# Incentives for Biomarker Development*

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**Abstract**

Biomarker tests reduce adverse drug reactions, overtreatment, and waste of resources on ineffective medicines. However, drug manufacturers have limited economic incentives to collaborate with the developers of these tests, as the drug price is generally inflexible during the patent period and the tests reduce the number of eligible drug consumers. As a consequence, the adoption of personalized medicine in the form of biomarker tests has been underwhelming. We investigate what policies can be taken to increase pharmaceutical firms' incentives to collaborate on the development of tests and how they affect drug R&D investment. We consider a situation in which the drug firm is offered two prices, with or without a biomarker test, and a cost-sharing subsidy for R&D if it accepts test implementation. We show that a greater price incentive induces the firm to adopt a strategy with biomarker testing, and by comparing the drug price to a marginal R&D investment subsidy, we show that they are in fact perfect substitutes in encouraging the development of a biomarker test. In addition, we find that the social cost of paying the price and/or the subsidy is an obstacle to achieving socially optimal welfare unless the profits of the firm are taxed.

**Keywords:** Biomarker, Personalized medicine, Pharmaceutical Innovation, Health Policy

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# 1 Introduction

There has been increasing interest in personalized medicine, with particular emphasis on the combination of drugs and companion diagnostic biomarker-based tests, to define a set of patients who are likely to respond to specific treatments. Biomarker tests identify biological factors that create individual variations in drug response. Indeed, the use of a companion diagnostic implies that the patient is first tested for a biomarker, and conditional on the result, the drug can be prescribed. The development of these tests is particularly relevant for drugs targeting diseases caused by molecular alterations, such as cancer.

Cancer drugs are rarely safe and effective for everyone. In general, it has been estimated that many of the major drugs for several important therapeutic areas are effective in just 50–75% of patients, and specifically, the response rate to major cancer drugs is as low as 25% (Spear et al., 2001). This implies that without biomarker testing, a large proportion of healthcare spending is wasted on expensive medicine prescribed to patients who do not benefit from it. More important, pharmaceutical products are one of the main causes of adverse events, such as morbidity and mortality, and a large number of patients are hospitalized due to severe adverse drug reactions (Phillips et al., 2001). Therefore, biomarker testing may improve patient safety by reducing unnecessary and potentially dangerous drug exposure and additionally help healthcare payers to reduce expenses on unsafe or ineffective therapies.

However, the adoption of this technology in clinical practice has been slower than expected, and economic incentives are a potential barrier (Garrison & Towse, 2014). Few drugs have been launched with biomarker tests. In fact, the majority of cancer drugs were initially launched without biomarker test, but academic researchers and competitors have found that those drugs had poor effects on significant subsets of patients, and the drug manufacturers had to face the decision of whether to implement the biomarker test (Agarwal, 2012).

In the development of a test kit, collaboration between the test developer and the drug manufacturer is crucial.[1] However, the company developing and commercializing a new, patented drug still has weak economic incentives to identify the subset of patients who are likely to respond well to the drug after it is brought to market. This is because after the testing requirement is added to the label, the drug sales decline due to fewer potential prescriptions and inflexible reimbursement pricing in most countries. Thus, the implementation of the test may

[1] Assuming that the biomarker test and the drug are developed by two different firms, the clinical trial data of the new drug held by the drug manufacturer must be shared with the test manufacturer to conduct the proper clinical trials for the test. Additionally, the label of the drug must be changed to state that the test must be performed before prescription.

not provide returns on investments for pharmaceutical firms.

However, some policy instruments with the potential to increase incentives for R&D on products with low economic value for private firms but high value for consumers have been suggested in the literature.[2] These policies include programs that increase revenues for the innovative firm and/or programs that subsidize the cost of R&D investments. First, a program that commits to a price schedule reflecting the benefit of the drug has been suggested in the literature as a way to encourage the development of drugs with biomarker tests (Danzon & Towse, 2002; Vernon et al., 2006; Cook et al., 2009; Garrison & Austin, 2007). Second, as made apparent by Hsu & Schwartz (2008), there can be a substantial social benefit in sponsoring such research. They explain that with an R&D subsidy, there is no need for the price to be as high as without the subsidy. This can result in lower drug revenue and higher expected consumer surplus.

In this paper, we develop a theoretical model to provide a solution to align the interests of private firms and the government, i.e., to create incentives for launching a drug and a biomarker test in combination. We consider a pharmaceutical firm that may or may not discover a new drug, depending on the amount of R&D investment it chooses. If the firm is successful, it must decide whether to allow a biomarker test to be developed for that drug. In line with features of the pharmaceutical market in most countries, the firm faces a regulated drug price, and the demand for pharmaceuticals is price inelastic (Brekke et al., 2007; Brekke & Straume, 2009). We show that if the price of the drug is the same regardless of whether the test is implemented, the drug firm will refuse to accept test development. To overcome this problem of limited incentives, we consider two potential instruments. The first option is that the drug manufacturer is offered one regulated price when the test is implemented and another price when the test is not implemented. The second option is a potential role for government funding of research (Hsu & Schwartz, 2008; Chandra et al., 2017). Thus, the government and the firm can enter a binding agreement where the investment in drug R&D can also be subsidized if the firm accepts the test. Note that the firm's R&D investment is subsidized on the margin. Given that the pharmaceutical firm receives a patent on the drug when it is discovered, we analyze the effect of these instruments on pharmaceutical innovation.

We obtain the following results. First, we show that the regulator can encourage the firm to accept the biomarker test by increasing the price of the drug. However, this implies a tradeoff for the regulator: a higher price increases the firm's R&D incentives, but it also increases the

[2]Examples of these products are vaccines for diseases in developing regions or orphan drugs (pharmaceutical products developed to treat rare diseases).

social cost of public funding due to increased efficiency loss. Second, under certain conditions, a price that reflects the value of the biomarker and an R&D subsidy on the margin are perfect substitutes. The regulator can either increase the price or the subsidy or choose a combination of both. However, this will imply an increase in the social cost of public funds, which will be above what would be socially optimal. Thus, offering a subsidy for R&D instead of increasing the drug price does not improve social welfare. However, we conclude that introducing a lump-sum tax on the profits of the pharmaceutical firm will transfer the monopoly profit to the government, resulting in first-best profits. In other words, a price and/or a subsidy for R&D incentivizes the development of a drug with a biomarker test, but a profit tax that makes the firm break even offsets the increase in the social cost of public funds.

We proceed by discussing some related work on personalized medicine in Section 2 and introduce the model in Section 3. The social optimum analysis is conducted in Section 3.1. In Section 4, we address the problem of the lack of incentives to implement a test in a patent regime. In particular, Section 4.2 provides an analysis of this problem by setting two drug prices depending on the acceptance or refusal of the test, and in Section 4.3, we tackle the problem with a subsidy for R&D. In Section 4.4, we analyze the effect of a tax on the firm. Finally, Section 5 discusses the framework of the model, and Section 6 concludes the paper.

## 2 Related Work

Thus far, theoretical modeling of the economics of biomarkers and personalized medicine has received limited attention in the literature. Among the existing contributions, there are studies that analyze the implementation of personalized medicine from the healthcare providers' perspective (Antoñanzas et al., 2015; 2016), while most studies focus on the effect of testing for the prediction of treatment response on the revenues of the drug producer (Danzon & Towse, 2002; Vernon et al., 2006; Cook et al., 2009), and one study also analyzes the test producer's incentives in an illustrative analysis (Garrison & Austin, 2007).

Examples of recent work that studies how precise the science behind biomarkers must be to be implemented in clinical practice includes Antoñanzas et al. (2015), who model the decision that a health authority faces when deciding whether to implement personalized medicine. They consider a health authority under budget constraints, which must choose either one of two drugs to administrate to every patient without a test or to use a test and personalize the treatment accordingly, and they conclude that the test is used for cases where the adverse effects of false positives and false negatives are low. Antoñanzas et al. (2016) analyze hospitals' decision-

making process to adopt personalized medicine. This problem is analyzed in a model where the manufacturer of the new drug with an associated test sets the price of the drug without knowing the prevalence of the patient types across hospitals. Based on these models, the authors conclude that the low number of these tests being used in hospitals is potentially due to limited scientific advances or to the high cost of testing. However, we show that even when the test technology is sufficiently effective and the cost of testing is low, drug producers still have limited economic incentives to associate their drugs with these tests.

The formal analysis by Danzon & Towse (2002) shows how biomarker testing could be beneficial for society but reduces the number of patients treated and thereby pharmaceutical firms' incentives to develop new personalized medicines. They show that the firm has no incentives to invest in drug-test combinations unless the final drug price is changed (i.e., higher with the test than without it), there are savings in R&D costs (for example, if testing allows for the efficacy of the drug to be demonstrated with smaller trials), or the pharmaceutical firm profits from the commercialization of the test. Furthermore, they note that the lower revenues due to testing are potentially not sufficient to justify the costs of drug R&D. However, their model does not take into account the welfare effect of testing due to changes in the level of drug R&D investment and the associated probability of drug discovery.

By considering different incentives to develop a drug and a companion diagnostic, Garrison & Austin (2007) develop an illustrative model where they recognize that patients benefit from reduced drug-response uncertainty and allow the social surplus created by the drug-test combination to be captured by either the firm developing the drug or the test. They show that if the test is introduced into the market after the drug has been marketed and priced, the incentives to invest in testing are stronger in a situation with intellectual property protection and value-based flexible pricing in both the test and drug markets. On the other hand, the incentives to test are limited in a situation with a fixed drug price and cost-based pricing for the test. In this way, they emphasize the need to encourage both drug and test manufacturers to develop personalized medicine.

In the same line of work, Vernon et al. (2006) find that a higher equilibrium drug price with a test, resulting from the higher therapeutic value for patients who benefit more, will partially overcome the loss in the number of consumers. Nevertheless, the drug producer's revenues with a test associated with its drug will never be greater than the drug revenues without the test. In contrast to Vernon et al. (2006), Cook et al. (2009) argue that if some potential patients avoid a drug because they fear its adverse effects, the implementation of a test to predict drug response can generate higher revenues. They suggest that patients can

learn that the drug is more effective with the test, which in turn causes the adoption rate by the proportion of "responders" to increase. Thus, testing can increase drug revenues if the increase in the adoption rate by the "responders" is higher than the loss of consumers who are "nonresponders".

Although these models emphasize the need for flexible and value-based pricing to incentivize more personalized medicine, there is no analysis on how it affects pharmaceutical R&D investment and the inherent uncertainty of drug discovery. Additionally, there are social consequences from raising public funds to pay for high prices, which are often not taken into account in the literature on personalized medicine.

In this paper, we combine the theory on R&D incentives in the pharmaceutical industry with personalized medicine models. There have been extensive studies on the link between regulation and R&D investment in the pharmaceutical industry. Brekke et al. (2007) consider a model with one on-patent drug, one off-patent drug and one generic where they compare the effect of different types of pricing controls and show that therapeutic reference pricing encourages the least amount of innovation. Brekke & Straume (2009) examine a patent race between two pharmaceutical firms and find that a less strict price regulation (or a more generous patent premium) leads to higher strategic spending on advertising of existing drugs and less on R&D investments to reduce the entrant's incentives to invest in R&D. Bardey et al. (2010) analyze the impact of reference pricing regulation (i.e., drug reimbursement based on therapeutic equivalence) and show that investment in R&D is less intense when reference pricing is adopted since it negatively impacts drug prices. They also point out that reference pricing leads to more research on pioneer drugs and less research on small or incremental innovation drugs. However, Ganuza et al. (2009) show that pharmaceutical R&D is biased toward drugs with small incremental benefits rather than pioneer or breakthrough drugs because of the inelasticity of demand. In contrast to other authors, they argue that although price regulations to control pharmaceutical expenses, such as copayments or reference pricing, reduce firms' profits, they can increase incentives for R&D by making demand more inelastic. Finally, Grossmann (2013) analyzes the case of pharmaceutical firms that sell imperfect substitute drugs and shows that lower insurance coverage of prescription drugs and stricter price regulations, which lower drug prices, reduce R&D spending.

In sum, it is clear that the pharmaceutical industry is highly R&D intensive, and a conclusion from this literature is that the control of pharmaceutical expenses through strict price regulation decreases drug innovation and can shift interest to more or less beneficial drugs depending on the effect of price on demand. The implementation of a biomarker test that

reduces the number of potential consumers of a drug may change the incentives for pharmaceutical innovation. Thus, this paper relates to studies of personalized medicine while focusing on policy measures that can encourage pharmaceutical firms to accept the biomarker test and undertake R&D to discover new drugs.

# 3 The Model

In this model, there is a large pharmaceutical firm that invests in developing a new drug to treat a disease. Another company, which can either be an academic research group or a biotechnology firm, discovers a biomarker and may further develop a biomarker test if the pharmaceutical firm agrees to collaborate. If the biomarker test is introduced in the market, the test identifies patients as responders or nonresponders to the new drug. The game is described in Figure 1 and has the following sequence of actions:

- Stage 1: The health regulator announces the drug pricing policy.
- Stage 2a: The pharmaceutical firm invests in R&D to develop a new drug.
- Stage 2b: Next, if the new drug is successfully developed, another company discovers a biomarker responsible for patient segmentation into responders and nonresponders,[3] and the pharmaceutical firm decides whether to collaborate on the development of a test kit for that biomarker. If the pharmaceutical firm agrees to collaborate with the biomarker company, the test is implemented, and the drug is sold to patients identified as responders. However, if the pharmaceutical firm rejects the prospect of collaboration, the test is not implemented, and the drug is sold to all patients.

We assume that there is a unit mass of patients suffering from the disease and that each patient consumes one unit of the drug. However, only a fraction $\lambda$ has a positive reaction to the new drug and benefits $\epsilon$ from it. The remaining patients experience adverse effects, and their health deteriorates by $a$ if they consume the new drug. The benefit $\epsilon$ and the disutility $a$ can be interpreted as the quality-adjusted life years (QALYs) or the economic value of the

[3]Due to the low success rate of drug approval, it may be too risky for the academic research group or biotechnology company to develop the test during the drug's developmental phase. Therefore, the company will work on biomarker discovery after the drug has been approved rather than collaborate with the pharmaceutical firm before the drug's market approval (Mittra & Tait, 2012). For drug producers, it also makes little economic sense to invest in such tests during the drug development process unless they have a strong prior about how to stratify the patients for trial (Towse & Garrison, 2013).

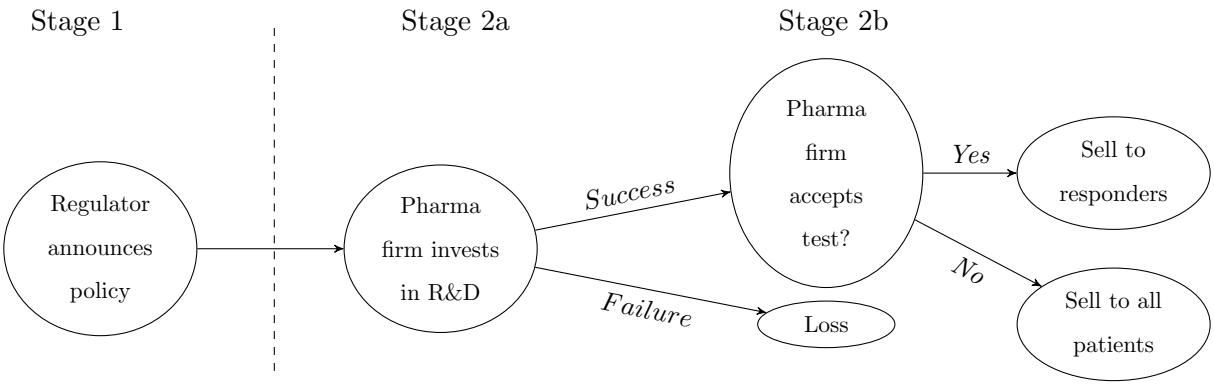


Figure 1: Stage-transition diagram

QALYs. The biomarker test is assumed to accurately identified these two sets of patients. It is unknown beforehand who will have a positive response to the drug if the test is not available.

Many healthcare systems have third-party payments for prescription drugs. Even if patients pay for these drugs, the fee is often very low. Moreover, doctors may also prescribe drugs without knowing the prices. As a consequence, the demand for prescription drugs is typically highly price-inelastic (Brekke & Straume, 2009). Hence, we assume that the demand for the new drug is price-inelastic and equal to 1 (a unit mass of consumers) if the drug is sold without the biomarker test and is equal to the fraction of responders $\lambda$ if the test is implemented.

The following model specifications are based on the model of incentives for R&D for pharmaceutical firms by Brekke & Straume (2009). We denote the probability that the pharmaceutical firm discovers the new drug by $x \in [0, 1]$. The cost of obtaining the probability of discovery $x$ is given by a convex function $C(x) = (1/2)(x^2)$, where $C'(x) > 0$, $C''(x) > 0$, and $C(0) = 0$.[4]

Furthermore, since markets for prescription drugs are mainly characterized by highly price-inelastic demand, many countries apply price regulations (Brekke & Straume, 2009). Under this regime, the regulator sets a maximum price that the firms can charge for their products to control the growth of healthcare expenditures (Barros, 2010). Therefore, we assume that the drug manufacturer faces a regulated drug price $p$. The socially optimal R&D incentive program, such as the pricing policy, is thus decided by the regulator at the first stage (Brekke et al., 2007).[5]

In reality, the marginal production costs in the pharmaceutical industry are very low (Brekke & Straume, 2009). Thus, we assume that production costs are zero in this model.[6]

Failing to develop the new drug implies receiving zero revenue. However, if the drug is

[4]The quadratic cost function of investment in R&D is also assumed by Jansen (2010).

[5]This can also be interpreted as a pull subsidy plan, in the form of a purchase commitment plan, where the sponsor offers a price schedule for the drug prior to development (Hsu & Schwartz, 2008).

[6]Zero-cost drug production is also assumed by Brekke & Straume (2009) and Bardey et al. (2010).

successfully developed, it is protected by the patent system. Thus, gross profits for the pharmaceutical firm from the new drug alone ($V_0$) and from the combination with the test ($V_1$),[7] are given by

$$V_0(p) = p, \tag{1}$$

$$V_1(p) = p\lambda. \tag{2}$$

Note that the demand for the new drug when the test is implemented is lower than when the drug is marketed without the test. This is because it is stipulated on the drug label that testing is required before the prescription of the drug.

Since there is some probability that the new drug is not discovered, the expected profits for the new drug without testing $E_0(x, p)$ and with testing $E_1(x, p)$ are given by the expected revenue minus the cost of drug R&D:

$$\begin{aligned} E_0(x,p) =& xV_0(p) - C(x) \\ =& xp - \frac{1}{2}x^2, \end{aligned} \tag{3}$$

$$\begin{aligned} E_1(x,p) =& xV_1(p) - C(x) \\ =& xp\lambda - \frac{1}{2}x^2. \end{aligned} \tag{4}$$

We assume a zero-profit condition for the test firm and that the price of the test is zero. This assumption is made for two main reasons. First, the biomarker test market is more competitive than the pharmaceutical market since intellectual property protection is not as strong, and the price is set based on the expected cost of production and distribution (Garrison & Towse, 2014). Second, we assume that the test is "ideal", meaning that it is not only accurate and safe for the patient but also very easy to perform in clinical practice (at zero cost). In this way, we exclude the biological complexity and lack of cost-effectiveness evidence as a reason for the currently low number of biomarkers entering clinical practice. Instead, the analysis is focused on the problem of limited economic incentives for the drug manufacturer to allow a test to identify the right patients for its drug.

### 3.1 Benchmark: social optimum analysis

In this section, we present the analysis of the model under a socially optimal situation. We assume that the social planner decides the price of the drug and the R&D investment level that are socially optimal, i.e., that maximize social welfare. Additionally, the social planner

[7] As in Brekke & Straume (2009), we assume a discount factor $\delta = 1$, for simplicity.

chooses whether to allow the test to be introduced, depending on what results in greater social welfare.

### 3.1.1 Social optimum without testing

Suppose first that the pharmaceutical firm develops the new drug, but no test is implemented. In this case, the utility from drug consumption consists of the health benefits $\epsilon$ for the fraction of responders $\lambda$ minus the adverse effects $a$ experienced by the fraction of nonresponders $1-\lambda$, and it is written as

$$U_0 = \lambda\epsilon - a(1-\lambda). \tag{5}$$

This utility must be greater than zero; otherwise, the drug would not receive market approval by the pharmaceutical regulator. Therefore, an assumption is made here that the benefits for the responders are greater than the disutility for the nonresponders:

**Assumption 1.** $\lambda\epsilon \geq a(1-\lambda)$

Additionally, we assume that the price of the drug is paid by a third party and that the payer is public. Therefore, we assume a distortionary effect of taxation to raise public funds (Bardey et al., 2016; Laffont, 1999). We account for a social cost of public funds $\theta > 0$, and the social welfare cost of consuming the new drug is $(1+\theta)p$.

The welfare function is given by the expected aggregate utility of consumers plus expected profits for the drug firm, net of the social cost of public funds needed to pay the drug price. Without the test, all patients consume one unit of the drug, and the social welfare is written as

$$\begin{aligned} W_0(x,p) =& x[U_0 + V_0(p) - (1+\theta)p] - C(x) \\ =& x(\lambda\epsilon - a(1-\lambda) - \theta p) - \frac{1}{2}x^2. \end{aligned} \tag{6}$$

The social planner sets the first-best level of R&D investment, which we find by maximizing the welfare function, subject to a nonnegative profit for the pharmaceutical firm:

$$\begin{aligned} \underset{x}{\text{maximize}} \quad & W_0(x,p) = x_0(\lambda\epsilon - a(1-\lambda) - \theta p) - \frac{1}{2}x^2 \\ \text{subject to} \quad & E_0(x,p) = xp - \frac{1}{2}x^2 \geq 0 \\ & \Leftrightarrow p \geq \frac{1}{2}x \end{aligned} \tag{7}$$

It is clear that if $p > \frac{1}{2}x$, one can always decrease $p$ to obtain a higher welfare without violating the participation constraint. Welfare increases, so this $p$ cannot be optimal. Therefore, the participation constraint is binding, and the drug price is given by $p = \frac{1}{2}x$.

The socially optimal investment (first best) when the test is not implemented is, thus, given by

$$\frac{\partial W_0}{\partial x} = 0 \Leftrightarrow x_0^* = \frac{\lambda\epsilon - a(1-\lambda)}{\theta + 1}, \tag{8}$$

which decreases as the social cost of public funds $\theta$ increases. This is because it is more costly for society to raise funds to pay for a higher drug price with a higher $\theta$. This implies that the firm's revenues are lower, which reduces the incentives for pharmaceutical innovation.

From the nonnegative profit constraint for the pharmaceutical firm, we find the optimal drug price:

$$p_0^* = \frac{\lambda\epsilon - a(1-\lambda)}{2\,(\theta + 1)} \tag{9}$$

As the social cost of public funds increases, it is more expensive for the sponsor to pay the price of the drug. As a consequence, the price paid for the drug to the firm is lower. Given this price and R&D investment level, the first-best welfare without testing is given by

$$W_0^* = \frac{(\lambda\epsilon - a(1-\lambda))^2}{2\,(\theta + 1)}. \tag{10}$$

As the fraction of responders $\lambda$ and the benefit $\epsilon$ from consuming the drug increase, society benefits more from having this drug on the market as more patients are cured. The optimal R&D effort level also increases with higher levels of $\lambda$ and $\epsilon$ (as we can see in (8)), which implies that the probability of drug discovery increases, resulting in higher social welfare. On the other hand, welfare decreases as the disutility $a$ from consuming the drug increases, i.e., as the drug becomes more unsafe for the fraction of nonresponders. Additionally, welfare is reduced when it is more costly to obtain public funds to pay the drug price (when $\theta$ is higher).

### 3.1.2 Social optimum with testing

Suppose now that the biomarker test is developed and used to predict the set of patients who will respond positively to the new drug. When the test is implemented, the set of patients who benefit from the treatment is revealed, and the drug is prescribed only to them. The patients' utility from the drug-test combination comprises only the health benefits $\epsilon$ for the fraction of responders $\lambda$, and it is given by

$$U_1 = \lambda\epsilon. \tag{11}$$

The welfare function when the test is implemented is given by the expected consumer utility net of the social cost of paying the drug price and the cost of R&D:

$$W_1(x, p) = x\,(\lambda\epsilon - \lambda\theta p) - \frac{1}{2}x^2 \tag{12}$$

The investment in R&D is set by the social planner. To find the first-best investment level, we maximize the welfare function, subject to a nonnegative profit constraint for the drug firm:

$$\begin{aligned} \underset{x}{\text{maximize}} \quad & W_1(x,p) = x\left(\lambda\epsilon - \lambda\theta p\right) - \frac{1}{2}x^2 \\ \text{subject to} \quad & E_1(x,p) = xp\lambda - \frac{1}{2}x^2 \geq 0 \\ & \Leftrightarrow p \geq \frac{x}{2\lambda} \end{aligned} \tag{13}$$

We can see that if $p > \frac{x}{2\lambda}$, one can always decrease $p$ to obtain a higher welfare without violating the participation constraint. Welfare increases, so this $p > \frac{x}{2\lambda}$ cannot be optimal. Therefore, the participation constraint is binding, the firm will have zero expected profits, and $p = \frac{x}{2\lambda}$.

The optimal R&D investment level is given by

$$\frac{\partial W_1(x,p)}{\partial x} = 0 \Leftrightarrow x_1^* = \frac{\lambda\epsilon}{\theta+1}, \tag{14}$$

which is decreasing in the social cost of public funds $\theta$.

Thus, the socially optimal drug price is given by

$$p_1^* = \frac{\epsilon}{2(\theta+1)}. \tag{15}$$

Under a regime where the test is implemented, the optimal drug R&D investment is $x_1^*$, the price of the drug is set to $p_1^*$, and the first-best welfare is given by

$$W_1^* = \frac{\lambda^2\epsilon^2}{2(\theta+1)}. \tag{16}$$

Welfare is increasing in $\lambda$ and $\epsilon$. When the fraction of responders $\lambda$ is high, more patients benefit from the new drug. Consequently, the socially optimal level of R&D investment is higher, implying that the probability of drug discovery is higher. When $\epsilon$ is high, the patients benefit more. Therefore, there is value in setting a higher level of drug R&D investment to increase the probability of drug discovery. Since it is costly to obtain funds through taxation to pay the drug price, welfare is decreasing in $\theta$, which is the social cost of public funds.

### 3.1.3 Social optimum preferences

We compare the social welfare resulting from the situations analyzed above – i.e., with and without testing – to find the conditions under which testing the patients is preferable. The social planner prefers to implement the test whenever

$$\begin{aligned} W_1^* \geq W_0^* \Leftrightarrow & \frac{\lambda^2\epsilon^2}{2(\theta+1)} \geq \frac{\left(\lambda\epsilon - a(1-\lambda)\right)^2}{2\left(\theta+1\right)} \Leftrightarrow \\ & \lambda\epsilon \geq \frac{1}{2}a(1-\lambda). \end{aligned} \tag{17}$$

Society benefits more from implementing the test if the health benefit from taking the drug for the responders is higher than half of the disutility for the nonresponders. Since Assumption 1 holds, the regulator prefers to implement the test.

# 4 Regimes with R&D incentives

In this section, we analyze the incentives to accept the test when a patent for the drug is given to the pharmaceutical firm. In these cases, the firm's objective is to maximize its own profits, deciding how much to invest in R&D to discover the new drug and whether it accepts test implementation. The role of the regulator is, in this case, to give incentives to the firm to agree to implement the test while encouraging investment in drug R&D.

We focus on two main types of incentive programs for drug R&D where the regulator designs a price contract: one fixed price or two prices depending on therapeutic efficacy (one price with testing and another without testing). Furthermore, we analyze one incentive scheme where the regulator offers a price and a cost-sharing R&D subsidy. We analyze whether these programs can be used to encourage the acceptance of a biomarker test to identify the responders of the drug and their effect on social welfare.

## 4.1 One drug price

We first analyze the case in which the regulator commits to one price for the new drug independent of whether the drug is combined with a predictive test. This means that the regulator offers only one drug price, which remains the same regardless of whether the test is used ($p$). This is equivalent to setting a fixed drug price when the drug is approved, which does not change even after the test is implemented. This inflexible pricing policy for drugs corresponds to reality for many therapeutic areas in many developed countries (Garrison & Towse, 2014).

Given a drug price $p$, the problem of the firm without testing is given by

$$\max_x E_0(x,p) = xp - \frac{1}{2}x^2. \tag{18}$$

From the first-order condition, we obtain the optimal investment for the firm when no test is introduced, which is given by $x_0 = p$.

Let us suppose now that the pharmaceutical firm accepts the test. Given the fixed price $p$, the problem of the firm is given by

$$\max_x E_1(x,p) = xp\lambda - \frac{1}{2}x^2. \tag{19}$$

From the first-order condition, the optimal drug R&D investment level for the firm when it accepts the test is $x_1 = p\lambda$.

Hence, for a given $p$ and $\lambda < 1$, the expected profit without the test will be higher than that with the test:

$$E_0(p) = \frac{1}{2}p^2 > \frac{1}{2}p^2\lambda^2 = E_1(p) \tag{20}$$

As long as the price offered for the drug is fixed, the pharmaceutical firm will always refuse test implementation. The intuition for this is straightforward. Implementing the test will only serve to reduce the market for the firm. Since it receives a fixed price for each sale, it can never be profitable to implement the test. Knowing this, the regulator offers the price that maximizes welfare without testing given that the firm invests $x_0 = p$:

$$\max_p W_0 = p(\lambda\epsilon - a(1-\lambda) - \theta p) - \frac{1}{2}p^2 \tag{21}$$

From the first-order condition, $\bar{p} = \frac{\lambda\epsilon - a(1-\lambda)}{2\theta+1}$. The resulting welfare is $\bar{W}_0 = \frac{(\lambda\epsilon - a(1-\lambda))^2}{2(2\theta+1)}$. This may be compared to the first-best social welfare when the test is implemented:

$$W_1^* \geq \bar{W}_0 \Leftrightarrow 2\lambda\epsilon \geq a(1-\lambda) - 2\theta\lambda^2\epsilon^2 \tag{22}$$

The fact that the test is not implemented is undesirable given that Assumption 1 holds.

Although this program is useful to contain pharmaceutical spending through price control while encouraging drug R&D investment to some extent, it discourages the pharmaceutical firm from allowing a predictive biomarker test to be developed and associated with its drug.

### 4.2 Two drug prices

Consider now a program where the price offered to the pharmaceutical firm depends on whether the test is implemented. Therefore, the regulator offers two prices for the drug: $p_0$ when no test is used, and $p_1$ when the test is implemented. In this way, the price of the drug is adjusted to its realized therapeutic efficacy in the population. We analyze this design by backward induction.

At stage 2, the firm decides the level of drug R&D investment. When no test is implemented, the problem of the firm is given by

$$\max_x E_0(x, p_0) = xp_0 - \frac{1}{2}x^2. \tag{23}$$

The profit maximizing R&D investment level is $x_0 = p_0$, and the expected profit given $p_0$ is $\widetilde{E}_0(p_0) = \frac{1}{2}p_0^2$. When the test is implemented, the problem of the firm is given by

$$\max_x E_1(x, p_1) = xp_1\lambda - \frac{1}{2}x^2. \tag{24}$$

In the case with the test, the profit maximizing investment level is $x_1 = p_1\lambda$, which results in the expected profit given by $\widetilde{E}_1(p_1) = \frac{1}{2}p_1^2\lambda^2$.

At stage 1, the regulator offers a contract with two drug prices, depending on whether the test is used ($p_1$) or not ($p_0$). Given that private investment is decided by the firm, the problem of the regulator is to find the pair of drug prices that maximizes social welfare. The regulator can always adjust the prices to make the firm choose to implement the test or not. Let us first assume that the regulator does not want the firm to implement the test. In this case, the regulator sets the prices such that it maximizes welfare without testing, and it is incentive compatible for the firm to refuse the test. Thus, the problem we want to solve is the following:

$$\begin{aligned} \underset{p_0,p_1}{\text{maximize}} \quad & W_0 = x_0(\lambda\epsilon - a(1-\lambda) - \theta p_0) - \frac{1}{2}x_0^2 \\ \text{subject to} \quad & \widetilde{E}_0(p_0) \geq \widetilde{E}_1(p_1) \Leftrightarrow p_0 \geq p_1\lambda \\ \text{and} \quad & x_0 = p_0 \end{aligned} \tag{25}$$

The result is the following welfare maximizing price without test:

$$p_0 = \frac{\lambda\epsilon - a(1-\lambda)}{2\theta + 1} \tag{26}$$

In line with the compatibility constraint, the price offered for the drug with testing is

$$p_1 \leq \frac{\lambda\epsilon - a(1-\lambda)}{\lambda(2\theta+1)}. \tag{27}$$

If these prices are offered, the drug manufacturer will prefer to refuse test implementation, and social welfare will be given by

$$\widetilde{W_0} = \frac{(\lambda\epsilon - a(1-\lambda))^2}{2\,(2\theta+1)}, \tag{28}$$

which is obtained by inserting the price in (26) into the welfare function.

Suppose now that we are in a regime where the regulator wants to implement the test. In this situation, the regulator offers a set of prices that maximizes social welfare with testing. The incentive compatibility constraint is defined such that the drug firm prefers to accept the test while investing the profit maximizing amount:

$$\begin{aligned} \underset{p_1,p_0}{\text{maximize}} \quad & W_1 = x_1\,(\lambda\epsilon - \lambda\theta p_1) - \frac{1}{2}x_1^2 \\ \text{subject to} \quad & \widetilde{E}_1(p_1) \geq \widetilde{E}_0(p_0) \Leftrightarrow p_1\lambda \geq p_0 \\ \text{and} \quad & x_1 = p_1\lambda \end{aligned} \tag{29}$$

The result is the following welfare maximizing price with testing:

$$\widetilde{p_1} = \frac{\epsilon}{2\theta+1}, \tag{30}$$

and the price of the drug without testing is

$$\widetilde{p_0} \leq \frac{\lambda\epsilon}{2\theta+1}. \tag{31}$$

If these prices are offered, the drug manufacturer will prefer to accept test implementation, as the price contract rewards it for the efficacy of the drug.

Under this two-price contract, social welfare will be given by

$$\widetilde{W_1} = \frac{\lambda^2\epsilon^2}{2(2\theta+1)}. \tag{32}$$

which is obtained by inserting the price in (30) into the welfare function with the test.

Given these contracts, the regulator will prefer to implement the test if and only if

$$\widetilde{W_1} \geq \widetilde{W_0} \Leftrightarrow \frac{\lambda^2\epsilon^2}{2(2\theta+1)} \geq \frac{(\lambda\epsilon - a(1-\lambda))^2}{2\,(2\theta+1)} \Leftrightarrow$$
$$\lambda\epsilon \geq \frac{1}{2}a(1-\lambda). \tag{33}$$

Assumption 1 holds, and the regulator wants to implement the test by offering a contract with two drug prices. Thus, the drug manufacturer will be offered a price of $\widetilde{p_1} = \frac{\epsilon}{2\theta+1}$ when the test is introduced and a price with no test set to a maximum of $\widetilde{p_0} \leq \frac{\lambda\epsilon}{2\theta+1}$. Note that $p_1 \geq \frac{p_0}{\lambda}$; thus, the drug firm will accept the test.

### 4.2.1 Regulated two-price scenario vs. first-best scenario

The contract with two drug prices offered to the firm is effective at encouraging the development of the test. We further compare this contract with the benchmark social optimum results to study how effective it is to offer prices that reward the efficacy of the drug (one price with testing and one without testing) in inducing R&D investment.

The price offered to the drug firm to encourage the adoption of the test, $\widetilde{p_1}$, is higher than the socially optimal price with the test:

$$\widetilde{p_1} = \frac{\epsilon}{2\theta+1} \geq \frac{\epsilon}{2(\theta+1)} = p_1^* \tag{34}$$

and, with $\theta > 0$, the R&D investment level given this set of prices is below the socially optimal investment level $x_1^*$:

$$\widetilde{x_1} = \frac{\lambda\epsilon}{2\theta+1} \leq \frac{\lambda\epsilon}{\theta+1} = x_1^*$$

Consequently, social welfare under this price program is lower than the social optimum:

$$\widetilde{W_1} \leq W_1^* \tag{35}$$

**Proposition 1.** *By adjusting the regulated drug price $p_1$, the first best is unattainable. The second-best solution is to adjust $p_1$ such that the firm underinvests and is given a slightly higher price than the social optimum. Hence, there is a tradeoff between inducing the investment $x_1$ and incurring more social costs from taxation to pay the price $p_1$.*

The intuition for this result follows from who is making the decisions in this market. In the socially optimal case, the social planner can decide the price, the level of R&D investment, and whether the test is implemented, such that social surplus is maximized. In reality, however, the level of R&D investment and the acceptance or refusal of the test is decided by the firm, such that it maximizes its profits. Since the first-best social surplus $W_1^*$ is greater than the firm's profit $\widetilde{E_1}$, the firm underinvests. Moreover, the only instrument the regulator is used to encourage test introduction and investment in drug R&D is the drug price. By giving the pharmaceutical firm a high price, which must be set above the social optimum, the regulator increases the incentives to fund R&D. However, since there is a cost of public financing, which generates an efficiency loss, the regulator is unwilling to give very high profits to the firm. As a consequence of this tradeoff for the regulator, social welfare under this patent regime is below that of the first-best scenario. However, if there is no social cost of public funding, $\theta = 0$, the first best is achieved.

A contract with two prices can not only raise consumer surplus by setting a price cap to allow patients to have access to the treatment but also increase welfare by encouraging the adoption of the test. However, it does not lead to the first best. The problem is that the pharmaceutical firm underinvests in R&D, and the price of the drug is raised above the social optimum, which leaves the firm with excessive profits. Therefore, in the following section, we consider a contract that combines the features of a two-price contract with a subsidy for drug R&D. In this way, we seek to understand whether the combination of two policy instruments – the price of the drug and a subsidy for drug R&D – will achieve the regulator's objective to implement the test and encourage socially optimal R&D investment while containing spending of public funds and reducing the social costs of pharmaceutical expenditures.

### 4.3 Drug R&D subsidy

We consider an R&D subsidy in addition to a price contract as another type of policy to be used by the regulator. Suppose that the government offers a price for the drug and can also sponsor the R&D on the new drug if the pharmaceutical firm accepts the development of the test. Here, we consider a cost-sharing subsidy, a type of push incentive program, where the cost

of R&D for the developer is reduced (Hsu & Schwartz, 2008). This subsidy increases the level of R&D investment, and as a consequence, it increases the probability of developing a successful drug. In this way, the social planner can influence the choices of the firm (Spencer & Brader, 1983). However, public funds must be used to subsidize the R&D investment. Therefore, the social cost of subsidizing is taken into account.

Let us assume that if the pharmaceutical firm commits to agree to the biomarker test to be developed for its drug, it receives $\gamma \geq 0$ for each $x$ it invests in R&D. In this way, the firm is given incentives on the margin to invest more.

Similar to the model described in Section 3, the game with the subsidy has 2 stages: first, the regulator announces the drug pricing policy ($p_{0s}$ without a biomarker test and $p_{1s}$ with a biomarker test) and the R&D subsidy conditional on test acceptance; then, the drug manufacturer decides whether to accept the subsidy and the test and its R&D investment level.

Suppose that the firm does not develop the drug with a biomarker test. The regulator offers a price $p_{0s}$ for the drug. The objective of the firm without a biomarker test under this contract is to choose an amount of $x$ that maximizes the expected profit, which is equal to the problem of the firm under the two-price contract in (23). Hence, the expected profit without a biomarker test under a contract with two prices and a subsidy is given by $\widetilde{E}_{0s}(p_{0s}) = \frac{1}{2}p_{0s}^2$.

Now, suppose that the firm accepts the test. Thus, a price $p_{1s}$ and a subsidy $\gamma$ for drug R&D are given to the firm. The problem of the firm is given by

$$\max_x E_{1s}(x, p_{1s}, \gamma) = x p_{1s}\lambda - \frac{1}{2}x^2 + \gamma x. \tag{36}$$

From the first-order condition, the profit maximizing R&D investment is

$$x_{1s} = p_{1s}\lambda + \gamma. \tag{37}$$

This means that an increase in $p_{1s}$ or an increase in the subsidy on the margin $\gamma$ leads to an increase in the firm's effort to discover a new drug, which also means a higher probability of drug discovery.

At stage 1, the regulator chooses the welfare maximizing drug price and an R&D subsidy. When the regulator prefers the test to be accepted by the drug firm, it will offer a welfare maximizing price and a subsidy on the margin. Under this regime, social welfare is given by the expected responders' utility, net of the total cost of drug R&D and the social cost of taxation needed to fund the subsidy and the price, as follows:

$$\begin{aligned} \underset{p_{1s}}{\text{maximize}} \quad & W_{1s}(x_{1s}, p_{1s}, \gamma) = x_{1s}\lambda\epsilon - \frac{x_{1s}^2}{2} - \theta\left(\gamma x_{1s} + p_{1s}\lambda x_{1s}\right) \\ \text{subject to} \quad & \widetilde{E}_{1s}(p_{1s}, s) \geq \widetilde{E}_{0s}(p_{0s}) \Leftrightarrow \frac{\lambda^2\epsilon^2}{2(1+2\theta)} \geq \frac{1}{2}p_{0s}^2 \\ \text{and} \quad & x_{1s} = p_{1s}\lambda + \gamma \end{aligned} \tag{38}$$

From the first-order conditions, we find that the welfare maximizing drug price is given by

$$\widetilde{p_{1s}} = \frac{\lambda\epsilon - \gamma(1+2\theta)}{\lambda(1+2\theta)}. \tag{39}$$

Any combination of the price $p_{1s}$ and the subsidy on the margin $\gamma$ satisfying (39) is optimal. This derives from the linear way in which both $p$ and $\gamma$ affect $x$; they are perfect substitutes. To make the development of the drug without a biomarker test undesirable for the firm, the regulator will offer the price without a test $p_{0s} \leq \frac{\lambda\epsilon}{1+2\theta}$. Consequently, the drug is developed with a biomarker test, and the profit maximizing level of R&D investment is given by:

$$\widetilde{x_{1s}} = \frac{\lambda\epsilon}{2\theta+1}. \tag{40}$$

Welfare is given by

$$\widetilde{W_{1s}} = \frac{\lambda^2\epsilon^2}{4\theta+2}, \tag{41}$$

which is equal to $\widetilde{W_1}$. Therefore, we have the following result:

**Proposition 2.** *A contract where a price and a subsidy on the margin of R&D are offered results in the same social welfare as a two-price contract.*

Proposition 2 implies that giving incentives on the margin to invest more in R&D does not make social welfare closer to first best. As in the two-price contract, the payment for the drug price and the subsidy set the social cost of public funds above what would be socially optimal. With this policy, public spending on the price and R&D subsidy accrues to the firm as monopoly expected profit. If it is possible to save on the government budget, it may be possible to get closer to the social optimum.

### 4.4 The best policy – profits tax

Consider now the implementation of a tax or payback policy. We search for an optimal solution that combines three policy instruments: the price of the drug, a subsidy for drug R&D, and a tax on the firm's profits. A lump-sum tax on the firm counterbalances the tax bill by transferring the profit of the firm to public funds. In this way, the social cost of paying the

price and for the subsidy is reduced, and the profit of the firm (which is a side effect of the patent system) is removed. In other words, under a contract with both a drug price and a subsidy for R&D, the third-party funding cost accrues less to the pharmaceutical firm as expected profit and more to the social surplus.

Suppose that the pharmaceutical firm must repay a fixed amount $S$. Now, the subsidy scheme can be expressed as $s(x) = \gamma x - S$, $\gamma, S \geq 0$.

If the firm commits to accept the test, it is given the subsidy $\gamma$ for drug R&D and price $p_{1s}$. When the test and the subsidy are accepted, the problem of the firm is given by

$$\max_x E_{1s}(x, p_{1s}, \gamma, S) = x p_{1s}\lambda - \frac{1}{2}x^2 + \gamma x - S. \tag{42}$$

From the first-order condition, the profit maximizing R&D investment is

$$x_{1s} = p_{1s}\lambda + \gamma. \tag{43}$$

Thus, the expected profit given the subsidy $s(x)$ and the drug price $p_{1s}$ is

$$\widetilde{E}_{1s}(p_{1s}, \gamma, S) = \frac{1}{2}(\gamma + p_{1s}\lambda)^2 - S. \tag{44}$$

Given that the subsidy scheme is set to make the firm break even, the lump-sum amount taxed is given by

$$S^*(p_{1s}, \gamma) = \frac{1}{2}(\gamma + p_{1s}\lambda)^2. \tag{45}$$

The drug manufacturer chooses between accepting and refusing test implementation depending on which decision results in the highest expected profit. The firm accepts the test if

$$\widetilde{E}_{1s}(p_{1s}, s) \geq \widetilde{E}_{0s}(p_{0s}) \Leftrightarrow \frac{1}{2}(\gamma + p_{1s}\lambda)^2 - S^*(p_{1s}, \gamma) \geq \frac{1}{2}p_{0s}^2. \tag{46}$$

At stage 1, the regulator chooses the welfare maximizing drug price and an R&D subsidy.

When the regulator prefers the test to be accepted by the drug firm, it will offer a welfare maximizing price and a subsidy on the margin. Under this regime, social welfare is given by the expected responders' utility, net of the total cost of drug R&D and the social cost of taxation needed to fund the subsidy and the price (which is reduced by the lump-sum tax), as follows:

$$\begin{aligned} \underset{p}{\text{maximize}} \quad & W_{1s}(x_{1s}, p_{1s}, \gamma, S^*(p_{1s}, \gamma)) = x_{1s}\lambda\epsilon - \frac{x_{1s}^2}{2} - \theta\left(\gamma x_{1s} - S^*(p_{1s}, \gamma) + p_{1s}\lambda x_{1s}\right) \\ \text{subject to} \quad & \widetilde{E}_{1s}(p_{1s}, s) \geq \widetilde{E}_{0s}(p_{0s}) \Leftrightarrow 0 \geq \frac{1}{2}p_{0s}^2 \\ \text{and} \quad & x_{1s} = p_{1s}\lambda + \gamma \end{aligned} \tag{47}$$

Note that we assume that taxing the firm has no social cost. Since this is an individual lump sum tax, it is nondistortionary taxation to raise public funds.

From the first-order conditions, we find that the welfare maximizing drug price is given by

$$p'_{1s} = \frac{\lambda\epsilon - \gamma(1+\theta)}{\lambda(1+\theta)}. \tag{48}$$

To summarize, when the regulator wants the firm to implement the test and to invest the socially optimal amount, it will offer the drug price $p'_{1s}$ and an R&D subsidy on the margin $\gamma$, such that $p'_{1s} = \frac{\lambda\epsilon-\gamma(1+\theta)}{\lambda(1+\theta)}$, and obtain a lump-sum payment from the firm $S^* = \frac{\lambda^2\epsilon^2}{2(\theta+1)^2}$, which makes the firm break even. Note that the substitutability between the subsidy and the price is a consequence of the linear way they affect the probability of R&D success $x_{1s}$, given that both the price and subsidy are paid in full by the sponsor and not by the consumer. Additionally, the regulator offers the price $p'_{0s} \leq 0$ if the test is not implemented to make this choice undesirable for the pharmaceutical firm.

Given the optimal tax $S^*$ and any drug price and subsidy combination satisfying Equation (48), the profit maximizing level of R&D investment is socially optimal:

$$x'_{1s} = \frac{\lambda\epsilon}{\theta+1} = x_1^* \tag{49}$$

The social welfare when the test is accepted under this scheme is given by

$$W'_{1s} = \frac{\lambda^2\epsilon^2}{2(\theta+1)}, \tag{50}$$

which is equal to socially optimal with testing ($W_1^*$). We can state the following:

**Proposition 3.** *The first-best allocation can be achieved by a social planner by setting a fixed transfer from the firm to the government equal to the firm's expected profit with a biomarker test.*

As noted above, the payment of the drug price and subsidy for drug R&D accrues high expected profit to the firm. By taxing the firm, those profits are transferred back to the public sponsor, and the first best is achieved.

The regulator prefers to give incentives for test acceptance if welfare with the test and the subsidy scheme is greater than that without the test:

$$W'_{1s} \geq W'_{0s} \Leftrightarrow 2\lambda\epsilon \geq a(1-\lambda) - \frac{\lambda^2\epsilon^2\theta}{a(1-\lambda)(\theta+1)} \tag{51}$$

Since Assumption (1) holds, the regulator wants to implement the test by using the three policy instruments: price, and/or subsidy for R&D, and tax. With these instruments, the regulator

allows access to the best treatment while controlling public pharmaceutical spending. Any combination of price and subsidy for R&D that satisfies (48) encourages R&D investment and biomarker testing. The resulting profit is repaid to the government, leading to an increase in public funds.

# 5 Discussion of the framework

The aim of this paper is to provide insight into how to encourage pharmaceutical firms to adopt a biomarker test that predicts drug response while investing the optimal level in R&D. In this section, we discuss some assumptions with respect to the features of the market that were made to simplify the model.

The assumption that the price of the drug is fully paid by a third-party payer has an important role. Patients are unresponsive to price changes in this model. Therefore, there is perfect substitutability between the price offered for the drug with the biomarker test and the subsidy on the margin of R&D investment. Under the contracts analyzed in Sections 4.3 and 4.4, welfare is unaffected whether the firm is offered a higher price for the drug or a higher subsidy on the margin because there is no utility loss from increasing the price. However, this assumption may not hold in some cases. In some countries, copayments exist in the form of a fixed amount or of a proportion paid by the patient. The copayment for pharmaceuticals may also vary according to the patient's condition. For example, pharmaceuticals for the treatment of severe chronic diseases such as cancer (the medical area where many biomarker tests are developed) have very low or no payment by patients (Barros, 2010). Nevertheless, if a copayment rate is in place, consumers may react to higher prices by consuming less. In that case, a high price decreases consumer surplus. Thus, it may be more efficient to give incentives to the pharmaceutical firm by directly paying a subsidy on the margin for R&D instead of through an increase in the price. On the other hand, copayments save on the need for taxation to obtain public funds, which tends to favor a lower social cost of paying the drug price. This tradeoff depends on how the copayment is structured, whether it is given as a fixed amount or as a percentage of the maximum price. As long as the patient's copayment changes in absolute terms, there will be a demand response from higher prices.

We have assumed that the firm is taxed such that it breaks even. If we allow for positive firm profit, the first best is no longer achievable. Hence, in the model, there is a tradeoff between welfare and private profit. Let us assume that the regulator allows the firm to have positive profits ($E_{1s} > 0$). The lump-sum tax is $S < (p\lambda + \gamma)^2/2$. The social planner chooses

$p$ and $\gamma$ to maximize welfare. The optimal choice of the price and the subsidy on the margin is any combination that satisfies $p = (\lambda\epsilon - \gamma(1 + 2\theta))/\lambda(1 + 2\theta)$. The resulting welfare is $W_{1s}(S) = (2\theta S(1 + 2\theta) + \lambda^2\epsilon^2)/2(1 + 2\theta)$. Taxing the firm results in greater welfare than otherwise as long as $S \in (0, (\gamma + p\lambda)^2/2)$, since the social cost of public funds is reduced by the fixed amount taxed $S$. However, the difference between this welfare and the first best is $\frac{\theta\lambda^2\epsilon^2}{2(2\theta^2+3\theta+1)} - \theta S > 0$. Only when the firm is taxed such that it breaks even is the first best achieved.

Note also that the subsidy scheme solution is extreme and relies on accurate information on the part of the social planner. There might be frictions, i.e., asymmetric information problems, which make the first-best solution unattainable. Private investment costs are often private information. However, the assumptions in this paper shed some light on the mechanisms of an optimal incentive scheme for personalized medicine.

Furthermore, the results from the two-price contract are essentially the same as a risk-sharing agreement between a pharmaceutical firm and the regulator in this model. This is in agreement with the principle of "pay for performance". It has received some attention because it is mainly designed to control the continued growth of pharmaceutical expenditure while guaranteeing access to new drugs that improve health. In this type of agreement, the full price of the drug is only paid when the drug is successful. As there is uncertainty regarding the efficacy of treatment for each patient, this agreement shifts the risk of the drug to the pharmaceutical firm (Barros, 2010; 2011). Essentially, the price is lower if the drug reveals itself to be less successful than expected. This encourages the firm to guarantee that the drug is as successful as possible by implementing the biomarker test. Since we have assumed that the biomarker test perfectly identifies the responders for whom treatment with the new drug is successful for certain, the welfare maximizing drug price resulting from the two-price contract is equivalent to the risk-sharing agreement. However, this results from the fact that the firm in our model is risk neutral. With a risk-averse pharmaceutical firm, a risk-sharing agreement may require a lower drug price to encourage the introduction of the biomarker test. However, it is not clear whether a firm that invests in R&D is, in fact, risk averse. The R&D intensity of firms is typically a proxy for risk-taking (Barker III & Mueller, 2002; Devers et al., 2008). As pharmaceutical firms are R&D intensive, one could argue that they are taking risky projects and, thus, are not averse to risk. Moreover, Towse & Garrison (2010) explain that with risk-sharing agreements, "there can be mutual gains by a risk-averse party [healthcare decision maker] 'paying' the risk-neutral party [pharmaceutical firm] to accept more of the risk".

# 6 Summary and conclusion

In this paper, we shed some light on how the regulator can implement policies that create incentives for a pharmaceutical firm to accept the development and introduction of a test identifying the responding patients to its drug while maintaining the incentives for drug R&D. A price contract where the price offered to the pharmaceutical firm is fixed independent of the drug's efficacy (i.e., offering just one drug price) encourages drug R&D activity. However, it is not effective at encouraging the introduction of testing. We find that offering a higher drug price when the test is used than when it is not and offering an R&D subsidy conditional on accepting the test are policies that can be adopted to increase the willingness of the drug manufacturer to collaborate with the biomarker developer in the implementation of the test.

A contract in the form of two drug prices according to whether the test is implemented is effective not only at giving incentives for drug R&D investment but also at inducing the acceptance of the test. However, due to the social cost of public funds to pay the price of the drug, this contract does not lead to socially optimal welfare. While the price is set above the social optimum to encourage R&D, it cannot be too high due to its inherent social cost, and the pharmaceutical firm underinvests.

Additionally, we have shown that there are no social gains in offering a subsidy on the margin of R&D investment if the firm implements the biomarker test. Under certain conditions, the subsidy is a perfect substitute for the drug price. Therefore, the social cost of sponsoring the drug through price or subsidy is still an impediment to encourage socially optimal investment in R&D.

Introducing a lump-sum tax on the firm's profits results in first-best outcomes. This contract allows the profits to be repaid to the government, which compensates for the social cost of public funds spent on the price and/or subsidy. This method is more effective at increasing the probability of drug discovery while encouraging the implementation of the test and decreasing the social cost of paying the price and the subsidy. Therefore, under the framework of this model, we show that it is possible to make the firm break even and still invest the optimal amount in drug R&D.

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