controversial was the proposed definition of the severity of disease and its method for estimating it (78). Based on arguments of fairness and distributive justice[10], the committee suggested that severity was to be defined as expected lifetime health loss (meaning both past and future loss), and that estimated lifetime loss of quality adjusted life years (QALY) was the appropriate measure. This, critics argued, would imply that older people would systematically be given lower priority and was labelled as unethical.

As a response to this critique, the minister of health appointed a new working group to explore alternative measures of severity. In their report[11], taking a narrower

[10] Arguments that probably had a wider (and perhaps too wide) perspective than the traditional medical-based arguments for severity of disease.

[11] English summary available at https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/summary_the_magnussen_report_on_severity.pdf

medical perspective on severity, they recommended that severity of disease should not include past health loss and only consider future loss, measured as absolute QALY loss[12]. Another important recommendation was to describe the criteria separately for use at clinical and group levels. Based on this, and with comments from the public hearing process, the Ministry of Health and Care Services submitted their white paper "Values in patient health care" to the Parliament in June 2016 where it was unanimously endorsed (57).

The new set of criteria that now guides priority setting in publicly funded specialized health care[13] consists of three main criteria, and three other supplementary aspects.

1) Health benefit - the priority of an intervention increases with the expected health benefit of the intervention.
2) Resources - the priority of an intervention increases the fewer resources the intervention requires.
3) Severity - the priority of an intervention increases with the increasing severity of the condition.

These three criteria are considered together and may be weighed against each other: if a condition is very severe, and the intervention gives a high health benefit, a higher level of resource use may be accepted. The criteria have different descriptions at individual and group levels. At a group level, health benefit and resource use for the intervention (and the comparator) is estimated using cost-effectiveness analysis, and severity of disease for the group of patients involved is estimated with the QALY loss based on the average age of the patients.

In addition, there are three supplementary considerations that can influence the priority decisions: Quality of evidence (more uncertainty about the evidence gives

[12] Those with a minimal insight into these discussions quickly realized that absolute QALY loss treated age in a similar way as lifetime QALY loss and that critique of the latter was just as valid for the new measure. However, absolute QALY loss did not receive this critique.

[13] In 2018 a report from an official committee assessing priority setting at the municipality level was released. This report has not yet been debated in Parliament.

lower priority) and budget impact (high budget impact gives lower priority) may be given weight in the decision, and for very rare diseases with high severity, a lower quality of evidence and a higher use of resources may be accepted.

Another important result from the ipilimumab case was the recognition that Norway needed a system for assessing new drugs and health technologies and to decide which to include in the publicly financed health care system. In 2013 The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (New Methods system) was launched with its main ambition being the "systematic use of health technology assessments (HTA) to inform decision-making."[14] The system includes a wide range of actors with designated roles and purposes, where the decisions ultimately are made by the four CEOs of the four regional health thrusts in Norway in what is called the Decision Forum.

The New Methods system uses the priority setting criteria to decide if new health technologies (most often new drugs) are to be covered by and used in the publicly financed specialized health care sector[15]. A standardized process is established which includes the use of HTAs to formally assess the three criteria and, if the new technology is found to be too costly compared to the effect, a process to negotiate a lower price.

An attempt to characterize the Norwegian system for priority setting is useful. The system is based on principles that are clearly consequentialist[16]. The aim is to maximize health, with fair distribution as an important adjustment. Equality is a core value, which requires that patients that are equal in all relevant medical and ethical aspects are to be treated equally, but this also opens up for unequal treatment of

[14] www.nyemetoder.no/english

[15] In Norway the specialized health care sector is almost exclusively publicly funded. That means that almost all treatment for cancer, neurological diseases, etc., are done in public hospitals. There is, however, a small but growing number of treatments available at small private hospitals, especially with drugs that have been rejected in the New Methods system. Patients who want treatment with these drugs must cover them out of pocket or through private insurance.

[16] It should also be noted that the Norwegian system is influenced by John Rawls and his Theory of Justice (see 47 page 26).

patients that are unequal in some relevant medical and ethical aspect. Equality is also important in terms of equal access and treatment, irrespective of gender, religion, place of living and more.

1.2.5 Priority setting in other countries

It is not difficult to argue that compared to many other countries, the development of the Norwegian priority setting system has been open and inclusive. The public discussion has been visible for many decades. The White Paper was unanimously endorsed by the Parliament. Norway's combination of a single-payer publicly financed health care system and a well-developed system for priority setting is not seen in many other countries.

Still, other countries have systems and traditions that are similar to Norway, especially concerning their systematic approaches to priority setting at a policy level. A very brief introduction to three of these follows here.

Sweden

Sweden, with approximately twice the number of inhabitants than Norway, has a similar taxed-based publicly financed health care system[17]. The Swedish ethical platform for priority setting is based on three ethical principles: 1) the principle of human dignity, 2) the principle of need and solidarity and 3) the cost-effectiveness principle. The Swedish principles are lexically ordered, which means that the principle of human dignity must always be considered first, before considering the other two principles. Equally, the principle of need and solidarity must always be considered before the cost-effectiveness principle. As for Norway[18], the recommendations was first given in an official report (79), before being endorsed by parliament (55). A key actor in the Swedish priority setting landscape, lacking a Norwegian counterpart, is Prioriteringscentrum, the Swedish National Centre for

[17] Although not forgetting that there also are many details in their health care system that are different from Norway, like the strong decentralization of health care provision from state level to county and municipality levels.

[18] A useful overview of the development in Sweden, Norway and also Denmark can be found in Hofmann 2013 (142).

Priority Setting in Health Care, located at Linköping University[19]. Based on the official white paper, Prioriteringscentrum provides, among other things, tools and recommendations for open and transparent priority setting in the Swedish health care system (80).

In Sweden coverage decisions for new drugs and technologies for out-patient care are based on the three ethical principles and managed by the Dental and Pharmaceutical Benefits Agency (TLV). Much similar to the Norwegian approach, TLV operationalize the priority setting principles into cost-effectiveness and severity of disease, and also allow the cost-per-QALY threshold vary depending on severity (81). An important contrast to the Norwegian system is that Sweden has a more decentralized organisation, and regional county-based pharmaceutical committees can modify the priorities. This is even more visible for in-patient care, where drugs provided at hospitals are solely the responsibility of the regional counties. The TLV provides health economic assessments but do not make any recommendations[20].

The Netherlands

The Netherlands has about 17.4 million inhabitants and has a social health insurance system based on mandatory private insurance schemes. Like Norway and Sweden, they have a decades-long tradition of public discussions about priority setting in health, emphasizing a coherent and transparent process for priority setting. Four criteria for priority setting were originally presented by the Dunning Committee in 1991 and has later been modified a bit: 1) Necessity of care, 2) Effectiveness, 3) Cost-effectiveness, and 4) Necessity of insurance. A fifth criterion, feasibility, has also been added. To approve a new drug or technology, all the criteria must be fulfilled. Drug coverage decisions in the Netherlands are made by an appraisal committee in the Ministry of Health, regulating which treatments to be included in the insurance schemes (82).

[19] https://liu.se/en/research/national-centre-for-priority-setting-in-health-care

[20] A more detailed presentation of the Swedish system can be found in Shah et al. 2014 (143)

Of the five, interpretation and implementation of the necessity of care criteria has been the most discussed. In 2001 a report defined it as burden of illness and suggested it be operationalized as proportional shortfall (PS) (83). PS is estimated on a 0-1 scale and is then categorized to provide different willingness-to-pay thresholds for different levels of necessity (84). The Norwegian approach resembles this, but Norway uses absolute shortfall instead of proportional shortfall.

England

England has around 53 million inhabitants and has a publicly tax-based health care system that is mainly organized through National Health England (NHS). In 1999 The National Institute for Health and Care Excellence (NICE) was established aiming to deliver high-standard care and to reduce variations in the quality of care, adopting five principles for their guidance(85): 1) Robust, 2) Inclusive, 3) Transparent, 4) Independent and 5) Contestable. Among the main tasks of NICE is the technology appraisal program which evaluates new drugs and technologies for the health care services and decides if it should be provided in the NHS. Its main criteria for evaluation is cost-effectiveness, understood as the incremental cost-effectiveness of the new intervention compared to the standard of care (86). In addition, NICE allows for other considerations to be emphasized, like uncertainty, innovation and end of life considerations. However, in an analysis by Helen Dakin and colleagues, they were unable to identify any other factor than cost-effectiveness as significant for approvals (87). Notable is also the establishment of the Cancer Drugs Fund[21] in 2010, which now operates in its second version (88).

1.3 Fair priority setting in precision oncology

At this point, a brief summary is useful in order to orient ourselves towards the gaps in knowledge this thesis aims to address.

[21] The fund has been heavily criticized, especially the first version, for allowing rapidly increasing costs being spent on low-value care.

Cancer is responsible for a relatively large proportion of mortality and morbidity in the world. There is a need for new and better treatment which may have a significant impact on health. The promise of precision oncology is to tailor cancer treatment to patients' individual biological characteristics and thereby increase treatment effect and avoid unnecessary side-effects. In the context of fair priority setting (at least) three main concerns may be raised.

1.3.1 Three challenges for priority setting

First, available studies on drug approvals in FDA and EMA demonstrate a relatively modest average benefit of new cancer drugs (89,90). Many of the approvals are based on surrogate endpoints[22], for which the clinical endpoints may be uncertain (91,92). At the same time, a notable proportion of patients may have substantial benefit from some of these new drugs, benefits that may not be properly evaluated in current methods (93,94). This creates uncertainty about how beneficial many of the drugs actually are, and for which patients they can be of help.

Second, what is certain is that the price of these new cancer drugs tend to be very high, with annual treatment costs regularly above 100 000 USD (95), with some drugs cost far more, like tisagenlecleucel, a novel CAR-T cell therapy priced at 475 000 USD (96)[23]. Such high treatment costs increase the health gap and within the fixed health care budgets, more resources to cancer care means less resources to other types of health care.

Third, despite a more precise biological mechanism for new treatments there are both practical and more inherent traits in precision oncology that increase uncertainty about the clinical evidence. The practical design of clinical trials can generate more uncertainty about the trial findings. Basket or umbrella trials have multiple treatment arms, lack randomization and evaluate surrogate endpoints with a short follow-up time (97). This makes the evaluation of trial outcomes more challenging, especially

[22] This may actually be seen as a type of prognostic biomarkers, but will not be the focus of discussion in this thesis.

[23] In Norwegian currency this equals about 830 000 NOK and 4 000 000 NOK, but these sums are not directly comparable as prices are negotiated and kept confidential. Still, the point is valid: the drugs can be very expensive.

compared to the classical randomized controlled phase 3 trials that historically have been central in drug regulations (98). The biomarkers and companion diagnostic tests used may also have various degrees of accuracy validity and reproducibility, which also increase uncertainty. Combining test into more complex algorithms and large scale genomic testing, as with next generation sequencing (NGS) panels, may further add to this uncertainty (99).

Uncertainty is also present at a more fundamental level of precision oncology. Defining proper criteria and cut-off levels when stratifying patients into subgroups is difficult, and there will always be uncertainty (both medical and ethical) concerning whether some patients are correctly classified. Do all patients with a positive predictive biomarker benefit equally from a certain treatment? If not, how can we in a fair way draw the line between responders and non-responders? Even with a biomarker that with certainty can identify patients that will respond to a treatment, it is likely that there will be a continuum of responses. This is what Leonard Fleck[24] has called "personalized medicine's ragged edge" (100).

1.3.2 Persisting controversy

More treatments with low benefit, high cost and greater uncertainty creates new challenges for regulatory authorities and health care providers worldwide. Many cancer drugs are not very cost-effective, which is an important criterion in most priority setting systems. Still, decisions rejecting new cancer drugs generates much public controversy. Patients, doctors, and the pharmaceutical industry are regularly in the media, most often dissatisfied with a drug coverage decision (101–103).

Often, the ragged edge is a point of controversy: how can some patient be denied a potentially beneficial treatment? Broader and more principal questions are being raised too: is it right to accept the fixed budget for health care or should one advocate for more funding? How much importance should be put on the small minority of patients that sometimes demonstrate a high and prolonged clinical benefit of a

[24] The term "ragged edges" was first used by the philosopher Daniel Callahan to describe the edge of medical progress

treatment, an effect that may be hidden in estimates of average benefit in a group? Does the current system, although it is a product of a democratic process, have the needed trust and legitimacy required to make the coverage decisions?

1.3.3 Biomarkers as the solution?

While it is certainly true that most new cancer drugs only provide a modest average benefit, there is also often a small group of patients with a large and meaningful response. Is denying them treatment fair? One can easily see why biomarkers and precision oncology is seen as a rescue. Biomarkers, both predictive and prognostic, may inform the priority setting criteria directly by identifying groups of patients that are more likely to respond to a treatment, and patients that have a more severe disease (32). Nevertheless, as we also are aware of many potential shortcomings in precision oncology, there are important questions to address: do biomarkers actually inform real life priority setting? How do they inform the priority setting decisions? Or are they primarily increasing uncertainty in priority setting?

And if one takes questions about trust and legitimacy seriously (which I believe one should), another set of questions also emerge: Does the introduction of precision medicine, with biomarkers, stratification of groups and increasing uncertainty also require us to examine our system for priority setting in a new way? Can other perspectives on fairness promote trust and legitimacy in a system where controversy never seems to stop?

2. Aims

The primary aim of this thesis is to describe and discuss how biomarkers and personalized medicine are being incorporated into priority setting decisions for new cancer drugs in Norway and to explore how this may challenge concepts of fairness in the priority setting system.

Secondary aims:

I. To describe the Norwegian system for priority setting and drug coverage and analyse if decisions made are in accordance with the established criteria for priority setting. We also seek to investigate whether approvals for cancer drugs with companion biomarkers are treated equally as approvals for other drugs. These aims are addressed in study I.

II. To study Norwegian cancer doctors' preferences when making hypothetical treatment decisions within the current priority setting system, particularly investigating and discussing how biomarker status is perceived in relation to more traditional patient characteristics such as comorbidity and age. These aims are addressed in study II.

III. Analyse and criticize the current priority setting practice for personalized medicine, emphasizing the interdependence between science, technology and society. This aim is addressed in study III.

3. Methodology

This section starts with presenting the context of my work and how this relates to its generalizability, then discusses some general methodological considerations and finally goes into detail about each papers' methods.

The methods applied in this thesis are perhaps a reflection of the truly interdisciplinary endeavour this dissertation has become. A statistical analysis of coverage decisions, a survey with a discrete choice experiment, and a theoretical analysis using a science and technology framework may not be the component of a traditional medical dissertation. Nevertheless, the questions I try to address in this dissertation are not purely medical. Perspectives of legitimacy, equality and fairness in society warrant a broader methodological approach but do not reduce the importance of careful scrutiny and reflection.

3.1 Context

Precision oncology is global, but still operates in many different contexts. My work and my analysis are done in a Norwegian setting, not only with materials and data from Norway, but also with the Norwegian approach to priority setting as a backdrop. So even if some of the ideas and perspectives in this thesis are universal, they are produced in a very specific context and may therefore not be applicable in other settings. Details about the priority setting system in Norway are already presented in the introduction, so in the following I will only provide a short description about the organization of the system in which my work has been performed.

Norway, with a population of about 5.3 million inhabitants, is a social democratic welfare state with a public health insurance scheme. Spending on health care is high, 6187 USD PPP per capita is the third highest in the world, and 85 % of the total health care spending is publicly financed (34). Broadly, the health care system is

divided in two: the municipalities are responsible for primary care and long-term care, while four regional health thrusts deliver specialized health care [25].

From a global perspective, most Norwegians are in good health. Life expectancy in 2018 was 82.7 years, 7th highest in the world (34). In 2019 cancer (neoplasms) accounted for the largest loss of disability adjusted life years (DALYs) in Norway, with 18 % of all mortality and morbidity caused by cancer. Cardiovascular disease ranked second, and musculoskeletal disease third (104).

The other Scandinavian countries have a similar social democratic welfare state where most health care services are publicly funded, mostly as single payer, tax-based systems (34). Other countries with a similar public funding and organization of their health care systems are the United Kingdom, New Zealand and Canada. Countries like the Netherlands and Germany also have a broad coverage of health care services, but financing is predominately organized with compulsory health insurance. Another element of similarity between these countries is that they have good and developed systems for priority setting. Details for some of the countries have already been elaborated earlier, but at this point I will only highlight the fact that this may make my work more generalizable to these countries than to other countries with different health care funding and attitudes towards priority setting in health.

3.2 Methodological reflections

Study I and study II are empirical analyses. Study I is an analysis of a dataset based on drug coverage decisions in Norway. In study II we sample a group of Norwegian doctors' preferences and analyse the data collected. Both articles are observations, of policy decisions and stated preferences, and can therefore be categorized as descriptive or observational. These observations themselves are not ethical

[25] A detailed presentation (and evaluation) of the Norwegian health care system can be found in Emanuel 2020 (144), which also has the strength of being an external description of the current Norwegian system.

judgements, like in the survey, but are still linked directly to the framework and ethics of priority setting in Norway.

Study III is a philosophical essay, where concepts from science and technology studies and post-normal science are used to analyse central empirical observations from the field of personalized medicine.

3.2.1 Study I - How Norway rations new drugs

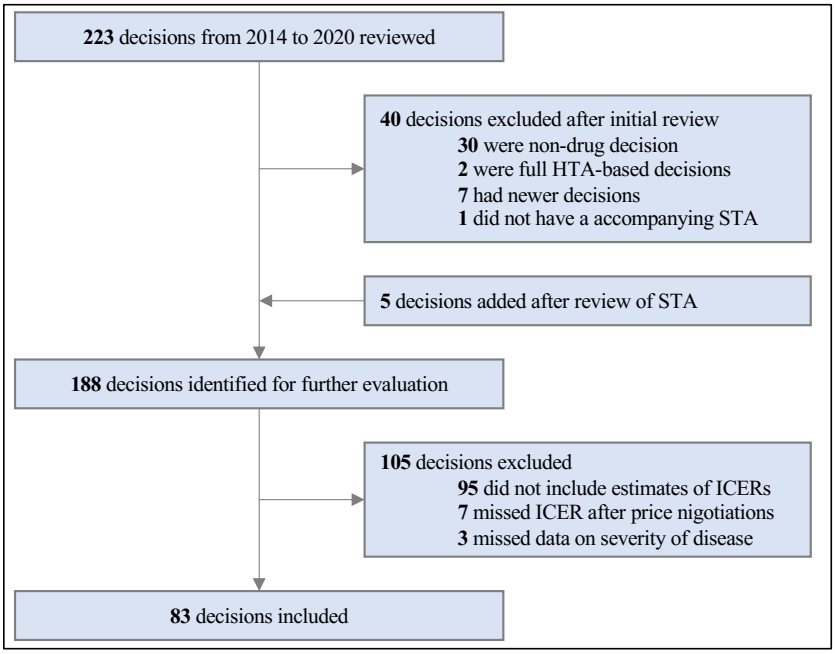
Motivation and aim

Study I was an empirical study where we described and analysed coverage decisions made by the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (the New Methods system). This was motivated by the possibility to evaluate real life policy decisions that are based on the current priority setting criteria in Norway. The other aim was to investigate whether cancer drugs evaluated were approved based on the same standards as drugs for other diagnoses, and if personalization of cancer treatment using predictive biomarkers leads to other thresholds for cost and effect in the coverage decisions.

Material

We received a list of all decisions made in the New Methods system in April 2020. The content of the list was modified as described in Figure 3 below. Of the 223 decisions in the original file, 188 decisions were used for further analysis. Relevant indicators for the 188 decisions were extracted from publicly available health technology assessments, and access to incremental cost effectiveness ratios based on confidential rebated drug prices were obtained after a formal application to the Norwegian Directorate of Health.

Figure 3: Flow chart illustrating inclusion and exclusion of drug reimbursement decisions for our analysis. STA = Single Health Technology Assessment, HTA = Health Technology Assessment, ICER= Incremental Cost-Effectiveness Ratio.



In Norway, the negotiated drug prices are confidential as decided in §13 of the Public Administration Act (105). The Directorate of Health's decision to grant us access to the data was given based on an exemption in §13d concerning information for use in research. The paragraph also states that there may be applied conditions related to the access to confidential information. Two conditions were given for us to access the data: 1) No single drug coverage decision and its corresponding ICER could be identifiable in the published material, and 2) no willingness to pay-threshold could be identifiable in the published material. This was formalized in a signed agreement with representatives from the New Methods system, and results used in publications were presented and approved by them.

Study design and analysis

We analysed all drug coverage decisions between 2014 and 2019 made in the New Methods system. The data was analysed using standard descriptive methods and two

regression analysis: a logistic regression with drug approval or refusion as the outcome variable and cost effectiveness (ICER based on publicly available drug prices, ICER based on negotiated drug prices, and ICER adjusted for severity of disease) as explanatory variables. Results were presented as odds ratios. In the second regression analysis we used linear regression with ICER based on negotiated drug prices as the outcome and severity of disease (absolute QALY shortfall) as the explanatory variable, conducting analysis for 2014-2017 and 2018-19, and stratifying by whether the drug was approved. Results were presented as coefficients and p-values.

3.2.2 Study II - Precision Medicine and the Principle of Equal Treatment

Motivation and aim

Study II was an empirical survey aiming to elicit the preferences of Norwegian doctors working with cancer patients in a hypothetically designed priority setting dilemma: when only one in a pair of two cancer patients can be given a treatment, which patient characteristics are perceived as relevant for deciding? The patients had on average the same potential effect of treatment and remaining life expectancy. Our motivation was then to examine which individual factors that were seen as acceptable for doctors to provide unequal treatment to what could be considered equal patients at a group level.

Participants

Participants were invited by email using e-mail lists from professional organizations of doctors working with cancer patients. Permission to use these e-mail lists was obtained by asking leaders of the organizations to forward an invitation to participate in the survey. E-mail lists from the Norwegian Oncology Society (n = 620), The Norwegian Lung Cancer Society (n= 192) and The Norwegian Society for Haematology (n = 175) were used. The survey was also forwarded to Sections for gynaecological cancer at the following Norwegian hospitals (n = 42): Bergen, Stavanger, Kristiansand, Oslo, Trondheim and Tromsø. The invitation with a short introduction to the project and with links to the survey and a consent form, was

forwarded to participants on March 5th 2019, with a reminder e-mail sent on March 21st. Participation was open until April 12th.

Our sample consisted of 1 029 persons and was a convenience sample, meaning participants were invited based on their e-mail affiliations. This strategy is a non-probability sampling method.

Study design

We designed a conjoint analysis to elicit stated preferences from our respondents. Stated preferences are what respondents say that they will do in a hypothetical choice scenario, as compared to revealed preferences which are what they actually do in real life. Asking about hypothetical choices has some obvious benefits: questions and scenarios may be tailored to investigate particular areas of interest and fit certain statistical models. It may also be easier to ask sensitive questions and allow for respondents to answer such sensitive questions.

A conjoint analysis is a type of discrete choice experiment (DCE). In DCE respondents rank or choose between hypothetical alternatives that are characterized by attributes that they have various levels. In our study the hypothetical patients had seven different attributes (like age, comorbidity, biomarker status, etc.) which again had different levels (e.g., our patients were 63, 75 or 87 years old). DCE have been increasingly used in stated preference studies in recent decades to elicit preferences from patients, health professionals and policymakers about important elements in health care, like valuation of health outcomes, treatment decisions and priority setting practices (106).

Attributes and levels

Seven attributes were given different levels (see Table 1). In the survey methodology they are called attributes and levels, while in clinical medical terminology they are individual patient characteristics with corresponding values. In the ethics literature, they may be referred to as factors relevant for priority setting.

We expected some of the attributes, like sex and education level, to not be perceived as relevant factors for priority setting, based on published studies. Other factors, like physical function and comorbidity, have been shown to be perceived as relevant in many studies, and for some factors, our expectations were agnostic: how patient age, smoking status and biomarker status were perceived was unclear for us.

Table 1: Patient characteristics and accompanying levels included in the conjoint analysis

Patient characteristic	Value
Patient age (years)	63
	75
	87
Biomarker status	Positive*
	Negative
ECOG† performance status**	0
	1
	2
Comorbidity**	None
	Moderate
	Severe
Smoking status	Smoker
	Non-smoker
Sex	Woman
	Man
Education**	Low
	Medium
	High

*Defined as a 50 % probability of better effect than average
** These characteristics were given a more detailed description. This is available in the supplementary material.
† Eastern Cooperative Oncology Group

The corresponding levels for each of the attributes were discussed with clinical experts and tested in a pilot study with eight doctors. In our survey description of diagnosis, treatments and biomarkers are all generic and neutral. No specific cancer diagnosis is given, nor any details about treatment or biomarker type. Data about

benefit of treatment, remaining life expectancy and information about biomarker status are also neutral and generic.

Analysis

A traditional DCE would typically have required us to apply a factorial design, to pre-select some combinations of attributes and levels to keep the total number of combinations to display in the survey low enough. In our experiment we had a total of 648 possible patient profiles, a number far too high for them all to be evaluated by the respondents. The conjoint design that we applied, developed by Jens Hainmueller and colleagues (107), avoid this. Building on three assumptions, that all hold true in our design, it is possible to estimate the casual effects of multiple attributes even if not all possible combinations are evaluated.

Assumption 1:
Stability and no carry-over effect, meaning that a respondent will always make the same decisions if presented with exactly the same pair of profiles again.

Assumption 2:
No profile-order effects, meaning that the order of the two patient profiles does not affect the respondent's response.

Assumption 3:
Randomization of the profiles, meaning that the individual patient characteristics describing the patients are randomized independent of the other characteristics.

The average marginal component effect (AMCE) can be estimated, if the assumptions hold true, by a simple linear logistic regression. AMCE is described as "…the effect on the expected probability if preferring or choosing the profile when an attribute change from one value to another (averaging over the randomization distribution on the profiles included…)" (108 p. 22). And to re-formulate the example then given by Bansak and colleagues to our experiment: "Changing the age of the patient from 87 years to 63 years increases the probability of choosing the patient profile by x percentage points."

The AMCE evaluates the aggregate relationship between attributes (that is, individual patient characteristics) and preferences (that is, the doctors' preferences for prioritizing a patient based on their characteristics). A strength of the conjoint analysis is that it can systematically include a large set of attributes, meaning that many different characteristics can be included in the patient descriptions. Many other types of DCE applies a factorial design, where one must pre-select only a few attributes and limit the number of levels so that the total number of profiles are kept low. As we were interested in how biomarker status was perceived in relation to other individual characteristic, the possibility to include more attributes was an important factor when choosing this method.

3.2.3 Study III - Rethinking the co-production of evidence and priority setting practices

Motivation and aim

Study III is a theoretical study discussing fair priority setting for new cancer drugs in a wider political and societal context. We start by describing the current system and rationale for priority setting in Norway and how rationing decisions seem to fuel public controversy, especially when patients are denied access to new drugs. The achievements of personalized medicine can in one sense be seen as merits of biomedical science. But biomedical science, or science in general for that sake, does not operate in isolation. Many will acknowledge the impact science has on society, but society also impact science. By applying a science and technology studies (STS) lens to personalized medicine and how to ration new drugs in a fair way, we aimed to offer new perspectives and perhaps new ways of thinking about these challenges.

Theoretical approach

The field of STS has a complex and interdisciplinary background developed over decades, originating from what have been identified as two separate streams (109): Studies of technology and studies of science. In addition, the discipline of STS may have a broad and narrow definition: in the broad space of STS, as Hess and Sovacool describe it, lays all scholarly studies of science and technology from any social

science perspective (109). In contrast, in the narrow field is STS the "…study of the processes by which scientific knowledge and technological artifacts are constructed (developed, maintained, and changed) and also the study of the changes in the broader social and material worlds that occur as part of the mutual shaping, co-constitution, or coproduction of science and technology with society and the natural environment" (109). It is the process in which science and technology interact with society, in both directions.

In this study we apply the concept of *future socio-technical imaginaries* from the STS field. Created and defined by Sheila Jasanoff and Sang-Hyun Kim as "collectively held, institutionally stabilized, and publicly performed visions of desirable futures, animated by shared understandings of forms of social life and social order attainable through, and supportive of, advances in science and technology" (110 p. 120), future imaginaries may have both an analytic and constructive purpose. How society collectively constructs and sees a future "good society", and how science and technology can contribute to this, is an important part of such future socio-technical imaginaries.

We also use perspectives from post-normal science (PNS) in our study. PNS originated in the 1980s, from the work of Silvio Funtowicz and Jerome Ravetz as a problem-solving strategy in risk-assessments. In conditions characterised by irreducible complexity, deep uncertainties, a plurality of legitimate perspectives, value dissent, high stakes, and decision urgency, what is considered normal science was considered insufficient (111). The goal of the post-normal methodology is to produce socially and technically robust information fit for sustainable decision-making, as uncertainty about decisions are prominent and stakes are high.

Two insights from PNS are also relevant in the context of priority setting (112): Facts and values are not always separable from each other, which also means that science cannot be separated from the society in which it operates. Moreover, when science and society are together rather than separated, new opportunities for development of narratives and collective imaginaries for desirable futures can be developed.

Analysis

In the study we first give a description of how we see the current situation of priority setting for new drugs in Norway, such as how the controversy surrounding these decisions is persisting, and argue that personalized medicine may continue to fuel this controversy. By then applying an STS lens and the concepts of post-normal science and future socio-technical imaginaries, we try to explore an alternative perspective on the priority setting practice.

3.3 Ethical approvals

Article II was reported to and evaluated by the Norwegian Centre for Research Data (reference number 583480). We did not collect any patient information whatsoever. Accordingly, the study was exempt from the requirement of medical ethics approval as regulated by the Norwegian Health Research Act. Respondents were informed about the project in a consent form attached to the invitation email. Choosing to then participate in the survey was seen as a valid informed consent, a practice approved by The Norwegian Centre for Research Data. Participation was voluntary.

Article I did not involve any personal information, nor did article III, and no ethical approvals are therefore required.

4. Results

In this chapter I will present the main findings from my three studies.

4.1 Synopsis of study I

How Norway rations new drugs: The role of cost-effectiveness, price negotiations and severity of disease in coverage decisions. *Eirik Joakim Tranvåg, Øystein Haaland, Bjarne Robberstad, Ole Frithjof Norheim.*

In this study the Norwegian system for priority setting, and especially how new drugs are evaluated for coverage, is presented. Between 2014 and 2019 a total of 188 drugs were appraised, of which 113 were cancer drugs, of which 49 was accompanied with a biomarker. The overall approval rate was 73 %. The number of annual appraisals increased during the observation period, so did the number of biomarker-accompanied cancer drugs. The approval rate for these drugs was 80 %.

Table 2: Regression analysis of coverage decision. List ICER are ICERs based on publically available list prices for drugs, Negt ICER are based on the negotiated drug prices, and Sev ICER are based on negotiated drug prices adjusted for the severity of the disease group. OR for ICER are per USD10000/QALY. The outcome variable is "approved"

	All decisions		2014-17		2018-19	
	OR	95% CI	OR	95% CI	OR	95% CI
List ICER	0.92	(0.86 to 0.98)	0.92	(0.84 to 1.00)	0.92	(0.83 to 1.00)
Negt ICER	0.71	(0.58 to 0.86)	0.74	(0.58 to 0.94)	0.64	(0.45 to 0.90)
Sev ICER	0.68	(0.54 to 0.85)	0.69	(0.51 to 0.93)	0.60	(0.42 to 0.86)

We find a strong inverse relationship between ICER and the probability of approval after price negotiations and severity have been taken into account. This relationship is strengthened for both outcomes in the second time period after the formal implementation of severity into the appraisal process. The relationship is, however,

weak for ICER based on list prices, which is the non-confidential and uncensored information available to the public.

Figure 4: Severity adjusted incremental cost effectiveness (ICER) for approved and rejected drugs in 2018 - 2019, plotted as mean (X), median (|), 25th and 75th percentile values. Groups are, from the top (I), all drugs irrespective of disease, (II) drugs treating other diseases than cancer, (III) drugs treating cancer, (IV) cancer drugs without companion biomarkers and (V) cancer drugs with companion biomarkers. The dotted vertical line indicates the highest willingness-to-pay threshold for the lowest severity group, to which all ICER have been adjusted.

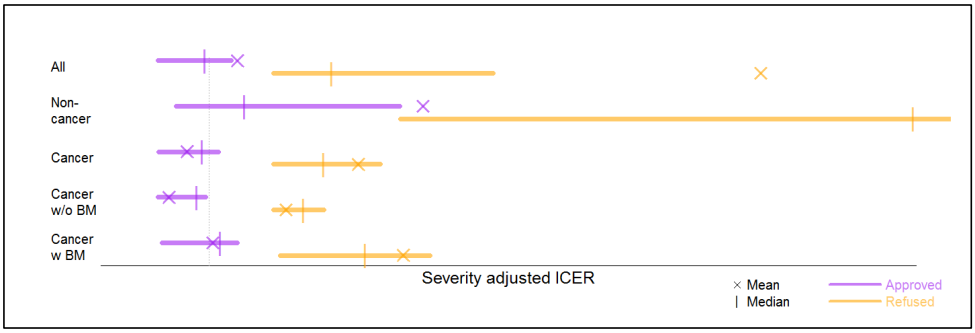


Figure 4 demonsrates that rejected drugs have a much higher ICER than approved drugs. When comparing cancer drugs to non-cancer drugs we find that that approved non-cancer drugs have a higher mean severity adjusted ICER than the other drugs, including cancer drugs. Also, biomarker accompanied cancer drugs have a slightly higher mean and average severity adjusted ICER than non-biomarker cancer drugs.

In this study we demonstrate how Norway's strategy for adjusting cost-effectiveness estimations with concerns for severity of disease in drug coverage approvals have been applied, and we find that the New Methods system makes their decisions seemingly in accordance with the official criteria.

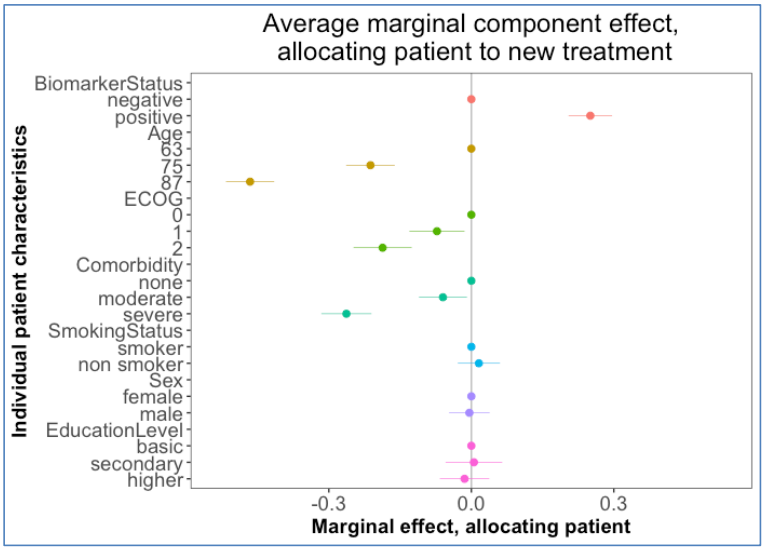
4.2 Synopsis of study II

Precision Medicine and the Principle of Equal Treatment: a Conjoint Analysis.

Eirik Joakim Tranvåg, Roger Strand, Trygve Ottersen, Ole Frithjof Norheim

In this study we distributed a web-based survey by email to Norwegian doctors treating cancer patients. Our aim was to elicit stated preferences for how personal patient characteristics, including biomarker status, influence priority setting decisions for cancer patients who were considered to be equal at a group level. The average marginal component effect of each characteristic was estimated.

Figure 5: The average marginal component effect (AMCE) of changing one individual patient characteristic compared to its baseline characteristic. Lines represent 95 % confidence intervals. A positive AMCE indicates a higher probability of being allocated the new drug, while a negative AMCE indicates a lower probability.



We found a 25 percentage point (pp) increased probability that respondents would give the new drug to a patient with a positive biomarker, compared to a patient with a negative biomarker, when averaged on all other possible combinations of patient characteristics. Biomarker status produced the third largest effect of the patient

characteristics in the experiment: a patient aged 87 years has a 47 pp reduced probability of being allocated the new treatment compared to a patient aged 63, and a patient with severe comorbidity has a 26 pp reduced probability of being allocated the new treatment compared to a patient with no comorbidity. All these findings were statistically significant.

Other patient characteristics with a significant effect on the probability of being allocated the new treatment were patient age 75 years (21 pp reduced probability compared to age 63), ECOG performance status 1 and 2 (7 pp and 19 pp reduced probability compared to ECOG performance status 0) and moderate comorbidity (6 pp reduced probability compared to no comorbidity). Importantly, sex, smoking status and education level had no significant impact on the probability of being allocated the new treatment.

These results demonstrate that biomarker status is considered as relevant information when providing unequal treatment to patients that are considered as equal. Biomarker status was not found to be the most important factor, but ranked third after patient age and comorbidity, and this may illustrate valid concerns about uncertainty.

4.3 Synopsis of study III

Rationing of personalized cancer drugs: Rethinking the co-production of evidence and priority setting practices. *Eirik Joakim Tranvåg, Roger Strand*

In this theoretical study we start by stating some observations about health care systems and the current priority setting practice. Health care costs are rising, and many countries have established systems and institutions for fair and rational priority setting, including drug coverage decisions. Equality, transparency and neutrality are key values. Still, controversies surrounding these decisions persist.

Personalized medicine is seen by many as an important solution. By tailoring treatment to patients with predicted benefit, drugs are given only to those who respond best, while withholding the drug from those who do not respond to avoid

side-effects and reduce costs. In the study we argue that personalized medicine can instead also further increase costs as the market-based system can price new drugs for smaller groups of patients higher than old drugs for larger groups. This aim for precision may also reduce the quality of evidence and actually increase uncertainty.

With perspectives from science and technology studies and post-normal science, we examine this situation and show that the scientific development itself may further undermine the priority setting practice when faced with the challenges of personalized medicine. Factors that distinguish legitimate from illegitimate discrimination of patient groups may not be easy to find. Objective and purely medical characteristics may not be easy to separate from the normative characteristics, and with increasing uncertainty, it will be even easier for everyone to claim that decisions are unfair.

A possible solution to this may build on the fact that science is not independent from society and that what is seen as facts is not independent from values. From a co-production perspective, scientific, technological and societal developments are causally entangled with each other. Alongside refining priority setting principles, one can and ought to raise normative questions about the trajectory of personalized cancer medicine and how to create a well-functioning public sphere. When uncertainty is dominant, and stakes are high, normal science will not provide certainty and truth to solve the problem. A sustainable and inclusive process of deliberation is key, with the aim of agreeing on a set of knowledge and values of mutual acceptable quality for all participants.

For the challenge of persistent controversies surrounding cancer drugs, despite systematic and rational processes for priority setting, we as a society should engage in sociotechnical imaginaries. Scientific, technical and societal orders are co-produced, meaning that they are developed and produced together. Biomarkers, cancer drug development and priority setting cannot be seen as only scientific but must be reimagined together with the whole constellation of medical research, technology and

practice together with the institutions and practices of priority setting. This will involve a procedural dimension of participation, inclusiveness and transparency.

5. Discussion

The aim of this thesis is to describe and discuss how cancer biomarkers and personalized medicine are being incorporated into priority setting decisions for new cancer drugs in Norway and explore how this may challenge concepts of fairness in the priority setting system. In the introduction I have presented personalized medicine, the system for priority setting in Norway, and the challenges faced in the intersection between them. Based on this I have introduced my research aims and presented the methods I have used to investigate these aims. Lastly, I have presented a synopsis of my findings.

In this chapter I will first very briefly summarize my main findings and then discuss the strengths and limitations of my work and how this may influence the interpretation. I will then discuss and interpret the results in light of the introduction, my aims and relevant research.

5.1 Main findings

In study I, we find that the current system for coverage decisions for new drugs in Norway adhere to the official criteria for priority setting. Cancer drugs with companion biomarkers are approved against the same threshold as other drugs, although mean and average incremental cost-effectiveness ratios are a bit higher than for approved cancer drugs without companion biomarkers. We also find that current appraisal practice does not assess and integrate information about uncertainty regarding evidence in a systematic way.

In study II, we find that our sample of Norwegian cancer doctors perceive biomarker status as a relevant patient characteristic in priority setting decisions for new and costly cancer drugs alongside patient age, physical function and comorbidity. We use the results to discuss how and when individual patient characteristics can be seen as ethically relevant reasons for providing unequal treatment to similar patients, and we suggest that uncertainty about biomarkers' validity and utility may influence its use.

In study III, we first discuss some of the basic values and traits of the Norwegian priority setting system and observe that the current practice based on fairness, equality, rationality and well-founded criteria is challenged by uncertainty and controversy, and that personalized medicine is likely to increase these problems further. Building on a science and technology perspective, we then argue that co-production of knowledge, embracing both procedural and substantial elements, may reduce controversy and provide a more robust strategy for handling uncertainty and ensure fair priority setting practices.

5.2 Strengths and limitations

In the methods chapter I discussesd methodological choices and general considerations relevant for the thesis. In this section I will be more specific about the methods applied and critically examine how they may influence interpretation of results and the subsequent discussion.

Before discussing each study individually, I think it is relevant to reflect a bit upon my own position and role as a researcher. In qualitative research, reflexivity is an important term describing how "a researcher's background and position will affect what they choose to investigate, the angel if investigation, the methods judged most adequate for this purpose, the findings considered most appropriate, and the framing and communication of conclusions" (113). Or, in the words of Jonathan Ives and Micheal Dunn: "the arguments one finds appealing, and the evidence one is willing to accept, depend on who we are and what we have experienced" (114).

I trained in medical school, meaning that I learned much more about myocardial infarction and depression than about normative ethics and philosophy of science, yet this PhD is more about the latter than the former. And in clinical practice imminent decisions are required, often based on very practical problems: "What kind of treatment should this patient have right now". To disconnect from this view that every problem requires a solution has been difficult and is something that I have had several discussions about with my supervisors.

The fact that two of my supervisors were central in the development of the current priority setting criteria and practice also influences my point of view. I am almost starting from within the system. This, together with my strong affiliation to the Centre for Cancer Biomarkers, has most certainly influenced how I have approached and planned my research. Importantly, this could also invite questions about whether a critical position on the priority setting system and use of biomarkers would be possible. I believe this is something that is possible, much due to the open and constructive discussions between me and my supervisors.

Study I

This study is the first ever to describe the priority setting practice in Norway using the actual cost-effectiveness data estimated from negotiated and confidential drug prices. The statistical methods applied are not very complicated and I therefore consider the limitations in this study primarily to be issues about access and the content of the data, rather than how it is analysed.

An important limitation to our work in this study is the systematic censoring in public documents, lack of detailed documents describing discussions between the decision makers, and the constraints given to us as part of access to the confidential data. As we only can describe and analyse the available data, there may be important considerations, systematically applied or not, that have influenced drug coverage decisions. This I think is an important societal and democratic problem, which I have written about elsewhere (62). In this study, we had to acknowledge it and make sure our interpretation was in line with these limitations.

Uncertainty about evidence, which is a key factor in decisions and a theme for this thesis, is not systematically reported in a quantifiable way in the available data. Whether the degree of uncertainty has been a relevant and potentially decisive consideration for decision makers cannot be answered in our study, as we did not find indications that uncertainty is handled in a systematic way.

Of the 188 drug coverage decisions we identified for further analysis, only 83 were included in our analysis. For 95 of the decisions no incremental cost-effectiveness ratio was estimated. This is a strategic decision by the authorities, made to make the appraisal process quicker and more effective as the number of drugs for appraisal increases each year. Alternative appraisal processes can typically be applied for some drugs that may enter a tendering competition, or drugs that are considered as having a comparable clinical effect as similar class drugs. For another ten decisions, either ICER based on negotiated drug price or estimates of severity of disease was missing. This makes our findings less generalizable, as it may be that these other 105 decisions are made with different considerations taken into account.

Study II

Our conjoint analysis is the first to include biomarker status in a discrete choice experiment alongside other patient factors like patient age and comorbidity, providing a robust experimental design for eliciting hypothetical preferences. Two important critiques of the AMCE method require some further reflection. First, De la Cuesta, Egami and Imai argue that the AMCE rely too much on a random distribution of the (patient) profiles in the real world (115). For our analysis this would mean that, in theory, the method assumes that there is an equal distribution of cancer patients aged 63, 75 and 87, for example, or an equal distribution of patients with ECOG status 0, 1 and 2. The fact that the median age of incidence for all cancers in Norway is 69 years (116) makes patients aged 87 less frequent than patients aged 75 and 63. Still, as the average life expectancy in Norway is over 80 years, it is far from uncommon that cancer patients in their 80s are provided treatment, and with the projected increase in cancer incidence among older adults in the decades to come (33), an even larger share of patients will be in their 80s.

Second, Abramson and colleagues provide important comments to the use of AMCE, and I will address two of them here (117). First, they emphasise that the AMCE is an average estimate of the direction of preference and its intensity and hides

heterogeneity in preferences[26]. In practice, this means that even if a large majority of my respondents have a weak preference for not giving priority to the youngest patients, this may be dominated by a minority of respondents having a strong preference for prioritizing the youngest. I believe this is a valid point, and it also relates to the second comment from Abramson, Koçak, and Magazinnik: the AMCE must be carefully interpreted. Although their examples are from political science, they can be easily re-formulated to my experiment: The AMCE does not estimate what the majority of doctors state about their preferences for priority setting, nor does it estimate what the average doctor's preferences for priority setting are.

To these comments I think the best reply is to agree and emphasize what AMCE actually is and does estimate and not interpret it in any other way, and also to acknowledge that yes, both direction and intensity are part of the AMCE estimates, a fact that may also bee seen as a strength, as the AMCE method is a useful tool for "understainding mulit-dimensional choices on a uni-dimensional problem" (108).

Using online surveys has many advantages compared to traditional mail-based surveys (118): low costs, a flexible questionnaire, and faster processing of data. There are also disadvantages, and among these it is well-known that response rates tend to be lower compared to mail-based surveys. Two meta-analyses compared response rates between the two distributional strategies and found reduced rates for e-mail surveys compared to traditional mail surveys (119,120). An explanation for this has been that internet-based surveys require internet access and computer literacy (118), but an updated meta-analysis from 2020 using the same strategy as Manfreda et al. (2008) found approximately the same result: in general, e-mail surveys have poorer response rates than mail-based surveys (121).

Low response rates make generalizability difficult. Some argue that a low response rate does not necessarily bias results (122); however, with our response rate of 11.2 % it is clear that our findings cannot be generalized. We applied a convenience sampling

[26] This important point has been raised by both my supervisor Roger Strand and my colleague Kristine Bærøe.

and did not recruit a representative sample of doctors, and we cannot claim that our findings are representative of all Norwegian cancer doctors. Importantly, we do not do so in our article. As we write, "We opted for a broad distribution of our survey using convenience sampling and designed the experiment to ensure good internal validity." Our discussion is therefore primarily considering principles and normative elements, and we only use findings from our survey to illustrate and inform the discussion.

Could we have applied a different strategy to improve generalizability?[27] I will comment on two aspects of this: how to increase the response rate, and how to collect more information about non-responders. First, there are known measures to improve survey response rates, systematically presented and discussed by Jennifer Dykema and colleagues (118). Incentives, like small sums of money paid in advance, have been found to be particularly effective. Pre-notifications, well-written invitations and reminders have an impact on response rates.

A comparison of those who respond with those who do not respond, can say something about the generalizability of the findings. To assess this nonresponse bias, one would need a good sample frame (123). Information about respondents is typically collected in the survey, such as demographic variables like age, sex, working experience, etc. Information about those who do not respond must be available outside of the survey and are typically found in established panels used to recruit respondents[28]. In our convenience sample we did not have data about those on the e-mail lists. Membership data from the largest e-mail list (620 of 1019 respondents), the one pertaining to the Norwegian Oncology Association, indicate that our sample was representative in terms of age and sex. However, similar information was not available for the other invitees.

[27] This would obviously also be important learning for planning and the distribution of future surveys.

[28] One example of this could be the panel of representative members in the Norwegian Medical Association, used in Bringedal et al. 2018 (145) and several other surveys on doctors in Norway.

In the methods section I explained how and why we chose to use generic descriptions of disease and personal characteristics. Another option could have been to give more details about the diagnosis and also base treatment and biomarker data on real life observations. As an example, we could have designed the survey based on data from the programmed death ligand 1 (PD-L1) biomarker, which is currently integrated into clinical practice (124,125). But as our survey was distributed to different medical specialities, where some work only with lung cancer and others only with haematological cancers, we did not want to highlight any particular cancer type. Moreover, we did not want to use specified biomarkers in the survey. A possible limitation is that doctors may be reluctant to include information from unknown sources in their decision making, and if doctors that are familiar with the PD-L1 biomarker recognised it, they may have put more emphasis on the information it provided.

Norwegian treatment guidelines also give clear guidance on which treatments can be given at a group level, and a patient's biomarker status is currently only relevant for allocating a drug that has been given coverage approval at a policy level[29]. It is known that Norwegian doctors have confidence and follow such guidelines (126). However, neither predictive or prognostic markers are given much weight at an individual priority setting level, perhaps as a reflection of the strong status the principle of equal treatment has (47). This is partly why we decided to create a hypothetical scenario for our survey, and this may have been perceived as unfamiliar by the respondents. An important reason for still doing this was that despite its limited use at an individual level at present, I believe the development of precision medicine will make such use more accepted in the near future. To be able to investigate the dilemma this brings, we decided to create a hypothetical scenario.

Study III

[29] An example is the National Guidelines for lung cancer diagnostics and treatment, found (in Norwegian) at http://nlcg.no/wp-content/uploads/210104-Nasjonalt-handlingsprogram-for-lungekreft-mesoteliom-og-thymom-04.01.2021-1.pdf

The strength of study III is that its format allows us to extensively discuss theoretical challenges and potential solutions. This makes it a useful addition to the two first studies that have a more limited and constrained perspective. Building the theoretical discussion around uncertainty is an obvious next step following the two first studies.

There are important points for discussion that also relate to the interpretation and discussion of the thesis overall. The first concerns the lens through which we examine the problem of uncertainty and controversy. Choosing perspectives from science and technology studies and post-normal science does influence how we interpret and analyse the problem. Another perspective for our analysis could have been the accountability for reasonableness framework of Sabin and Daniels, a strategy used by others in different priority setting analysis. A different perspective would have given a different analysis but would not have made the result any better or worse.

In STS the development of science is not accepted as something that just happens by itself, without any control. The scientific development is not something one can only accept and adapt to; rather, it is also shaped by science and politics. With the attention uncertainty has in this thesis, it felt appropriate to apply a post-normal perspective, knowing that how uncertainty is handled is a central theme. That these perspecives also are fairly new in the priority setting literature was also something I see as a benefit.

In our analysis we decided to contrast the current priority setting practice (which we call Plan A) with our new perspective (called Plan B). This can certainly be criticized for being too categorical, but this is a methodological choice made to enhance the differences and make our arguments clearer. As such, I believe the distinction is useful.

A critique of the STS perspective, and particularly something I feel is relevant from someone with a medical background like me, is that the result from analysis can seem abstract and overwhelming. To criticize the market-oriented capitalist structure of drug research and development and argue for a different research policy may appear strange and perhaps uncomfortable to some, but this is our intention. As we write in

Study III: “As long as these dependencies between science and technology and its interactions are not noted and pointed out, the assumption of their non-existence may be upheld and the modern institutions that are built upon this assumption may continue to appear functional. The moment they are noted and pointed out, however, disturbances arise: uncertainties, controversies, contestation and loss of legitimacy. These are expressions of the modern frame being overflowed.” Therefore, I believe this choice of perspective is justified.

Another argument, more along the lines of politics, is that as medicine has learned that socioeconomic determinants of health shape and influence the individual health of persons, it is also important to acknowledge that other overlying structures and determinants also influence medicine and technology. To change these structures to the better should be an accepted goal, just as it is for changing socioeconomic determinants of health. As we write in study III, “The future *may be otherwise,* and we are entitled to imagine and strive for different futures.”

5.3 Discussion of results

In this thesis I have tried to describe how the Norwegian system for priority setting is organized and how personalized medicine in general, and cancer biomarkers especially, are being incorporated into the system. In study I we find that drug coverage decisions are made in accordance with the established priority setting criteria, so also for new cancer drugs with companion biomarkers. In study II we find that biomarker status is perceived as relevant in hypothetical priority setting decisions where two cancer patients can be considered as equals at a group level. Still, at both policy and clinical levels, issues about uncertainty challenge the system. In study III we have discussed how this uncertainty fuels public controversy about priority setting decisions and critically examined the current practice and how personalized medicine is likely to increase uncertainty even more. This can be adressed with a more inclusive and transparent priority setting practice, and also by opening up and challenging the many value-laden assumptions underlying how precision oncology is imagined, practiced and governed.

Based on the introduction, my aims, and the main findings from the three studies, I will go on to develop and discuss four perspectives.

A) The application of biomarkers in priority setting practice

In earlier work, Ole Frithjof Norheim and I have suggested how biomarker status can contribute to priority setting practice (32). The key premise for this is that biomarkers can identify subgroups of patients that respond better to a certain treatment, acting as a predictive biomarker[30]. In that work we did not discuss the issue of uncertainty.

In study I, we find that the number of cancer drugs with a companion biomarker appraised in the Norwegian system is increasing. A total of 49 coverage decisions that included biomarkers have been made, 33 of these in 2018 and 2019. The approval rate is higher than for all cancer drugs in total, with 80 % of biomarker-accompanied drugs being approved, and with a willingness-to-pay threshold similar to most other approved drugs. This may suggest that the Norwegian system is able to appraise personalized cancer drugs.

It is well documented in approvals from the FDA and EMA that most new cancer drugs (on average) only provide modest benefits[31] (89,90,127), are often based on surrogate endpoints (95,128) and often not compared to standard treatment or other effective drugs (129). All this increases uncertainty for decision makers (130)[32]. An important aspect not covered in our study is detailed information about the negative coverage decisions. Of particular interest would be how the decision makers emphasize uncertainty of evidence as this is an important additional consideration in the priority setting practice, and especially relevant for personalized medicine. Are

[30] Or that a biomarker can identify subgroups of patients that have a more severe disease (a prognostic biomarker). In my thesis, this has not been as central.

[31] To demonstrate how low the bar for approval can be: the tyrosine kinase inhibitor neratinib was granted approval in February 2020 against a sub-type of breast cancer, based on a statistically significant increase in progression-free survival of three days (146).

[32] This is part of a larger and important drug policy discussion and an extensive discussion about drug development and pricing, clinical endpoints, the role of regulatory authorities and the global health perspective would have been interesting. See, for example, Gyawali 2019 (147) for an introduction to these matters.

cancer drugs with biomarkers more often refused due to uncertainty about benefit compared to other types of drugs? Our results suggest that the incremental cost-effectiveness is estimated to be too high in almost all negative decisions, and consequently, when a drug is too costly, the degree of uncertainty is much less relevant.

In study II we find that biomarker status is perceived as relevant for individual treatment decisions. Although there are methodological issues that make generalization of our findings unwise, we believe that the results can be used as a base for further discussion. The results seem to suggest that biomarker status can be incorporated into clinical decision making alongside patient characteristics already established as relevant, such as comorbidity, performance status, and (somewhat more controversial) patient age. As already discussed, considerations about uncertainty are central in coverage decisions at a policy level. There are two reasons why this may also be more relevant for clinical decisions in the years to come: First, uncertainty is already part of clinical decision making, and second, tailoring diagnostics and treatment to the individual patient is a clear ambition of precision medicine, making individual clinical decisions based on biomarker status more likely in the future.

When stratifying individual patients at a clinical level using biomarker status, the ethical acceptability is dependent on the quality of the biomarker, that is again judged by the certainty of which it predicts treatment effect. As we discuss in study II, quality does not only relate to the biomarker's accuracy and validity, but also the use of clinical endpoints, actual availability and affordability of drugs for patients, how doctors trust and follow clinical guidelines, and more. Considering the discussion in study III, where we in a post-normal science perspective describe quality as fitness for purpose, this makes sense. A biomarker's quality cannot be judged only by the probability of predicting treatment effect (what can be considered as the "truth") but must be seen in a larger context, and what is to be judged as relevant in this context should be decided by the involved parties.

B) Uncertainty is a complex methodological challenge in personalized medicine

Uncertainty will be a central consideration in priority setting decision for personalized medicine. It is known that a range of issues in trial design and regulatory strategies contribute to this, such as application of non-randomized trials, the use of surrogate endpoints and pathways for accelerated approvals (131,132). In a recent study comparing contemporary randomized control trials (RCT) for personalized cancer drugs with older cancer drug RCTs, the authors find significantly shorter follow-up time, a substantial increase in the use of surrogate endpoints, and that almost all trials are industry-funded (133). They also find that the use of biomarker-guided treatment increased over the years, but still only 60 % of RCTs with targeted therapies used a biomarker.

As we have argued in study III, uncertainty is a consequence of the ambition of personalized medicine to stratify patients into smaller (and smaller) subgroups. Some of this uncertainty, I believe, is completely avoidable. They are not due to unsolvable methodological problems, but merely due to choices made by the trialists and their funders. Trial design, like selection of endpoints, inclusion of patients, choice of comparator, and follow-up time are strategic decisions made by those who design and fund the trials, most of the time the drug manufacturers[33]. Shorter follow-up time is cheaper than longer follow-up time. In many cases is it fully possible to design a randomized trial with a relevant comparator and to run the trial for as long as it needs to evaluate relevant endpoints like overall survival. The question for the pharmaceutical industry is if it is worth it. As we write in study III, it is fully possible to envision a future with a different and better strategy for research funding, clinical trials and biomarker development.

Even though some of the uncertainty generated by personalized medicine is amendable, there are methodological issues that are more difficult to overcome. This

[33] In their study of contemporary cancer drug RCTs, Del Paggio and colleagues find that in the last decade, 89 % of phase III RCTs were industry-funded, and of targeted therapies tested 96 % were funded by the pharmaceutical industry. Among palliative studies (against metastatic disease) industry-funded studies were more likely to use progression-free survival as an (surrogate) endpoint (133).

relates especially to trial size. As diagnostics becomes more and more personalized, patient groups become smaller and smaller, and this is inevitably generating uncertainty about the evidence, even from perfectly designed trials. In the Norwegian system this is already included as a special consideration (57): For rare diseases, the authorities acknowledge that generating evidence is more difficult, and that it may cost more to develop effective treatment. Therefore, and if certain criteria are fulfilled, a higher resource use and a lower quality of evidence may be accepted for interventions targeting very rare diseases. This special consideration is reflected in the results from study I where we find that the three coverage decisions approved with a higher ICER than otherwise accepted all are interventions targeting rare diseases.

If personalized medicine evolves and its ambition of stratifying patients into smaller groups is achieved, a consequence of this may be that more and more diagnoses can be seen as rare diseases. However, the current system does not give extra priority to rarity in it self, but instead acknowledges that there are special considerations linked to evaluating treatments for small patient groups with very severe conditions: the quality of evidence may be lower (few patients make clinical trials more challenging - a similar argument as in precision medicine) and treatment may be more costly (because few patients make incentives to develop new drugs weaker (which seem not to be a problem in precision medicine)[34]. In the system there are three requirements that all need to be fulfilled to be given special consideration: 1) less than one patient per 100 000 inhabitants globally, and at the same time a steady state prevalence of less than 50 patients in Norway; 2) a severity of disease measured as an absolute QALY loss greater than 30; and 3) an expected benefit of more than two QALY. This means that in addition to targeting an actual rare disease, the disease must be severe, and the treatment must provide a high benefit. These requirements may be more challenging to fulfil than the stratification into a small enough group, knowing that

[34] An Norwegian summary of the guidelines and a detailed discussion of the criteria can be found at https://legemiddelverket.no/offentlig-finansiering/dokumentasjon-for-metodevurdering/hvordan-sikre-tilgang-til-legemidler-for-serskilt-sma-pasientgrupper-med-svert-alvorlig-tilstand

most new cancer drugs only provide modest benefits (89,133) and that cancer types usually have a QALY loss between 10 and 20[35].

Up until now this discussion has been about outcomes: Biomarkers have the potential to stratify patients into smaller groups with higher benefit. Uncertainty about evidence makes decision making more difficult. Extra considerations may be given to some interventions that are more uncertain because it is more difficult to generate evidence. All this may be considered as fair, but as reviewed in the introduction, fairness can be more than fair outcomes.

C) Fair process and fair outcomes

The three established criteria for priority setting in Norway, health-benefit, resource use and severity of disease, are all outcome-based. Therefore, it can be claimed that the fair priority setting in Norway is predominantly outcome-based.

In the work leading to the set of criteria, procedural fairness was extensively discussed. In the third official report from 2014 a full chapter discusses transparency and participation (47)[36]. Especially prominent are the references to Daniels and Sabin's accountability for reasonableness framework (59), a framework that was developed as an aid to ensure a fair procedure for priority setting decisions. The four conditions can be repeated here: 1) Priority setting decisions and their rationale must be publicly available; 2) arguments and rationale used in decision-making must be relevant; 3) it must be possible to appeal and revise decisions as new arguments and evidence are available; and 4) mechanisms must be in place to enforce the first three conditions.

When examining priority setting decisions like those for drug coverage made by the Decision Forum, they seem to fall short of these standards. First, the arguments and

[35] The typical age of diagnosis is around 60-70 years (116) and that this age is indirectly linked to how QALY loss is estimated (148).

[36] The White Paper also contain a chapter devoted to transparency and participation (57). This is, compared to the 2013 report, substantially shorter and lacks referral to the accountability and reasonableness framework.

rationale are perhaps available at a higher level, as the criteria applied are well-known. However, the rationale behind the specific decisions made is not fully available, as price confidentiality and redaction of documents are standard procedure. Nor are detailed minutes or reports from discussions held in the meetings available. Appeals are not an option, and a system that ensures that these first three conditions are met is not available.

An interview study with 12 Norwegian oncologists from 2018 has interesting findings (134). Analysing the interviews using the accountability for reasonableness framework, the authors find distrust in the New Methods system and identify four main reasons for this: 1) lack of engagement in the process; 2) disagreement with the use of priority setting criteria; 3) lack of transparency and procedures to resolve disputes; and 4) a negative impact on the patient-doctor relationship. This is a multidimensional critique, concerning both procedural elements and substantial elements, like disagreement about criteria.

Further, if a science and technology studies perspective is applied, as we do in study III, an even stronger critique is permitted. In Tiago Moreira's view, based on Michael Callon's classification, the Norwegian system is an example of the public education level, where there is a clear distinction between scientific knowledge and public views (135). In his view, any "public contestations [is] derive from ignorance and mistrust which should be addressed by policies and programmes of scientific education" (p.1334).

Today this critique is perhaps a bit harsh, as the system has developed in the ten years after Moreira published his paper, and it may not be equally relevant to all parts of the system. Nevertheless, the lack of participation and inclusion of laypeople, patients, clinicians and other stakeholders in the practice of drug coverage decisions by the New Methods system is striking. In the Decision Forum sit the four CEOs of the four regional health authorities, as well as a user representative who only has

status of an observer[37]. This is, as we argue in study III, similar to what Andy Sterling refers to as an instrumental rationale for public engagement (136). With such lack of inclusion and participation of a broader sample of stakeholders, it is no wonder that persisting public controversy is the result. If no system for appeals or accessible channels for input is available to those who feel that they are unfairly treated, reaching out to journalists to make your case in the media is a logic next step in their pursuit of justice, and this again creates more public controversy and critique.

D) More uncertainty calls for other perspectives on fairness

In this last section I will argue that personalized cancer medicine and the use of biomarkers may challenge priority setting systems like Norway's even further, and that this can be met by allowing other perspectives on fairness a more prominent role in the priority setting system.

It seems clear that personalized medicine in some[38] cases create dilemmas and challenges for the priority setting system. These dilemmas resemble four well-known challenges from the literature on ethics and priority setting highlighted by Norman Daniels in 1994 (64): 1) The fair chances/best outcomes problem: How much should we favour producing the best outcomes, at the expense of providing a fair chance to all? 2) The priorities problem: How much priority should we give to treating those worse off? 3) The aggregation problem: When should we allow an aggregation of modest benefits to larger numbers to outweigh significant benefits to fewer people? 4) The democracy problem: When must we rely on a fair democratic process as the only way to ration?

Many years later these problems are not only still unresolved but stand perhaps even stronger when faced with the challenges of personalized medicine. When the

[37] More observers are also present, but they all come from within the system. See www.nyemetoder.no/om-systemet/hvem-gjor-hva

[38] Not all priority setting decisions for all personalized cancer drugs are true dilemmas. When the cost is very high and the benefit marginal, it is less complicated. But for some decisions, where a minority of patients may receive significant benefit, the incremental cost-effectiveness ratio is around the accepted threshold, uncertainty is high, etc., I believe this is a correct statement.

uncertainty about who will benefit is high, should we give more weight to fair chances and less to best outcomes? After all, some patients may experience substantial benefit (even perhaps a cure) from some of the new cancer drugs. This can also be linked to the question about aggregation. Is today's practice of aggregating benefits into mean and median survival acceptable when we know that some patients may be super responders and can enjoy substantial benefit from personalized cancer treatments?

Another debated question is whether we should give higher priority to younger patients with terminal disease, as they can be seen as worse off in terms of disease severity? The discussion about age, severity and priority setting has been ongoing for many years and have almost run parallel to the introduction of precision cancer medicine. Using age in clinical decision making is complex (137), and as we briefly discuss in study II, arguments like the fair innings approach can and is being used to claim that higher priority to younger patients is fair, all else being equal. The last of Daniel's four problems concerns procedural fairness. When and how could we balance and incorporate stakeholders' views on priority setting in a fair way? This we discuss extensively in study III.

There seems to be no ethical theory or reasoning that can fully or sufficiently address these problems that are also relevant for personalized medicine. This creates a moral space Leonard Fleck describes as a domain of non-ideal justice (71). He argues that

"Some moral problems are too complex, involve too much factual uncertainty, are open to reasonable (but conflicting) conceptual characterizations, or call into play conflicting moral judgements rooted in distinct analogies that seem relevant to the issue at hand; consequently, our theories cannot yield an objectively, dominant, reasonable, moral judgement in such matters that all reasonable moral agents in that specific moral conflict rationally ought to accept." (71)

In this moral space, Fleck writes, there can be several practical moral judgements that can all be seen as "just enough" - meaning that they are not perfect, but good enough. In priority setting decisions for new cancer drugs this could mean that other moral

perspectives were given more weight, and that the priority setting decisions were not seen as having only one ethically acceptable solution. Fleck argues that in a domain of non-ideal justice, there is the space for rational democratic deliberation.

A key question in such methods of deliberation is whether any result from such a practice shoud be considered as ethically acceptable, or if some sort of constraint is needed to ensure that the result has a minimal standard of fairness and legitimacy. There are different strategies for this challenge. Fleck suggests specific guidance for the deliberation process, called six constitutional principles (71 chapter 5). In study III we provide a different perspective and discuss how broader participation can provide *better* outcomes and introduce the concept of post-normal science, co-production, and quality as fitness for purpose, as measures to guide the participation. We engage in socio-technical imagination and argue that the whole system of medical research, technology and practice must be reimagined together with the practice of priority setting. This has both procedural and substantial elements. In today's priority setting practice, many stakeholders are only indirectly (and poorly) represented, and relevant and important information is not available, due to censoring and confidential agreements. Moreover, the current standards and facts are not value-free, but a product of how precision oncology is currently imagined, governed and practiced.

What then could the role of cancer biomarkers be in these methods of deliberation? I will finish the discussion with a few brief thoughts. Allowing a more inclusive and deliberative priority setting practice would move discussions about strengths and weaknesses of biomarkers out from methods chapters and appendixes into an open and accessible deliberative process. By this I mean that information about cut-off points, ragged edges, surrogate endpoints and all the other quality aspects that we in study II argue are relevant for the biomarkers' ethical acceptability would actually be exposed and could inform and be part of deliberations and priority setting decisions. Perhaps some of the biomarker evidence is so weak that it in the end it is judged unfair to use it to stratify patients at all. Could more responsibility about decisions be given to clinicians? Or perhaps the deliberative process would result in the same

decision as the authorities recommended, but with a much stronger legitimacy and public support?

In this thesis I have investigated how cancer biomarkers are integrated into the current priority setting practice for new drugs in Norway and find that while on one hand it could be seen as well integrated there are also fundamental concerns about how the current system will ensure fairness in priority setting as uncertainty increases. This, I have discussed, may call for a wider perspective on fairness and a broader inclusion of stakeholders than currently reflected in the priority setting practice.

6. Conclusion

Precision oncology aims to classify patients based on individual biological information about their genes and proteins. Instead of providing the same treatment to large groups of patients, treatment might be directed towards those who will respond best, and at the same time spare unnecessary side effects for those who will not benefit. But this method of stratification can create uncertainty about the quality of evidence for such treatments, as sample size in trials are reduced, which may challenge the principle of equal treatment, and fair priority setting.

The aim of this dissertation was therefore to describe and discuss how biomarkers and personalized medicine are being incorporated into priority setting decisions for new cancer drugs in Norway, and to explore how this may challenge concepts of fairness in the priority setting system.

In our study of the Norwegian system for drug coverage decisions we found that all drugs, including drugs with companion biomarkers, are evaluated consistently against the three priority setting criteria. An increasing number of drugs with companion biomarkers have been appraised in recent years. In our survey of Norwegian cancer doctors' stated preferences in a hypothetical scenario involving clinical treatment decisions, we found that our respondents saw biomarker status as relevant for prioritizing between patients.

This may suggest that precision oncology can be incorporated into the priority setting system. But as we argue in the third study, public controversy and claims about uncertainty may still continue and ultimately challenge the whole priority setting practice. In our study of drug coverage decisions, no systematic evaluation of uncertainty is publicly available, nor is the full rationale for the decisions. And in study II uncertainty about biomarker quality may complicate clinical decision making and challenge the principle of equal treatment.

Based on the integration of findings from study I, II and III, I argue that a stronger emphasis on co-production of knowledge and procedural aspects of fairness will

strengthen the priority setting system and maybe also reduce public controversy. Co-production of future desirable scientific, technological and societal orders would require opening up and challenging the value-laden assumptions underlying how precision oncology is imagined, practiced and governed. A wider participation of stakeholders is essential, and deliberation must address both the production of knowledge and of standards. The former includes organization of trial design, research and development of new drugs, and even the whole political economy of drug development, and the latter the normative foundations of priority setting, its principles and practices. In such reimagining there is still a role for biomarkers, but their role would be reimagined too.

7. Future perspectives

Implications for future research

Building on Study I it would be interesting to examine in detail the evidence used for approval, and especially for rejection of biomarker-accompanied cancer drugs. Clinical trial design and strategies, the number of patients recruited, and the type of clinical endpoints could all say something about the strength of the evidence used in coverage decisions. Importantly, most of this information is already available in reports and HTAs. It would also be interesting to interview people in central positions within the New Methods system to investigate their thoughts and reflections about the practice and how they see the challenge of precision medicine.

From Study II I think there are two interesting paths to pursuit. The first is to plan a survey with better external validity by using a better sample frame, more information about non-respondents and a higher response rate. The other path would be to interview clinicians who make treatment decisions for new cancer drugs and learn more about how they resonate in their decision making, as well as how they see the trade-off between different aspects of fairness. Such interviews would also be very interesting to do with patients and relatives.

In study III we argue for a more inclusive and transparent priority setting process, but we do not go into detail about how this could be done in practice. A reasonable step forward could be to arrange and study a deliberative citizen's panel on priority setting in order to collect views from a broad set of stakeholders.

Implications for practice

While not delivering any definite evidence that will change priority setting practice, I hope this thesis can contribute to the scientific, political, and societal discussions concerning priority setting and precision medicine. The debate and public controversy surrounding coverage decisions for cancer drugs have been ongoing for many years and are not likely to end soon. My work might also be of relevance for

the evaluation of the New Methods system, a project ongoing at the time of submission.

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