# Essays on Economic Incentives and Implications of Biomarker Tests

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*Ana Beatriz Luís*

# Abstract

This thesis consists of four chapters: an introductory chapter and three research papers on specific economic aspects of personalized medicine. The approach is empirical in the first paper and theoretical in the second and third papers. In the introductory chapter, I give an account of the factors that have contributed to the slower-than-expected growth of the use of biomarker tests in clinical practice to predict drug response. There have been challenges at the scientific, regulatory, and economic levels, but there have also been some successes. The goal of this dissertation as a whole is to clarify the implications of some of these challenges and successes for the development and use of biomarker tests. In this chapter, I discuss how the research questions relate to the personalized medicine literature and summarize each of the three papers.

The first paper seeks to determine the importance of the scientific complexity and predictive capability of biomarker tests. In particular, it studies how the introduction in the Norwegian health system of biomarker tests that guide cancer therapy by predicting drug response has affected the health of cancer patients. The previous literature has provided results related to the benefits to patients of cancer drugs rather than biomarker tests specifically or based on clinical trial data. This article makes two main contributions to the literature: it provides new insights concerning the effect of biomarker testing in particular on cancer treatment, and it makes use of real-world data on cancer patients. The identification strategy relies on the fact that treatments with biomarker test guidance have been introduced for different types of cancer at different points in time. We perform the analysis on Norwegian patients who were diagnosed with cancer and/or died of cancer from 2000 to 2016. We use two main objective measures of health outcomes. These are premature mortality before ages 75 and 65 and the probability of surviving three years after diagnosis. Our main results indicate that biomarker testing decreases premature mortality before ages 75 and 65 and increases the probability of surviving three years after diagnosis, but the effect of biomarker testing on survival weakens as the number of cancer drugs available increases. We also document that while an increase in the number of therapies that require biomarker testing before prescription (biomarker-guided drugs) reduces premature mortality before ages 75 and 65, an increase in the number of therapies that do not require it (nonguided drugs) increases the probability of being alive three years after diagnosis. We conclude that the potential cost per life-year gained from biomarker-guided drugs is below the threshold value used in the literature at which an intervention is considered cost-effective.

The second paper investigates the impact of policies to encourage drug producers to col-

laborate in the development of biomarker tests to predict drug response. Economic incentives are needed because although biomarker testing has the potential to improve patients' health outcomes, it limits drug sales to patients whom the test identifies as responders. Moreover, the pricing of pharmaceuticals is inflexible in many countries, so the drug price will likely remain unchanged after biomarker testing is added to the label. Therefore, we analyze the incentives and welfare effects when the regulator can set one drug price when the test is implemented and another price when the test is not implemented and/or can subsidize drug R&D if the pharmaceutical firm agrees to collaborate in the development of the test. In the model, we consider a pharmaceutical firm that invests in developing a new drug whose price is regulated and decides on whether to allow a biomarker test to be developed for that drug. We show that the regulator faces a tradeoff between increasing the price such that the firm's incentives to invest in drug R&D increase and increasing the social cost of public funding needed to pay the higher price. We also provide the conditions under which increasing the drug price or providing a subsidy on the margin of drug R&D investment are perfect substitutes. To achieve the first-best outcome, a lump-sum tax can be used to transfer the monopoly profits of a drug developer to the government and offset the increase in the social cost of public funds.

The third paper considers two drug manufacturers that face the decision of whether to use a biomarker test to select clinical trial participants and a health authority that chooses which drug to approve for the market. The firms must take into consideration the effect of the biomarker on technological R&D uncertainty and on strategic interactions due to competition for market approval. Indeed, although a biomarker test reduces potential drug sales, it increases the probability of finding statistically significant trial results and the quality of the drug, making the drug more appealing to the health authority. We show that it can be more profitable to include a biomarker in clinical trials under a duopoly than under a monopoly due to the consideration that the rival firm's product may be selected by the health authority if the firm does not use the biomarker test. This suggests that personalized medicine can be developed even without policies to encourage it that increase public expenditures. It may, however, be important to have antitrust policies in place to generate competition between drug developers.

# Contents

# Chapter I

# Introduction

# Introduction

This thesis consists of three essays discussing economic aspects of biomarker tests and personalized medicine. The goal of this thesis is to gain further understanding of the success factors driving and the barriers impeding the progress of biomarker technology in clinical practice. To this end, the first essay takes an empirical approach and focuses on establishing a connection between biomarker testing and health outcomes in the real world. The approach of the next two essays is theoretical. The second essay looks at the economic incentives of a pharmaceutical firm to develop a new drug with a biomarker test that predicts drug response. The third essay shows how competition between two pharmaceutical firms affects the incentives to include a biomarker test in the clinical trials of a new drug. To introduce and motivate the research in this thesis, I begin with a discussion of the context of the personalized medicine market: why it is relevant, what characterizes it, and how it relates to the research questions.

## 1 Background

In 2001, the sequencing of the human genome prompted great enthusiasm for the idea that a patient's genetic predisposition could be used to predict her drug response. The development enabled a new approach to the treatment of many diseases, usually termed "personalized medicine". The role of personalized medicine is to better match the treatment to a patient's health condition based on biomarkers. Such treatments typically involve combining drugs with the use of biomarker tests (also called companion diagnostics). A biomarker test measures molecular mutations, gene amplifications, or protein expressions in a patient that are correlated with her drug response. In other words, a biomarker test identifies the subset of patients for whom a treatment is likely to work. Hence, the choice of treatment is conditioned on the result of a biomarker test.

Diseases are complex, and the drug response of individuals who differ genetically is heterogeneous. In the absence of biomarker testing, a drug, on average, is ineffective for approximately half of the prescribed patient population (Antoñanzas et al., 2018), and it can even lead to adverse outcomes. Instead of a "one-size fits all" or "trial and error" paradigm and acceptance of these low response rates, biomarker tests can be used to increase response rates by targeting the treatment to those who will benefit from it. Hence, the ability to identify responders to a drug through a biomarker test has the potential to allow for better-informed medical decisions, improve the health and quality of life of patients, and contribute to sustainable healthcare systems (Blanchard & Strand, 2017). First, a biomarker test helps health practitioners choose

between treatments to find the drug best fitted to the needs and characteristics of the patient. Second, a good biomarker test improves treatment efficacy and minimizes adverse reactions. The patients who are likely to benefit from a drug are selected before treatment starts. Those unlikely to benefit from the drug are identified and can avoid being given an ineffective and potentially harmful treatment. Third, given the current pressure to control public health budgets, personalized medicine has the potential to contribute to savings in pharmaceutical expenditures. Personalized medicine helps limit adverse reactions and the consequent medicalization to treat these adverse reactions. It also helps reduce purchases of expensive drugs that may not be effective by allowing purchases to be limited to responders only and by preventing overtreatment.

There has been a gradual development and approval of personalized medicine, and the vast majority of companion diagnostics are currently for oncological treatments. The first companion diagnostic was approved in the United States in 1998. It was the human epidermal growth factor receptor 2 (HER2) test for trastuzumab (Herceptin) to treat metastatic breast cancer. It was shown that women who overexpress the HER2 protein experience therapeutic benefits from trastuzumab. Over time, other drugs that require testing for HER2 were approved, such as pertuzumab (Perjeta). Today, the most common personalized medicines are used to treat not only other types of cancer, such as lung, colorectal, and skin cancer, but also other complex diseases, such as diabetes and HIV (Garrison & Towse, 2014).

Initially, the idea that biomarker tests could be used to match the right therapies to the right patient generated excitement in the healthcare sector. However, progress has been slower than many expected, with only a few drugs on the market whose response can be predicted by a biomarker test (Garrison & Towse, 2017; Meadows et al., 2015), and large pharmaceutical firms still mostly engage in the "blockbuster" business model (Mittra & Tait, 2012). A number of factors—scientific, regulatory, and economic—have contributed to the slow development of personalized medicine. These issues are intertwined and create a cycle of low investment in personalized medicine. First, the science behind diseases and drug development is more complex than expected. Second, the lack of regulatory standards of evidence and the proliferation of unregulated diagnostics are barriers to the development of personalized medicine. Third, there are some economic barriers, namely, limited economic incentives to use biomarker tests to identify drug responders due to drug price inflexibility and to pricing of tests based on administration costs. Finally, the business model and the existence or absence of competition, the impact of personalization on drug R&D costs, and physician incentives to test also affect the way the implementation of biomarker tests in clinical practice has evolved (Garrison &

Towse, 2014). All these issues are discussed in the existing literature and addressed in this introductory chapter, and the essays in this thesis aim to analyze some of them.

## 1.1 Scientific complexity challenges

The biology of diseases such as cancer is highly complex and uncertain. Consequently, biomarkers may have limited ability to predict treatment response. Nearly 9 out of 10 drugs under research and development (R&D) fail between phase 1 and phase 3 (Garrison & Towse, 2014). Despite increasing amounts spent on drug R&D, the number of new medicines approved has stagnated. Furthermore, very few of the biomarkers discovered in the lab have been implemented in clinical practice. For example, less than 1% of cancer biomarkers have reached clinical practice (Kern, 2012).

The challenges to developing a good biomarker test are present in every step taken until market approval. First, a good biomarker test should demonstrate analytical validity. This means that the test assay should measure the biomarker with a high degree of accuracy and precision. Its sensitivity (the degree to which the biomarker correctly identifies responders) and specificity (the degree to which the biomarker correctly identifies nonresponders) should be high. However, a totally accurate biomarker test is impossible to achieve (Blanchard & Strand, 2017).

Second, the biomarker test must demonstrate clinical validity by being able to identify separate groups of patients with different outcomes. For example, it must separate responders from nonresponders to a specific drug. However, a biomarker is measured as a continuous biological parameter, and the choice of the threshold that determines which patients should be given the treatment is an important part of developing a biomarker test. From the medical decision-making perspective, statistical criteria have been developed to choose the best threshold (for example, Rota et al., 2015). However, Dalen (2019) argues that a pharmaceutical firm may or may not choose the socially optimal threshold for the biomarker test, depending on the price scheme. The threshold choice of the firm will be aligned with the payer's if the price reflects the value of personalized medicine. Nevertheless, it is challenging to predict the drug response of a patient whose test result is close to the threshold. For example, if the threshold is set such that a patient with at least 50% of biomarker 'A' is eligible for a specific drug, what would the best treatment for patients with 49%?

Third, the biomarker test should demonstrate clinical utility, meaning that it improves patients' outcomes compared to a no-testing approach. Usually, this is evaluated in the last phase of biomarker development, which consists of a randomized clinical trial. However, it has

been challenging to standardize the trials and compare validity across studies. Furthermore, clinical trials are executed in highly controlled settings, where the participant patients are carefully selected, but biomarkers are likely to be used differently in actual routine practice (Oosterhoff et al., 2016). The first essay of the thesis focuses on this issue and aims to analyze whether biomarker testing to predict the response to specific drugs has played a role in the improvement of health outcomes.

Biomarker tests are still far from ideal. In the case of cancer biomarkers, the heterogeneity within a tumor or in different tumors in the same patient is a scientific challenge for the development of robust biomarker tests. Different areas of a tumor can contain different levels of expression of genes and proteins. Hence, the test result can be biomarker-positive or biomarker-negative depending on where in the tumor the sample on which the biomarker test is performed is taken.

Most complex diseases are affected by a large number of genes, and testing for only one specific biomarker is likely insufficient to achieve the ideal *personalized* medicine approach. More complex biomarker tests that measure various molecules could be useful for enhancing understanding of the biological mechanisms of a disease. However, more complex tests have an increased risk of yielding false positives (nonresponders identified as responders), which makes medical decision-making more uncertain. Nevertheless, even sophisticated biomarker tests can only focus on a limited number of biological elements, and the results are still uncertain and ambiguous (Blanchard & Strand, 2017).

The results of biomarker tests also depend on test timing. The test is usually performed once, showing the gene or protein expression at one point in time only. However, diseases evolve over time. Consequently, whether the patient will benefit from the therapy is still uncertain, even when a predictive biomarker test is available. Measuring biomarkers over the therapy time could provide a dynamic representation of the disease. However, biomarker measurements over time would require raising the overall therapy cost, which does not benefit the sustainability of healthcare systems and would be more difficult to implement in clinical practice (Blanchard & Strand, 2017).

The scientific unknowns make biomarker prediction fairly imprecise. This is a source of risk in personalized medicine, making the value of predictive biomarker testing still uncertain (Graves et al., 2018).

## 1.2 Regulatory challenges

The uncertainty and informational asymmetries inherent in the healthcare market create market failures. These must be corrected by institutions and regulatory agencies. For example, if the effectiveness of a drug is unknown for consumers, they will be disinclined to use it even if they would benefit from it. Therefore, regulatory agencies, such as the European Medicines Agency (EMA) or Food and Drug Administration (FDA), certify the safety and efficacy of drugs. Additionally, individuals face uncertainties regarding what to do if they fall ill. Hence, third-party payers, namely, public and private health insurers, allow individuals to pool the risk of needing treatment by purchasing or providing medical care on their behalf in the event of an illness (Garrison & Towse, 2017).

The fact that individuals do not face the full cost of treatment makes assessing the value of medicines challenging and raises the question: how can we achieve R&D investment and patient access to a socially optimal mix of drugs? Most drug innovation has been incremental (with few important breakthroughs). The majority of innovations are not major improvements over drugs that already exist. Therefore, several countries started taking this into account when drugs are considered for reimbursement from third-party payers. Typically, they assess the cost-effectiveness of new drugs by comparing the new treatment with the standard of care. The purpose of this approach is to reward innovative drugs making great improvements more and reward new drugs making smaller improvements less (Barros, 2010).

Cost-effectiveness is calculated by the ratio of the change in costs to the change in quality-adjusted life years (QALYs), which results in the incremental cost-effectiveness ratio (ICER). A QALY is thought of as a year of life adjusted for quality of life. Incremental QALYs reflect improvements in survival and morbidity. The costs include the price and associated medical costs of the new treatment and standard of care. An important element to consider is savings from avoiding adverse events associated with the standard of care, which especially applies in personalized medicine. A treatment is considered cost-effective if the ICER is lower than the maximum willingness to pay for a healthy year of life (Garrison & Towse, 2017).

The use of cost-effectiveness analysis with the QALY has some limitations. For example, a patient's preference for quality of life vs. survival is likely to change over her lifetime. Additionally, it is challenging to measure the value of a life-year for children or some cognitively impaired adults (Garrison & Towse, 2017).

The basic principles of cost-effectiveness of pharmaceutical drugs should be applied to biomarkers. However, due to the indirect impact of biomarker tests on the therapeutic efficacy

and cost-effectiveness of the corresponding drugs, the scope of the relevant costs and benefits of personalized medicine could capture the full impact on society. Hence, there are further issues to consider when one wants to appropriately measure the social value created by biomarker testing. For patients identified as unlikely to benefit from a drug, there is value not only in preventing adverse events from their use of that drug but also in avoiding the time wasted on an ineffective therapy. With personalized medicine, the search for a better alternative can start earlier in the treatment process. Additionally, for risk-averse patients, biomarker testing is especially valuable because it reduces uncertainty about their response to treatment, creating what has been called in the literature the "value of knowing" (Garrison & Austin, 2007). Indeed, patients who avail themselves of biomarker tests will have greater peace of mind: nonresponders know that they can avoid the negative effects of adverse events, and responders know that they will gain therapeutic benefit. Furthermore, there is a "real option value" in undergoing life-extending treatment so that the patient can benefit from future therapies that may have greater efficacy and safety than current ones (Li et al., 2019). There is also a social value from knowledge externalities or scientific spillovers created by what developers of personalized medicine learn from the successes and failures of other developers.

In addition to the issues related to properly assessing the social value of drugs and tests mentioned above, there are regulatory barriers to the development and adoption of personalized medicine. First, the regulation of marketing approval is insufficiently harmonized. It varies across countries and is different for drugs and diagnostic tests. In the United States, marketing approval for drugs and diagnostics is done by the FDA. The joint approval process performed by a single agency ensures scientific knowledge-sharing and provides an effective way to approve personalized medicines. However, in Europe, no single European agency regulates both medicines and tests. The European Medicines Agency (EMA) regulates the marketing approval of drugs, whereas it is each European Union member state's Notified Body that monitors the performance standards of diagnostic tests (Meadows et al., 2015). These differences in regulatory requirements create challenges to developing personalized medicines that are intended to be marketed on a global scale.

The requirements for marketing approval of tests are relatively lenient. In both Europe and the US, the test manufacturer is required to demonstrate the clinical validity (predictive capability) but not the clinical utility (effect on clinical outcomes) of the test. Furthermore, the manufacturer of a new test does not need to demonstrate its effectiveness if a similar test already exists. Moreover, laboratory developed tests (LDTs)—that is, tests performed within a single laboratory or hospital (not commercialized)—do not require a full regulatory review

(Meadows et al., 2015). Therefore, there is a lack of standardized evidence of the performance of biomarker tests in terms of their impact on health outcomes. This results in uncertainty for third-party payers and health authorities who make decisions on pricing and reimbursement based on the value of treatment produced by the biomarker test.

In sum, all these challenges need to be addressed with clear regulatory guidelines on methodology and standards for the collection of evidence on personalized medicine for both regulatory approvals and reimbursement decisions (Blanchard & Strand, 2017).

### 1.3 Economic challenges

The healthcare market is characterized by agency relationships that play a role in the economic incentives to develop personalized medicine. In this market, the payer is the agent for the potential patients and negotiates/sets prices and access to treatment. Physicians work on both the demand side and the supply side: they are both the agent of the patient in terms of the treatment choice and the provider of treatment (Garrison & Towse, 2017). In the health production function, hospitals, physicians, medicines, devices, and diagnostic tests are the major inputs in developed countries (Garrison & Towse, 2017). The supply and use of these inputs vary across countries. Between these inputs, there are cross-price elasticities of demand. They can be substitutes (for example, an increase in pharmaceutical consumption may reduce demand for physician services) or complements (for example, a new predictive biomarker-based diagnostic test that predicts response to a drug may make the drug more valuable). Furthermore, the pharmaceutical industry is highly R&D intensive, with high associated costs and uncertainty. Patent protection provides incentives for innovation, but these may not be enough to encourage innovation in personalized medicine.

These current agency relationships and market structures in healthcare have implications for the development and use of personalized medicines. Here, we present some economic challenges that derive from policy aspects and business models in the pharmaceutical market. We also identify some ways to keep future investment flowing that have been pointed out by the personalized medicine literature and that require further research.

The pricing and reimbursement of pharmaceuticals is one of the major issues with implications for the optimal incentives to invest in personalized medicine R&D. The problem is that most developed countries have been increasing their efforts to control pharmaceutical spending and, consequently, drug prices tend to be inflexible during the patent period. In the short run, this limits the economic incentive to create personalized medicines out of drugs that are already on the market. A manufacturer of a drug on the market is not interested in developing

a biomarker test to identify the subset of patients for whom the drug works best because its sales would then be restricted to that subset (Garrison & Towse, 2014). In the long term, if a pharmaceutical firm realizes that it is very likely that a biomarker test is forthcoming, price inflexibility will reduce the incentive to develop the drug in the first place. This problem linked to fixed drug pricing has been formalized in models by Danzon & Towse (2002) and Garrison & Austin (2007). Their results suggest that pricing and reimbursement authorities should allow for flexible pricing for drugs at launch and postlaunch. Nevertheless, Garrison & Towse (2014) argue that government subsidies may be needed in case the market size for biomarker tests is so small that it is not sufficient to justify the costs of drug development. An analysis of flexible pricing and subsidy contracts and their effect on the encouragement of biomarker test development and on drug R&D is conducted in the second essay of this thesis.

Although there are limited incentives to combine a biomarker test with a drug that is already on the market, including a biomarker test in the clinical trial phase of a new drug may actually benefit pharmaceutical firms since it can facilitate the demonstration of efficacy and safety and increase the likelihood of drug approval (Towse & Garrison, 2013; Garrison & Towse, 2014) by allowing for smaller or faster trials (The Economist, 2005). In reality, the timing of the decision to associate biomarker testing with a drug has varied. It can occur before or during clinical development of a drug or after marketing authorization, depending on the interests of the drug manufacturer. The decision to use a biomarker test before clinical development of a drug requires early collaboration between the pharmaceutical and test developers. For example, vemurafenib (Zelboraf) was developed together with the COBAS BRAF V600E test. In this case, a collaboration between developers was carried out in-house by Roche. Both the drug and the test received simultaneous FDA marketing approval for metastatic melanoma. This turned out to be one of the fastest FDA approvals in history and reduced the barriers to test adoption by hospitals (Meadows et al., 2015). However, firms usually hesitate to change drug development plans by including a biomarker test during clinical development, especially once phase III trials have started. Often, the decision to include the test at that point is justified by unexpected and serious adverse events, so the biomarker test can be used to rescue a failed clinical trial phase. For example, gefitinib (Iressa) appeared to be ineffective in phase III trials but was later found to work in patients with high levels of EGFR mutations. Gefitinib's developer, AstraZeneca, collaborated with DxS Diagnostics to create a test kit for the EGFR biomarker (Agarwal, 2012). Finally, in the period after marketing authorization, real-world information can demonstrate that adverse events can be reduced with the use of a predictive biomarker test. However, the size of the market will decrease to include only the responders

identified by the test. Unless drug sales are poor due to high treatment risk or incentive schemes are in place, pharmaceutical firms will not adopt a personalized medicine approach.

Another question that arises is how the incentives of test developers are affected by the current market structure. One economic barrier that has been pointed out in the literature is the rigidity of pricing and reimbursement of diagnostics such as biomarker tests (Garrison & Towse, 2014). The pricing policy for such tests differs from the pricing of drugs. For drugs, what happens in some countries is that pharmaceutical companies propose "list" prices, but price discounts or rebates are negotiated with health authorities. In the US, pharmaceutical firms are free to set their prices, and reimbursement and coverage are negotiated with payers (Garrison & Austin, 2007). However, as biomarker test development timelines are shorter and the risks of trial unsuccess are lower, the pricing of diagnostic tests is set based on the costs of similar tests or on the total costs of the steps needed to process the sample. Consequently, the prices of biomarker tests are lower than those of drugs (Meadows et al., 2015) and have been lowering due to technological improvements. For example, the cost of sequencing a human genome was nearly $100 million in 2001, but today it costs about $1,000 (Graves et al., 2018). Overall, this means that there are limited incentives for a biomarker test manufacturer to demonstrate the clinical utility of a biomarker test in combination with a drug. Hence, Garrison & Towse (2014) and Garrison & Austin (2007) argue that the price of new tests should be based on the value they generate, since testing extends life and/or improves quality of life and can also reduce uncertainty about a clinical condition. However, Zaric (2016) develops a framework with value-based pricing for biomarker tests and concludes that it leads to an increase in costs for the payer. His conclusion contrasts with the argument that personalized medicine has the potential to decrease healthcare costs (Towse & Garrison, 2013; Ramsey at al., 2011).

Assuming that both drug and biomarker tests should be priced based on the value they generate, the problem that arises is that the synergy between them is not easy to disentangle. The question thus becomes how the value generated by personalized medicine can be split efficiently between the drug and test manufacturers. Garrison & Towse (2014) argue that drug firm innovation generates health gains in responders, whereas the value generated by test manufacturers consists of sparing nonresponders the possibility of exposure to adverse events and consequent treatment costs and of reducing uncertainty about the treatment's efficacy. Furthermore, these authors argue that the relative amounts of R&D investment needed for the drug and for the biomarker test should be considered in the price. This issue is especially important when the drug producer and the test producer are not the same. However, if the drug manufacturer also owns the test, it can capture all value if the price of the drug reflects

the gains that the test generates.

Appropriate policies across countries are important because new drugs and biomarker tests represent knowledge that can be used all over the world. This knowledge has become a global public good; everyone in the world can benefit from it and should have an incentive to support research and development (Garrison & Towse, 2017). However, policy coordination among countries may be a considerable challenge. For example, price regulation creates a dilemma for governments between providing drugs at low cost to consumers and encouraging more innovation, not only in personalized medicine but also in pharmaceutical development in general. The weight and implications of this dilemma depend on the country. While a small country with little or no drug innovation does not face the downside of strict and inflexible price regulation, a large country will see its domestic innovation discouraged by such policies. Furthermore, one small international player's regulations may have little effect on overall investment in pharmaceutical R&D (Barros, 2010). The problem is the effect when there are several small countries with tight regulations that do not encourage innovation. However, it is still unclear how the coordination of policies impacts the incentives for pharmaceutical R&D.

The business model of personalized medicine also creates challenges for the development of more biomarker tests. The market structure is based on collaboration between test developers (for example, biotechnology firms or academic research groups) and pharmaceutical companies that manufacture the related drugs (Agarwal, 2012; Agarwal et al., 2015), which increases uncertainties in the value chain for stakeholders. On the one hand, when prescription and reimbursement of the drug is conditional on identifying the right subset of patients, the existence of a suitable biomarker test that is approved and ready for market is key for the drug manufacturer. On the other hand, test developers are typically reluctant to commit to test development at an early stage of drug R&D because drugs have a higher probability of failing than biomarker tests (Meadows et al., 2015). Nevertheless, test developers only have access to patients through collaboration with drug manufacturers because they need the clinical data of the drug to perform a proper assessment of the test, and the testing requirement or recommendation must be specified in the labeling instructions of the corresponding drug.

Furthermore, there is free entry into the business of developing tests (Garrison & Towse, 2014), which creates more complexity in testing strategies and more uncertainty for pharmaceutical firms and biomarker test developers. If different tests that vary in quality can be used for the same drug, it will be more difficult for the producer of that drug to predict its sales. Additionally, other test developers can more easily appropriate the benefits of evidence from studies that the biomarker test innovator has paid for, since patents for tests are less robust

and regulatory requirements are less strict. The commercial attractiveness of the companion diagnostic market is undermined by competition from unregulated LDTs with nearly no development costs. On the one hand, the exemption of LDTs from full regulation allows for rare diseases to be diagnosed. On the other hand, the quality and scope of those tests vary and can alter the value of personalized medicine in the clinical setting. For example, a cheaper immunohistochemistry (IHC) test and a more expensive and more accurate fluorescence in situ hybridization (FISH) test are available for the breast cancer drug trastuzumab. Use of the cheaper test is more common, but it is still unclear what the optimal testing strategy is (Garrison and Towse, 2014).

Finally, it is important to discuss the competitive implications of features of the pharmaceutical industry for personalized medicine. One issue that affects the demand for personalized medicine is physicians' and patients' incentives to test and adjust prescriptions according to the test results. This is particularly true in therapeutic classes facing competition from other drugs without testing requirements. The problem is that testing can be inconvenient since it takes time and can delay treatment, so physicians may prefer to waste no time and prescribe an alternative that does not require a biomarker test. For example, abacavir (Ziagen) for the treatment of HIV-1 infection experienced sales decline after a companion diagnostic was added to the label, and inconvenience of testing was pointed out as the main reason (Agarwal, 2012).

However, competition at the R&D level may actually have an effect on the incentives to include a biomarker test in clinical trials. Scenarios with competition in the pharmaceutical/personalized medicine market can resemble game theory models. For example, the interactions can take the form of a noncooperative game, where competing firms take each other's expected behavior into account when independently making R&D decisions (Berndt & Trusheim, 2017). A particularly interesting case is when the strategy consists of deciding whether to include a biomarker test that predicts drug response in clinical trials for a new drug that will be used in the market in combination with the test. A drug firm's decision will be the result of what maximizes its expected profit, assuming that its competitors are rational and maximize their own expected profits. This creates a firm prisoner's dilemma. While a drug without a biomarker test can be sold to more patients than a drug with a test, a biomarker test can improve observed efficacy and lead to successful clinical trials. The third essay of this thesis analyzes the effects of a competitive situation between two firms on the incentives to develop personalized medicine and compares it to a monopoly scenario.

## 2 Summary of the essays

As we have seen in the discussion above, the implementation of biomarker tests increases commercial, regulatory and scientific uncertainties, which have implications for patient outcomes and pharmaceutical firms' strategies. Therefore, we translate some of the main problems related to the scientific and economic challenges into three research objectives that correspond to each paper summarized below.

### 2.1 Has the development of cancer biomarkers to guide treatment improved health outcomes? (coauthored with Mikyung Kelly Seo)

Biomarker technology has brought the promise of tests that predict drug response and improve the health of patients by optimizing treatment for the right patient and reducing adverse drug reactions. However, the progress of this technology has been slower than initially expected. One potential reason for this is that the science behind the diseases related to biomarker testing is more difficult to understand and use than expected, which can undermine the predictive capacity of biomarker tests. Therefore, the aim of this study is to analyze whether biomarker testing to predict drug response has benefited patients by improving health outcomes.

While there is a growing literature on the impact of drugs on health outcomes, such as survival, premature mortality, and mortality rates (Lichtenberg, 2009, 2012, 2013, 2015a, 2015b, 2017a, 2017b, 2017c; Dubois & Kyle, 2016), little is known about the health impact of the real-world use of biomarker tests. Moreover, although there have been studies analyzing the effect of biomarker tests on health, they are based on clinical trial data and may not entirely reflect the reality of actual clinical practice. This creates uncertainty for regulators, who must provide appropriate coverage and prioritize different innovations, which, in turn, increases the risk posed by personalized medicine investments for drug and test developers. Therefore, assessing the impact of the clinical use of biomarkers and drugs guided by biomarkers on patient outcomes is relevant to inform stakeholders on the value of personalized medicine.

This paper takes advantage of the fact that the availability of biomarker testing and biomarker-guided therapies in oncology in Norway has varied across cancer types and time. Our analysis is performed on Norwegian patients who were diagnosed with cancer and/or died of cancer from 2000 to 2016. The aim is to determine the effect of the utilization of biomarker technology for cancer therapies on premature mortality, in terms of potential years of life lost before ages 75 and 65, and on the probability of surviving three years after diagnosis.

Similar to the aforementioned studies on the effect of drug innovation on health, our empir-

ical strategy is based on the theoretical model of endogenous technological change developed by Romer (1990). The idea is that an economy's output depends on the stock of ideas that have previously been developed. Here, the models estimated can be seen as health production functions, where the health outcome (survival or premature mortality) depends on biomarker testing availability and on the cumulative number of treatments approved. Nevertheless, the contribution of this paper to the literature is that it provides new insights concerning the effect of biomarker testing on cancer treatment and makes use of detailed registry data on cancer patients.

Our main findings suggest that biomarker testing has played a role in benefiting cancer patients. Indeed, cancer patients for whom at least one biomarker test is available display decreased premature mortality before ages 75 and 65 and an increased probability of surviving three years after diagnosis. However, the total effect of biomarker testing on survival decreases as the number of cancer drugs available increases, suggesting that the matching of patients to treatment is better when fewer drugs are available.

By distinguishing between therapies that require biomarker testing before prescription (biomarker-guided drugs) and therapies that do not (nonguided drugs), we find that the cumulative number of the latter is associated with an increase in the probability of being alive three years after diagnosis, while the cumulative number of the former is associated with a reduction in premature mortality before ages 75 and 65.

Finally, an important part of evaluating a new treatment paradigm is to compare the potential benefits with the potential costs. We shed light on this question by looking at the potential cost per life-year gained from biomarker-guided drugs, where the costs are estimates of expenditure on those drugs in 2016. According to the threshold value used in the literature, our analysis shows that the use of biomarker-guided drugs is cost-effective.

### 2.2 Incentives for biomarker development

Biomarker tests that predict drug response have the potential to improve patients' health outcomes by avoiding unnecessary and potentially dangerous drug exposure and to reduce pharmaceutical costs for therapies that would be unsafe or ineffective for many patients. In many cases, under the "blockbuster" treatment paradigm, drugs are developed to be sold to as many patients as possible, but competitors or academic researchers find that it is possible to identify those patients who are more likely to benefit from a drug and need the collaboration of the drug manufacturer to develop the biomarker test and sell the drug as a personalized medicine. However, the limited economic incentives of drug producers to develop personalized

medicines are a barrier to the growth of drug-test combinations in the market. The problem is that when a biomarker test must be administered before a drug can be prescribed, the drug can only be sold to those identified as responders, meaning that the number of potential consumers declines. As in many countries the pricing of pharmaceuticals is inflexible, drug sales decrease as soon as biomarker testing is implemented and are insufficient to provide returns to drug R&D investments.

While the literature has pointed out some policy instruments that can potentially encourage the development of biomarker tests, namely, a flexible price schedule reflecting the benefit of a drug (Danzon & Towse, 2002; Vernon et al., 2006; Cook et al., 2009; Garrison & Austin, 2007) and government subsidies (Hsu & Schwartz, 2008; Chandra et al., 2017), it is still unclear what their implications are for investments in drug R&D and for welfare. In this paper, we develop a theoretical model to analyze how the incentives to launch drug-test combinations change under these policies. In particular, we look at the incentives and welfare effects when the regulator can set one drug price when the test is implemented and another price when the test is not implemented and/or can subsidize drug R&D if the pharmaceutical firm agrees to collaborate in development of the test. We consider one pharmaceutical firm that faces a regulated drug price and may or may not discover a new drug, depending on the amount of R&D investment it chooses. This setup is similar to that in Brekke & Straume (2009), but in this study, we incorporate the firm's decision on whether to allow a biomarker test to be developed for that drug.

We first show that although the regulator can encourage the pharmaceutical firm to accept biomarker test development by increasing the price of the drug, there will be a tradeoff between increasing the price such that the firm's incentives to invest in drug R&D increase and increasing the social cost of public funding needed to pay that price. Furthermore, we show that under certain conditions, the regulator is indifferent between increasing the drug price and providing a subsidy on the margin of R&D investment or even a combination of both. However, this also implies an increase in the social cost of public funds needed to pay for the higher price, the subsidy, or both. Therefore, offering an R&D subsidy does not improve social welfare, so these contracts fail to achieve the first-best outcome. Interestingly, we find that when the monopoly profits are transferred to the government through a lump-sum tax, the first-best outcome is achieved. The reason for this is that a price increase and/or R&D subsidy encourages the development of a drug with a biomarker test, but a tax on the profit that makes the pharmaceutical firm break even offsets the increase in the social cost of public funds.

## 2.3 Biomarkers in clinical trials: incentives under competition between pharmaceutical firms

Clinical trials of new drugs have a high risk of not being successful because the safety and efficacy of a drug varies substantially across treated patients. To improve the success of trials, drug developers can use biomarker tests to select participating patients. By identifying the likely responders of a drug, biomarker testing allows for the use of a smaller sample of clinical trial participants and potentially shorter periods needed to reveal statistically significant therapeutic effects. The problem is that the combination of a drug with a biomarker test reduces drug sales because only responders will be treated with the drug. Hence, including a biomarker test in clinical trials is unlikely to be profitable for the firm unless the price of the drug increases when the biomarker is used (Scott Morton & Seabright, 2013). In some cases, however, drug manufacturers may include biomarker tests in their clinical trials with the aim of winning the research and development (R&D) race. For example, the Merck drug Keytruda was approved as the first treatment choice for lung cancer because a biomarker test selected patients for the clinical trial, which improved the drug's efficacy, while the Bristol-Myers drug, Opdivo, failed the required trials for the same disease because its trials were performed in a broad group without selection through a biomarker test. Consequently, sales of Keytruda surpassed those of Opdivo. These competitive settings create a prisoner's dilemma where drug developers face a strategic decision of whether to use a biomarker test; this scenario has not yet been explored in a formal model.

In this paper, we analyze the incentives to include a biomarker test in drug clinical trials when two firms that develop very similar drugs compete for marketing approval. The biomarker test eliminates the risk of a statistically inconclusive trial result, but it decreases drug sales. Additionally, testing benefits patients by preventing adverse effects in nonresponders. We consider a model where a health authority can only approve one of the drugs to treat patients and prefers the drug that provides greater health benefits. We compare the incentives under a duopoly with those in a monopoly version of the model. By assuming that the price of the drug is unchanged regardless of the use of a biomarker test, we focus on the effect of competition on private incentives and social welfare.

We show that competition can increase the incentives to include a biomarker test in clinical trials. This is because the test increases the health benefits generated by the drug, which makes the drug more appealing to the health authority than an alternative without a test. In other words, this incentive arises from the consideration that the rival's drug could be chosen by the

health authority to treat patients if the firm does not use the biomarker test. There is also a gain from including the biomarker with the purpose of increasing the probability of successfully showing the statistically significant therapeutic efficacy of the drug in the trial. However, this incentive is weaker under competition than in a monopoly setting because the rival also faces the risk of not finding statistically significant trial results if it does not include the biomarker, which makes the firm in less of a hurry to include the biomarker to win the R&D race with the rival. Additionally, we find that a firm that is less likely than its rival to develop a drug with a large fraction of responders has stronger incentives to include the biomarker test, with the aim of increasing its chance of its drug approved by the health authority over that of its more promising rival. We investigate the welfare effects and find that the inclusion of a biomarker test in clinical trials can be more socially beneficial in a duopoly than in a monopoly, since there are two firms working on developing a high-quality drug rather than just a monopolist.

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