Biomarkers in clinical trials: incentives under competition between pharmaceutical firms*

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Abstract

Firms devising biomarker investment strategies within a regulated environment must consider not only technological R&D uncertainty but also strategic interactions due to competition. This paper considers two competing drug manufacturers that decide whether to select clinical trial participants through a biomarker test that identifies the drug responders. We show that if the gains from increasing the probability of trial success and from improving the expected quality of the drug exceed the loss in expected drug revenues, it is profitable for a firm to include biomarker testing in the clinical trial. Furthermore, the interest in biomarker testing is stronger for a firm with a lower probability of developing a high-efficacy drug. Finally, we identify the conditions under which the incentives to include a biomarker in clinical trials are greater under competition than under monopoly.

Keywords: Biomarker, Personalized medicine, Competition, Pharmaceutical Innovation

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1 Introduction

When a new drug is developed, clinical trials must take place to assess its safety and efficacy on a statistical basis. Only when the drug is shown to be safe and effective can it be approved for use. However, a drug is rarely safe and effective for everyone, and drug response varies across individuals. Therefore, there is a risk that the clinical trial phase of a drug will not successfully demonstrate statistically significant therapeutic benefits.

Hence, some pharmaceutical firms are changing their R&D process to improve a drug's chance of success in clinical trials (The Economist, 2005). One emerging technology used to help them is biomarker testing. The use of biomarker tests in clinical trials has the potential to change the game of marketing approval for pharmaceutical firms. The purpose of these tests is to distinguish between those patients who are more likely and those who are less likely to respond to a drug. In this way, testing for a biomarker allows for smaller clinical studies, where fewer patients and shorter periods are needed to reveal statistically significant therapeutic benefits.[1] In clinical practice, these tests create better matching of subjects and treatment by distinguishing treatment responders from nonresponders. However, the use of a biomarker test results in a small-population market for the drug manufacturer since the drug will only be used to treat the responders.

In a model where one pharmaceutical firm decides whether to include a biomarker test in the clinical trial for a new drug, Scott Morton & Seabright (2013) find that, even if a biomarker-based selection of patients increases the likelihood of statistically significant trial results, the firm might not test for a biomarker in the clinical trials. This is because a biomarker test reduces the firm's potential consumers, which reduces the firm's potential revenue. Additionally, the private firm does not internalize the benefits for nonresponders from not taking the drug (adverse effects are avoided). They conclude that unless the patient benefit is reflected in the price of the drug, the firm does not have an interest in including a biomarker in its clinical trials.

In this study, we focus on strategic interactions between two pharmaceutical firms competing to receive market approval. In particular, we ask the following: does the existence of a competitor increase incentives to test patients for a biomarker in clinical trials? We extend the model of Scott Morton & Seabright (2013) by comparing a monopoly version with a duopoly version of the model, where the health authority has the capacity to accept only one drug in the

[1] Biomarker tests have the potential to change the aim of each R&D phase: phase I can establish the proof of concept, phase II can stratify patients into responders and nonresponders, and phase III can be limited to biomarker-selected responders, which can be a much smaller sample of trial participants (Joly & Knoppers, 2014).

market (for example, only one drug as first-line treatment). We also ask under which conditions does competition encourage the inclusion of a biomarker in clinical trials without government intervention (i.e., without an increase in the regulated price when the drug uses a biomarker, for instance).

To approach these questions, we consider a model with two pharmaceutical firms developing very similar drugs and competing to receive market approval. A health authority can choose only one of the drugs to be used in the market and bases its choice on the health benefits that each drug provides. Each firm faces the decision of whether to include a biomarker test in clinical trials. The test increases the likelihood of a successful clinical trial but decreases the market share of the approved drug. We compare the case of competition with that of a monopolist's incentives to include a biomarker test in its clinical trials. We focus on the effect of competition only by assuming that the price of the drug is unchanged regardless of the inclusion of a biomarker test in the clinical trials. We acknowledge that there may be policies that can be implemented to encourage the development of drugs with biomarker tests, such as an upward adjustment of the price of drugs subjected to biomarker testing to reflect its social value. However, the analysis of such policies is beyond the scope of this article.[2]

We motivate the model setup by a case published in The Economist (2018) and the Financial Times (2016), where two very similar cancer drugs, Opdivo (nivolumab) and Keytruda (pembrolizumab), were developed by two rival pharmaceutical firms, Bristol-Myers and Merck, competing to obtain approval for the first treatment choice. A biomarker test, to predict who is likely to have a positive response to the drug, was used to select patients for the trials of Keytruda.[3] In contrast, Opdivo's trial was performed on a broader group of patients and without utilizing biomarker tests. Interestingly, both drugs have the same classification and are very similar: immunotherapies targeting a protein called PD-1, which stops the body from destroying the cancer, work well in patients with high levels of PD-L1, corresponding to between 20% to 1/3 of the patients. Initially, when both drugs received approval for use as a second treatment choice in lung cancer, Opdivo outsold Keytruda. That was a result of Keytruda's need to test for a biomarker: it limited the sales to a small percentage of responders. However, Opdivo failed the subsequent trial, whereas Keytruda was shown to be effective in the next trials and was approved as the first treatment choice, in part because the biomarker test improved its efficacy by selecting those more likely to respond for the trials. By 2019, Keytruda's sales had surpassed Opdivo's (European Pharmaceutical Review, 2019). This case is provided

[2]The implications of such policy instruments are analyzed in Luís (2020).

[3]Note that the cost of the test is a minuscule fraction of the therapeutic cost (Berndt & Trusheim, 2019).

by Berndt & Trusheim (2019) as an example of a prisoner's dilemma in which drug developers face a strategic decision of whether to use a biomarker test.

The main takeaway from the model is that competition from another pharmaceutical firm increases the incentives to include a biomarker test in clinical trials under some conditions. In particular, the firm's incentive to include the biomarker test is decomposed into two different factors: (i) the gain associated with increasing the probability of successfully showing a statistically significant therapeutic efficacy of the drug in the clinical trial and (ii) the gain from developing a drug with greater patient benefits, i.e., with a reduced risk of adverse events in nonresponders, which is more appealing to health authorities. If these gains exceed the expected loss in revenues, the firm has an incentive to use the biomarker test under competition. However, the first type of gain is lower under duopoly than under monopoly because the fact that the rival also faces a risk of an unsuccessful clinical trial makes the firm in less of a hurry to include the biomarker. Thus, the incentive to include the biomarker test in the clinical trial under competition comes mainly from the consideration that the drug may not be approved by the health authority if the manufacturer does not use the biomarker test.

We also find that a less-promising firm – that is, a firm that is less likely to develop a drug with a large fraction of responders – has a greater incentive to include a biomarker test. This incentive is motivated by the need to increase its chance of being approved by the health authority over its more promising rival, specifically by making the expected quality of its drug more appealing to the health authority.

This study is related to the literature on preemptive innovation (Beath et al., 1989; Gilbert & Newbery, 1982; Reinganum, 1983). An important result from this literature is that the incentive to innovate is given not only by the benefits associated with the innovation but also by the incentive of the firm to win the race against its rivals. In this article, the role of innovation is the inclusion of a biomarker test in clinical trials. Although it does not increase drug revenues per se, it can increase expected profits under both monopoly and duopoly by eliminating the risk of statistically inconclusive trial results. Additionally, we show that the threat of a competitor plays an important role in the creation of incentives to include a biomarker test.

Furthermore, economic theory suggests that competition can increase information revelation (Gentzkow & Kamenica, 2017a). Here, the information revealed by the pharmaceutical company is the drug response of each patient – that is, responder or nonresponder – through the use of a biomarker test. According to Boleslavsky & Cotton (2018), "a capacity constraint induces competition between the agents, who respond by providing more informative evidence". If a health authority can only choose one drug, developers are induced to produce more informative

evidence to improve the expected quality of the drug. Hence, one may expect that competition increases the amount of information revealed even when the prices of both products are the same and fixed exogenously (Gentzkow & Kamenica, 2017b).

The results of this study provide interesting insights into which factors might affect the decision to develop new drugs with biomarker testing that predicts drug response. It provides insights into competition as an incentive in addition to policies that may, as a side effect, increase public expenditure (which in many countries is subject to substantial constraint). Examples of such policies include an increase in the drug price when a biomarker test is used (Danzon & Towse, 2002; Vernon et al., 2006; Cook et al., 2009; Garrison & Austin, 2007) and/or subsidies to the cost of R&D for personalized medicine (Hsu & Schwartz, 2008).

The remainder of this article is organized as follows. We present the model framework in Section 2 and explore the monopoly version in Section 3. Section 4 presents the analysis of the market equilibrium, the results of the firms' relative incentives, the comparison of incentives in a duopoly versus a monopoly situation, and the welfare effects. Section 5 discusses the framework, while Section 6 concludes the article.

2 The model

There is a health authority and a unit mass of patients with a disease. Furthermore, we consider two pharmaceutical firms, $i = 1, 2$, in the market developing one drug each. The firms do not know how many patients will benefit ($V > 0$) from their drugs, but it is common knowledge that with probability γ_i, firm i's drug will work for a high proportion $\overline{\theta}$ of the patients, and with probability $(1 - \gamma_i)$, it will work for a lower proportion $\underline{\theta}$ of patients, where $0 < \underline{\theta} < \overline{\theta}$ and $0 < \gamma_i < 1$. We assume that both drugs target the same patients but may differ in response rates.[4] Nonresponders to these drugs suffer from adverse effects $k > 0$. Here, V and k can be interpreted as the economic values of health effects.

[4]This is common for drugs within the same drug class. When drugs to treat the same disease have similar chemical structures (but a different active ingredient) and similar ways to be used, they are part of the same drug class. Both drugs in the case previously described, Opdivo (nivolumab) and Keytruda (pembrolizumab), work best in patients with high levels of PD-L1. Additionally, the epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab provide an example of drugs in the same class that are often considered interchangeable. Both require testing for EGFR and KRAS, and most studies suggest similar results with either cetuximab or panitumumab (García-Foncillas et al., 2019). However, drugs in the same class have the same therapeutic activity but differ in terms of safety (Furberg et al., 1999). Hence, two drugs can target the same type of patient, but one may cause adverse events in a larger fraction of patients than the other.

Each firm must run a clinical trial to determine whether its drug benefits a high proportion $\overline{\theta}$ or a low proportion $\underline{\theta}$ of patients. If the drug is effective for a high proportion $\overline{\theta}$ of patients, the trial will certainly show this result, and the drug can receive market approval. However, if the drug benefits only a low proportion $\underline{\theta}$ of patients, there is a probability ρ_i of a statistically insignificant result of the trial, causing the drug to not be approved.

A test can be used to identify the patients with a biomarker that makes them benefit from the drug. Each firm must decide, simultaneously and noncooperatively, whether to run their clinical trials while including or excluding the biomarker test to select the participants who will benefit from the drug. We assume that the test perfectly identifies the patients with the biomarker (the responders). In a situation where the biomarker test is included in a firm's clinical trial, we assume that it is certain that the trial will show a statistically significant benefit for the patients with the biomarker, i.e., $\rho_i = 0$.

We consider the following sequence of events:

- In stage 1, both firms simultaneously decide whether to use a biomarker test in their clinical trials. After the clinical trials, each firm learns its proportion of responders and reports it to the health authority.

- In stage 2, the health authority decides which drug to approve. The authority can approve only one drug in the market.[5]

If a drug does not have a biomarker test and is approved/chosen by the health authority, it is given to all patients since neither the health authority nor the firms know the type (responder or nonresponder) of each patient. However, when a drug that was subject to the biomarker test in its clinical trial is chosen, all patients are screened by the test, and the drug is given only to the responders. The benefit for non-treated patients is 0. For simplicity, the costs of administering the biomarker test to select the participants in clinical trials and the patients in actual practice are close to zero.[6]

We also assume that the firms' marginal costs of production are identical and normalized to

[5]We make a simplifying assumption, since one firm will likely obtain first-line treatment approval long before the other firm.

[6]On the one hand, there are additional costs of testing the participants, although the cost per test is, in principle, very small (Berndt & Trusheim, 2019). On the other hand, biomarker testing can make the trials smaller, reducing R&D costs, because it allows firms to select the most eligible patients (The Economist, 2005). Therefore, we make the simplifying assumption that these two factors cancel each other out and that the cost of testing in clinical trials is zero.

zero.[7] Hence, we assume that there are no capacity constraints and that the firms will always be able to supply the quantity demanded.

Finally, we make the assumption that the firms face an exogenous drug price, which is assumed to be equal for both drugs, independent of biomarker use. A regulated drug price is in line with the features of the pharmaceutical market in most countries (Brekke et al., 2007; Brekke & Straume, 2009).

The decision of the health authority

At the end of the clinical trial, each firm presents its results to the health authority, revealing whether each drug has a high or low proportion of responders[8] and whether trial participants were selected based on the results of a biomarker test.[9] Then, the health authority evaluates the response rates and efficacy of the drugs and chooses which one of the two drugs to grant market authorization to treat the disease. We assume that the health authority makes the choice based on which drug maximizes the health gain of all patients, as given by the results of the clinical trials.[10]

Note that we let the index i correspond to both the drug and the firm that develops it. Suppose that a drug i without a biomarker is chosen by the health authority. The health gain is given by the benefits for the responders, who correspond to the fraction $\theta \in \left\{\underline{\theta}, \overline{\theta}\right\}$ of the patients, net of the disutility for the nonresponders, as follows:

$$U_i^0(\theta) = \theta V - (1-\theta)k,\ \theta \in \left\{\underline{\theta}, \overline{\theta}\right\} \tag{1}$$

In contrast, if the health authority chooses a drug with a biomarker, the health gain is given

[7] Marginal production costs in the pharmaceutical industry are very low (Brekke & Straume, 2009; Bardey et al., 2010)

[8] Drugs are approved for their efficacy and safety, but response rates have also been used by the US regulatory agency, the Food and Drug Administration (FDA), as a basis for the approval of certain drug indications in cancer (George, 2007).

[9] The data submitted in a marketing authorization must include information on the selection of the group of patients participating in the clinical trial (EU Directive for Human Medicines 2001/83/EC). Therefore, the use of the biomarker test to select the participants in the clinical trial must be stated in the application for marketing approval.

[10] Health authorities such as the US FDA and the European Medicines Agency (EMA) grant marketing authorizations to drugs by assessing the benefits and risks of the drug. However, while each European Union (EU) country also makes pricing decisions, subtracting the cost of the drug from the health benefits does not affect the results, since we make the assumption that the price is regulated and equal for both drugs.

by the benefits for the responders:

$$U_i^1(\theta) = \theta V,\, \theta \in \left\{\underline{\theta}, \overline{\theta}\right\} \tag{2}$$

Regarding the choice of the health authority, there are four main scenarios to consider:

- (i) both drugs have the same θ, and both firms make the same choice regarding the inclusion of the biomarker test;
- (ii) both drugs have the same θ, but one of the firms chooses to include the biomarker test and the other does not;
- (iii) the drugs have different θ, and both firms make the same choice regarding the inclusion of the biomarker test; and
- (iv) the drugs have different θ, and one firm includes the biomarker test while the other does not.

The decision of the health authority depends on the scenario at hand. In scenario (i), the health authority chooses either drug with probability 1/2 since both drugs are identical. In scenario (ii), the health authority chooses the drug that included the biomarker test since $U_i^1 > U_j^0$ when both drugs work for the same proportion of patients. In scenario (iii), the drug with $\overline{\theta}$ is chosen, since both have a biomarker test (or neither has a biomarker test) but the drug that is effective for more patients is preferred.

Scenario (iv) is divided into two sub-scenarios: (iv.1) the drug with $\overline{\theta}$ responders uses a biomarker test, while the drug with $\underline{\theta}$ responders does not; (iv.2) the drug with $\underline{\theta}$ responders uses the biomarker test, while the drug with $\overline{\theta}$ responders does not. In (iv.1), it is clear that the health authority chooses the drug with $\overline{\theta}$ responders and a biomarker test. However, in (iv.2), the health authority's decision depends on the levels of the parameters. The $\underline{\theta}$-drug with a biomarker test would be chosen if the disutility for nonresponders of the $\overline{\theta}$-drug is greater than or equal to the decrease in benefits due to fewer responders of the $\underline{\theta}$-drug:

$$\Delta U = U_i^1(\underline{\theta}) - U_j^0(\overline{\theta}) = \frac{(1-\overline{\theta})k}{V} - (\overline{\theta} - \underline{\theta}) \geq 0 \tag{3}$$

The decision of the health authority to choose the drug with a biomarker test depends on the difference between the high proportion and the low proportion of drug responders and on the fraction k/V, i.e., how worse the health of nonresponders will be compared to how much the health of responders will improve. As the difference $(\overline{\theta} - \underline{\theta})$ decreases, the probability that the health authority chooses the drug with the biomarker test increases ($\partial \Delta U / \partial \overline{\theta} < 0$ and

$\partial \Delta U / \partial \underline{\theta} > 0$). This is because if $(\overline{\theta} - \underline{\theta})$ is small, the drug with $\overline{\theta}$ responders does not have a large advantage compared to the drug with a proportion $\underline{\theta}$ of responders. In addition, if the $\underline{\theta}$-drug is developed with a biomarker test to identify the responders, the health authority is more interested in selecting it. Furthermore, as k/V increases, the more costly it is to administer the drug to a nonresponder relative to the benefit a responder obtains from the treatment, and it is preferable for the health authority to choose the drug with a biomarker test. On the other hand, if condition (3) is not satisfied, the $\overline{\theta}$-drug without a biomarker test is chosen by the health authority. Hence, in (iv.2), we distinguish two possible cases: case (a) if (3) is satisfied and case (b) if (3) is not satisfied.

Table 1: Decision of the health authority

	$(\overline{\theta}, \overline{\theta})$ or $(\underline{\theta}, \underline{\theta})$	$(\overline{\theta}, \underline{\theta})$ or $(\underline{\theta}, \overline{\theta})$
(β_1,β_2)=(1,1) or (0,0)	(i) either with prob. 1/2	(ii) drug with $\overline{\theta}$
(β_1,β_2)=(1,0) or (0,1)	(ii) drug with biomarker test	(iv.1) drug with $\overline{\theta}$ and biomarker (iv.2) •*(a)* drug with $\underline{\theta}$ and biomarker test if $(1-\overline{\theta})k > (\overline{\theta} - \underline{\theta})V$; •*(b)* drug with $\overline{\theta}$ without biomarker test if $(1-\overline{\theta})k < (\overline{\theta} - \underline{\theta})V$

Table 1 summarizes the decision of the health authority in each scenario. The decision made by firms 1 and 2 regarding the inclusion of the biomarker test varies between rows. This decision is represented by the set (β_1,β_2), where $\beta_i = 0$ if firm i $(i = 1, 2)$ chooses to exclude the biomarker test and $\beta_i = 1$ if firm i chooses to include the test. The characteristics of the drugs vary between columns. In the first column, the drugs have equal proportions of responders, while in the last column, the drugs differ in the proportion of responders.

Profits

We assume throughout the analysis that the price of the drug that benefits either proportion $\overline{\theta}$ or $\underline{\theta}$ is the same irrespective of whether the biomarker is included, and it is given by P.

Here, we focus on the profit of firm i and denote firm j as the rival of firm i. The expected profits from each drug depend on the probabilities of a high and low number of responders and on which drug is chosen by the health authority. When drug i is not chosen, firm i receives zero profit. The expected profit for firm i is denoted $R_i^{\beta_i,\beta_j}$, where β_i (β_j) is equal to 0 if firm i (j) does not include the biomarker test, and β_i (β_j) is equal to 1 if firm i (j) includes the biomarker test. The expected profit of firm i depends on the probability (γ_i) of drug i benefiting a high proportion of patients and the probability (γ_j) of its rival benefiting a high proportion of patients. Without the biomarker test, the probability ρ that the clinical trial generates statistically insignificant results when the drug benefits just a small proportion $\underline{\theta}$ of patients is taken into account.

Consider the case in which neither firm includes the biomarker, i.e., $\beta_i = 0$ and $\beta_j = 0$. Then, drug i, which is developed by firm i, is chosen over its rival j with probability $1/2$ if both drugs benefit a large fraction of patients, which occurs with probability $\gamma_i\gamma_j$, as indicated by the first term in (4). The second term represents the case in which drug i benefits a larger fraction of patients than drug j (with probability $\gamma_i(1-\gamma_j)$), causing drug i to be chosen. The third term indicates that if both drugs benefit a small fraction of patients and the trials show statistically significant results, drug i is chosen with probability $\frac{1}{2}\times(1-\gamma_i)(1-\rho_i)(1-\gamma_j)(1-\rho_j)$. However, drug i is approved when both drugs work for a small fraction of patients but its rival's clinical trial does not show statistically significant therapeutic benefits, which occurs with probability $(1-\gamma_i)(1-\rho_i)(1-\gamma_j)\rho_j$, as indicated by the last term. The approved therapy will be applied to the unit mass of patients. Hence, the expected profit for firm i when both drugs exclude the biomarker test from clinical trials is given by

$$R_i^{0,0} = P\left[\frac{1}{2}\gamma_i\gamma_j + \gamma_i(1-\gamma_j) + \frac{1}{2}(1-\gamma_i)(1-\rho_i)(1-\gamma_j)(1-\rho_j) + (1-\gamma_i)(1-\rho_i)(1-\gamma_j)\rho_j\right]. \tag{4}$$

Let us suppose instead that both firms include the biomarker test in their clinical trials, i.e., $\beta_i = 1$ and $\beta_j = 1$. Drug i is approved over its rival and consumed by $\overline{\theta}$ patients with probability $1/2$ if both drugs benefit a high proportion of patients (with probability $\gamma_i\gamma_j$). If drug i benefits a large fraction of patients and drug j benefits a small fraction, drug i is chosen and sold to $\overline{\theta}$ patients, with probability $\gamma_i(1-\gamma_j)$. As indicated by the final term in (5), either drug is chosen with probability $1/2$ if both drugs work for a low proportion of patients. In that

case, drug i is chosen with probability $\frac{1}{2} \times (1-\gamma_i)(1-\gamma_j)$ and sold to $\underline{\theta}$ patients. Note that with a biomarker test, the probability ρ of not finding statistically significant therapeutic effects in clinical trials disappears. This yields the following expected profit:

$$R_i^{1,1} = P\left[\frac{1}{2}\gamma_i\gamma_j\overline{\theta} + \gamma_i(1-\gamma_j)\overline{\theta} + \frac{1}{2}(1-\gamma_i)(1-\gamma_j)\underline{\theta}\right]. \tag{5}$$

Finally, suppose that firm i's decision on whether to include a biomarker test differs from its rival's decision, i.e., either $\beta_i = 0$ and $\beta_j = 1$ or $\beta_i = 1$ and $\beta_j = 0$. When one of the firms includes the biomarker test and the other does not, the expected profit depends on the choice of the health authority in scenario (iv.2), which depends on whether (3) is satisfied.

First, let us consider case (a), in which the health authority chooses a drug with proportion $\underline{\theta}$ of responders and with a biomarker test rather than a drug with $\overline{\theta}$ responders and no biomarker test because (3) holds. In case (a), we denote the expected profit of firm i as $R_{ia}^{\beta_i,\beta_j}$ whenever $\beta_i \neq \beta_j$. Suppose that firm i includes the biomarker test and its rival does not, i.e., $\beta_i = 1$ and $\beta_j = 0$. Then, firm i's drug is always the one approved, and it is sold to the responders only. The expected profit of the firm that includes the biomarker test is given by

$$R_{ia}^{1,0} = P\left[\gamma_i\gamma_j\overline{\theta} + \gamma_i(1-\gamma_j)\overline{\theta} + (1-\gamma_i)\gamma_j\underline{\theta} + (1-\gamma_i)(1-\gamma_j)\underline{\theta}\right]. \tag{6}$$

Instead, if firm i does not include the biomarker test and its rival does, i.e., $\beta_i = 0$ and $\beta_j = 1$, then the rival is always chosen by the health authority, and firm i's expected profit is given by

$$R_{ia}^{0,1} = 0. \tag{7}$$

Now, let us consider case (b), in which the parameters are such that (3) is not satisfied, i.e., the health authority chooses to use a high-proportion $\overline{\theta}$ drug without a biomarker test rather than a low-proportion $\underline{\theta}$ drug with a biomarker test. This means that if firm i includes the biomarker test and firm j does not, firm i's drug is always chosen except when the rival's drug is effective for a larger fraction of patients. In case (b), $R_{ib}^{\beta_i,\beta_j}$ denotes the expected profit of firm i whenever $\beta_i \neq \beta_j$. The expected profit of the firm that includes the biomarker test is given by

$$R_{ib}^{1,0} = P\left[\gamma_i\gamma_j\overline{\theta} + \gamma_i(1-\gamma_j)\overline{\theta} + (1-\gamma_i)(1-\gamma_j)\underline{\theta}\right]. \tag{8}$$

Instead, suppose that firm i does not include the biomarker test and its rival does. Firm i will only be chosen over its rival if drug i is effective for a larger fraction of patients. Since firm i does not include the biomarker test, its drug will be used to treat all patients. The expected

profit of the firm that does not include the biomarker test is now given by

$$R_{ib}^{0,1} = P\left[\gamma_i(1-\gamma_j)\right]. \tag{9}$$

Therefore, we have two cases to consider in the analysis of the first stage of the model: case (a), the $\underline{\theta}$-drug with a biomarker test is chosen, and case (b), where the $\overline{\theta}$-drug without a biomarker test is chosen.

3 Benchmark – monopoly

Before analyzing the duopoly model, it is useful to briefly discuss the incentive to include a biomarker test in a monopoly setting. We follow the model in Scott Morton & Seabright (2013), except that we do not incorporate the marginal cost of production.

Let W_M^0 be the expected social welfare when the monopolist conducts a clinical trial without a biomarker test, and let W_M^1 be the corresponding welfare when the trial is conducted with a biomarker test. We assume that funds to pay the drug price can be raised in a non-distortionary manner, which simplifies the welfare function to the expected gross aggregate consumer utility ex ante.

$$W_M^0 = \gamma[\overline{\theta}V - (1-\overline{\theta})k] + (1-\gamma)(1-\rho)[\underline{\theta}V - (1-\underline{\theta})k] \tag{10}$$

$$W_M^1 = \gamma\overline{\theta}V + (1-\gamma)\underline{\theta}V \tag{11}$$

The expected social gains of including the biomarker test in the clinical trial of a monopolist are given by

$$\Delta W_M = W_M^1 - W_M^0 = \underbrace{\gamma(1-\overline{\theta})k + (1-\gamma)(1-\rho)(1-\underline{\theta})k}_{\substack{\text{benefit from sparing} \\ \text{nonresponders' health}}} + \underbrace{(1-\gamma)\rho\underline{\theta}V}_{\substack{\text{benefit from} \\ \text{more statistical} \\ \text{significance} \\ \text{in trial}}} > 0. \tag{12}$$

Hence, the health authority always benefits more from a drug with a biomarker in this case. In expectation, it is socially beneficial to include the biomarker due to two types of gains: (1) the benefits from sparing nonresponders' health, i.e., the disutility stemming from k is not incurred, and (2) the benefits from making it more likely that the clinical trial shows a statistically significant result, which improves the health of $\underline{\theta}$ responders by V. The first benefits are obtained if the clinical trial would show statistically significant results regardless of the inclusion of the biomarker. This occurs with probability γ if the drug has a high proportion of responders and $(1-\overline{\theta})$ nonresponders or with probability $(1-\gamma)(1-\rho)$ if the drug has a low proportion of responders and $(1-\underline{\theta})$ nonresponders. In either case, the nonresponders benefit

by k from avoiding the adverse events caused by the drug. The second benefits are obtained if the trial would not show statistically significant results when the drug has a low proportion of responders, which occurs with probability $(1-\gamma)\rho$. Then, including the biomarker will benefit a proportion $\underline{\theta}$ of patients who will gain V.

The associated expected profit of the monopolist when the biomarker is excluded or included is given, respectively, by

$$R^0 = P[\gamma + (1-\gamma)(1-\rho)], \tag{13}$$

$$R^1 = P[\gamma\overline{\theta} + (1-\gamma)\underline{\theta}]. \tag{14}$$

The difference between the expected profit with and without a biomarker test consists of the difference in revenues plus the benefit from avoiding the risk of statistically insignificant results in the clinical trial. The condition under which it is profitable for the firm to include the biomarker test in the clinical trial is as follows:

$$\Delta R_M = R^1 - R^0 = \gamma(\overline{\theta} - 1) + (1-\gamma)(\underline{\theta} - 1) + (1-\gamma)\rho \geq 0 \tag{15}$$

This condition can only be satisfied if the probability of conducting a trial that does not yield statistically significant results is high. Specifically, this probability, $(1-\gamma)\rho$, must be larger than the expected loss in revenues that would occur if the trial were to find statistically significant results regardless of the inclusion of the biomarker test, which is equal to $\gamma(1-\overline{\theta})+(1-\gamma)(1-\underline{\theta})$.

The increase in the probability of obtaining statistically significant therapeutic results due to the selection of trial participants through a biomarker test must be sufficient to compensate for the decrease in drug sales. Therefore, although it is socially beneficial to include a biomarker test in clinical trials, it may not be profitable for the firm to do so in a monopoly setting.

4 Market equilibrium

In this section, we consider the decision by two pharmaceutical firms to include biomarker testing in the clinical trials of their drugs. We focus on pure-strategy subgame perfect Nash equilibria. The firms' objective is to maximize the expected profit; hence, we direct our attention to payoff dominant equilibria. We distinguish two cases, depending on whether (3) holds.

4.1 Case (a): condition (3) holds

Let us consider case (a), in which the health authority chooses a drug with a small fraction $\underline{\theta}$ of responders with the biomarker rather than a drug with a large fraction $\overline{\theta}$ of responders without the biomarker, i.e., condition (3) is satisfied.

Table 2 summarizes the firms' expected payoffs conditional on the decision adopted by each of them on whether to exclude ($\beta_i = 0$) or include ($\beta_i = 1$) the biomarker in their clinical trials. The expressions in the table are simplified versions of the expected profits given by equations (4), (5) and (6).

Table 2: Firms' expected payoffs in case (a)

	$\beta_2 = 0$	$\beta_2 = 1$
$\beta_1 = 0$	$(R_1^{0,0} = P\left[\gamma_1(1-\frac{1}{2}\gamma_2) + \frac{1}{2}(1-\gamma_1)(1-\gamma_2)(1-\rho_1)(1+\rho_2)\right]$, $R_2^{0,0} = P\left[\gamma_2(1-\frac{1}{2}\gamma_1) + \frac{1}{2}(1-\gamma_2)(1-\gamma_1)(1-\rho_2)(1+\rho_1)\right])$	$(R_{1a}^{0,1} = 0$, $R_{2a}^{1,0} = P\left[\gamma_2\overline{\theta} + (1-\gamma_2)\underline{\theta}\right])$
$\beta_1 = 1$	$(R_{1a}^{1,0} = P\left[\gamma_1\overline{\theta} + (1-\gamma_1)\underline{\theta}\right]$, $R_{2a}^{0,1} = 0)$	$(R_1^{1,1} = P\left[\gamma_1\overline{\theta}\left(1-\frac{1}{2}\gamma_2\right) + \frac{1}{2}\underline{\theta}(1-\gamma_1)(1-\gamma_2)\right]$, $R_2^{1,1} = P\left[\gamma_2\overline{\theta}\left(1-\frac{1}{2}\gamma_1\right) + \frac{1}{2}\underline{\theta}(1-\gamma_2)(1-\gamma_1)\right])$

Note that there is at least one equilibrium in which both firms adopt biomarker tests, since not adopting when the competitor adopts biomarker testing excludes a firm from the market.

The existence of another equilibrium or lack thereof depends on whether each firm has an incentive to deviate from the outcome $(R_1^{0,0}, R_2^{0,0})$.

Suppose that the rival, firm j, does not include the biomarker test. Then, firm i has incentives to deviate and include the biomarker test if $R_{ia}^{1,0} - R_i^{0,0} > 0$, which is equivalent to:

$$\gamma_i\gamma_j\left(\overline{\theta} - \frac{1}{2}\right) + (1-\gamma_i)(1-\gamma_j)\left[\underline{\theta} - \frac{1}{2}(1+\rho_j)\right] + (1-\gamma_i)\gamma_j\underline{\theta} + (1-\gamma_i)(1-\gamma_j)\rho_i\frac{1}{2}(1+\rho_j)$$
$$> \gamma_i(1-\gamma_j)(1-\overline{\theta}). \tag{16}$$

The terms $\gamma_i\gamma_j\left(\overline{\theta} - \frac{1}{2}\right)$ and $(1-\gamma_i)(1-\gamma_j)\left[\underline{\theta} - \frac{1}{2}(1+\rho_j)\right]$ can either be positive or negative depending on the parameters. The first term represents the difference in expected revenue when both drugs work for $\overline{\theta}$ patients, while the second term represents the equivalent difference when both drugs work for $\underline{\theta}$ patients. They are positive if the revenue of firm i when it includes the biomarker test exceeds the probability of being chosen over the rival when both firms exclude the biomarker test. Next, the term $(1-\gamma_i)\gamma_j\underline{\theta}$ is specific to case (a), and it represents the expected gain from being chosen over the rival when drug i has a lower proportion of responders than drug j, which does not occur if firm i does not include the biomarker test. Finally, the term $(1-\gamma_i)(1-\gamma_j)\rho_i\frac{1}{2}(1+\rho_j)$ is the expected gain from winning over the rival by avoiding the risk of a statistically inconclusive clinical trial. If these gains are large enough to outweigh the loss of expected revenues when drug i has a larger proportion of responders than drug j, which is represented by the term $\gamma_i(1-\gamma_j)(1-\overline{\theta})$, it is profitable for firm i to include the biomarker test in its clinical trials.

The condition in (16) can be rearranged as expected gains from including the biomarker test:

$$\Delta R_{ia} = R_{ia}^{1,0} - R_i^{0,0} = \gamma_i \underbrace{\left[\overline{\theta} - 1 + \frac{1}{2}\gamma_j\right]}_{\substack{\text{gain from using} \\ \text{biomarker when } \theta_i = \overline{\theta}}} + (1-\gamma_i) \underbrace{\left[\underline{\theta} - \frac{1}{2}(1-\gamma_j)(1-\rho_i)(1+\rho_j)\right]}_{\substack{\text{gain from using} \\ \text{biomarker when } \theta_i = \underline{\theta}}} > 0 \tag{17}$$

Under this condition, firm i has incentives to include the biomarker test if firm j does not, thus deviating from the outcome $(R_1^{0,0}, R_2^{0,0})$. An increase in the proportion of patients who benefit from the drug ($\overline{\theta}$ and/or $\underline{\theta}$) increases the incentive to use a biomarker test simply because it raises the revenues of the drug with the test. The implications of the difference $(\overline{\theta} - \underline{\theta})$ for private firms' incentives are different from those for the health authority. The health authority is interested in always choosing a drug with a biomarker when the difference between the high and the low proportion of responders is small. However, each firm is simply interested in selling to as many patients as possible with biomarkers ($\partial \Delta R_{ia}/\partial \overline{\theta} > 0$, and $\partial \Delta R_{ia}/\partial \underline{\theta} > 0$). Nevertheless, the effect of a firm's i probability of developing a drug that benefits a high proportion of patients (γ_i) depends on the difference $(\overline{\theta} - \underline{\theta})$. If this difference is large, specifically if $(\overline{\theta} - \underline{\theta}) > 1 - \frac{1}{2}\left[\gamma_j + (1-\gamma_j)(1-\rho_i)(1+\rho_j)\right]$, a higher γ_i will increase the incentives to include a biomarker test simply because it increases the expected profit when the proportion of responders is high ($\overline{\theta}$).

Additionally, including a biomarker test eliminates the risk of a statistically insignificant result of the clinical trial (ρ_i). Consequently, the higher the risk of a statistically insignificant result, the stronger the incentive to include the biomarker test. On the other hand, the competitor's risk of an insignificant result (ρ_j) reduces the incentives of firm i to use a biomarker test. This is because a higher ρ_j indirectly increases the likelihood that drug i will be the only drug available on the market, even without a biomarker test, so firm i is less concerned that its rival will be chosen, and consequently, it has less interest in including the biomarker test. Furthermore, a higher competitor's probability of benefiting a high proportion of patients (γ_j) makes firm j more likely to be chosen by the health authority when each firm excludes the biomarker test. Therefore, a higher γ_j implies stronger incentives for firm i to include a biomarker test and, consequently, to be more likely to be the firm selected by the health authority.

If condition (17) is satisfied, the firm's inclusion of the biomarker test constitutes a unique best response to the rival's strategies, resulting in the equilibrium $(\beta_1 = 1, \beta_2 = 1)$ with outcomes $(R_1^{1,1}, R_2^{1,1})$. Hence, we can state the following:

Proposition 1. *Let us assume that condition* (3) *holds. Then, the following results are obtained:*

(i) both firms include the biomarker test if $\Delta R_{ia} > 0$*;*

(ii) both firms exclude the biomarker test if $\Delta R_{ia} < 0$*.*

Proof. See Appendix A.

The decision of whether to include the biomarker test and deviate from an equilibrium in which both firms exclude the test depends on whether biomarker testing creates an advantage over the rival firm. Unless the increase in the probability of being chosen by the health authority due to the biomarker test is greater than the decrease in expected drug sales due to having fewer consumers, the biomarker test will not be included in the clinical trial. The decision will also depend on the characteristics of the drug. If the "quality" of the drug is high in the sense that it will benefit a large proportion of the patients (i.e., if $\overline{\theta}$ and $\underline{\theta}$ take relatively high values), each firm has greater incentives to provide evidence of this by the use of a biomarker test to increase the chance of being chosen over its rival.

4.2 Case (b): condition (3) does not hold

Let us now consider the case in which the health authority chooses a drug with a high fraction $\overline{\theta}$ of responders without a biomarker test rather than a drug with a biomarker test and a low fraction $\underline{\theta}$ of responders, i.e., condition (3) is not satisfied.

Table 3 summarizes the expected payoffs of firm 1 and firm 2 if they exclude ($\beta_i = 0$) or include ($\beta_i = 1$) the biomarker test in their clinical trials. The expressions in the table are simplified versions following equations (4), (5) and (8).

Table 3: Firms' expected payoffs in case (b)

	$\beta_2 = 0$	$\beta_2 = 1$
$\beta_1 = 0$	$(R_1^{0,0} = P\left[\gamma_1(1-\frac{1}{2}\gamma_2)+\frac{1}{2}(1-\gamma_1)(1-\gamma_2)(1-\rho_1)(1+\rho_2)\right]$, $R_2^{0,0} = P\left[\gamma_2(1-\frac{1}{2}\gamma_1)+\frac{1}{2}(1-\gamma_2)(1-\gamma_1)(1-\rho_2)(1+\rho_1)\right])$	$(R_{1b}^{0,1} = P\left[\gamma_1(1-\gamma_2)\right]$, $R_{2a}^{1,0} = P\left[\gamma_2\overline{\theta}+(1-\gamma_2)(1-\gamma_1)\underline{\theta}\right])$
$\beta_1 = 1$	$(R_{1b}^{1,0} = P\left[\gamma_1\overline{\theta}+(1-\gamma_1)(1-\gamma_2)\underline{\theta}\right]$, $R_{2b}^{0,1} = P\left[\gamma_2(1-\gamma_1)\right])$	$(R_1^{1,1} = P\left[\gamma_1\overline{\theta}\left(1-\frac{1}{2}\gamma_2\right)+\frac{1}{2}\underline{\theta}(1-\gamma_1)(1-\gamma_2)\right]$, $R_2^{1,1} = P\left[\gamma_2\overline{\theta}\left(1-\frac{1}{2}\gamma_1\right)+\frac{1}{2}\underline{\theta}(1-\gamma_2)(1-\gamma_1)\right])$

Let us consider the case in which the rival does not include the biomarker test; firm i has incentives to deviate from the outcome $(R_1^{0,0}, R_2^{0,0})$ and include the biomarker test if $R_{ib}^{1,0} - R_i^{0,0} > 0$ or

$$\gamma_i\gamma_j\left(\overline{\theta}-\frac{1}{2}\right)+(1-\gamma_i)(1-\gamma_j)\left[\underline{\theta}-\frac{1}{2}(1+\rho_j)\right]+(1-\gamma_i)(1-\gamma_j)\rho_i\frac{1}{2}(1+\rho_j) > \gamma_i(1-\gamma_j)(1-\overline{\theta}). \tag{18}$$

The biomarker test provides a gain if the revenue with the test exceeds the probability of being chosen over the rival without it. Additionally, there is a gain from avoiding the risk of a statistically inconclusive clinical trial. If these gains are large enough to outweigh the loss of expected revenues when drug i has a larger proportion of responders than drug j, it is profitable for firm i to include the biomarker test in its clinical trials.

The only difference from the incentives in case (a) is that there is no gain from being chosen over the rival when drug i has a lower proportion of responders than drug j.

The condition in (18) can be rearranged as expected gains from including the biomarker test:

$$\Delta R_{ib} = R_{ib}^{1,0} - R_i^{0,0} = \gamma_i \underbrace{\left[\overline{\theta} - 1 + \frac{1}{2}\gamma_j\right]}_{\substack{\text{gain from using} \\ \text{biomarker when } \theta_i = \overline{\theta}}} + (1-\gamma_i)\underbrace{(1-\gamma_j)\left[\underline{\theta} - \frac{1}{2}(1-\rho_i)(1+\rho_j)\right]}_{\substack{\text{gain from using} \\ \text{biomarker when } \theta_i = \underline{\theta}}} > 0 \tag{19}$$

Given that condition (3) is not satisfied, note that when drug i has $\underline{\theta}$ responders, firm i can only receive gains if its rival's drug also has $\underline{\theta}$ responders, which occurs with probability $(1-\gamma_j)$.

An increase in the proportion of responders, either $\overline{\theta}$ or $\underline{\theta}$, increases the market for the drug with the biomarker test, so it increases the incentives to include the test. The effect of firm i's probability γ_i of developing a drug that benefits a high $\overline{\theta}$ proportion of responders depends on the difference $(\overline{\theta} - \underline{\theta})$. If this difference is larger than $1 - \frac{1}{2}\left[\gamma_j + (1-\gamma_j)(1-\rho_i)(1+\rho_j)\right] - \underline{\theta}\gamma_j$, a higher γ_i results in an increase of the incentives to include a biomarker test because it increases the expected profit from the high proportion of responders. Furthermore, the effect of a greater competitor's probability γ_j of benefiting a high proportion of patients depends on the other parameters. If $(1-\gamma_i)\underline{\theta} > \frac{1}{2}\gamma_i + \frac{1}{2}(1-\gamma_i)(1-\rho_i)(1+\rho_j)$, a higher γ_j decreases the incentives for firm i to include the biomarker test. The problem is that if the rival's drug has a high probability of being effective for a high proportion of patients, the risk of the rival being chosen is greater. Even if firm i includes the biomarker test when its rival does not, a high γ_j means firm i has a greater risk of not being chosen when its drug is effective for a low proportion of patients. This means that there is a high threat of losing the expected profit $(1-\gamma_i)\underline{\theta}$ that firm i would have received. If that threatened expected profit is greater than expected gain from using the biomarker test, an increase in γ_j decreases the incentives of firm i to include the test.

As in case (a), an increase in the risk of a statistically insignificant result of the clinical trial ρ_i increases the incentive to include the biomarker test. Additionally, an increase in the competitor's risk of an insignificant result ρ_j reduces the incentives of firm i to include the biomarker test, making it more lenient since the risk that the rival has a successful clinical trial

is reduced.

We can now state the conditions for an equilibrium in which both firms include the biomarker test in their clinical trials. Firm i has incentives to introduce a biomarker test when its rival introduces one if $R_i^{1,1} - R_{ib}^{0,1} > 0$, which can be rearranged as follows:

$$\frac{1}{2}\gamma_i\gamma_j\overline{\theta} + \frac{1}{2}(1-\gamma_i)(1-\gamma_j)\underline{\theta} > \gamma_i(1-\gamma_j)(1-\overline{\theta}) \tag{20}$$

When the rival includes the biomarker test, it is also profitable for firm i to include the biomarker if the benefit from the increased probability of being chosen when both drugs have the same proportion of responders is greater than the loss of expected revenue when drug i has a larger proportion of responders than drug j. Condition (20) can be rewritten as follows:

$$\Delta R'_{ib} = R_i^{1,1} - R_{ib}^{0,1} = \gamma_i \underbrace{\left[\overline{\theta}(1-\frac{1}{2}\gamma_j) - 1 + \gamma_j\right]}_{\substack{\text{gain from using} \\ \text{biomarker when } \theta_i = \overline{\theta}}} + (1-\gamma_i) \underbrace{\left[\frac{1}{2}\underline{\theta}(1-\gamma_j)\right]}_{\substack{\text{gain from using} \\ \text{biomarker when } \theta_i = \underline{\theta}}} > 0 \tag{21}$$

This incentive increases as the fraction ($\overline{\theta}$ and $\underline{\theta}$) of responders increases. The effect of the probability γ_i of a high proportion of responders for drug i depends on whether firm i gains more from using the biomarker test when its drug is effective for $\overline{\theta}$ or for $\underline{\theta}$ patients. If the gain from being effective for a high proportion of patients is greater than from being effective for a low proportion, i.e., $\overline{\theta}(1-\frac{1}{2}\gamma_j) - 1 + \gamma_j > \frac{1}{2}\underline{\theta}(1-\gamma_j)$, a higher γ_i increases the incentives to include the biomarker test when the rival includes it. Furthermore, the effect of γ_j depends on how much firm i gains over its rival by using the biomarker test when drug i is effective for a high proportion of patients versus how much firm i can lose to its rival when drug i is effective for a low proportion of patients. In particular, if the gain is greater than the potential loss, i.e., $\gamma_i\left(1-\frac{1}{2}\overline{\theta}\right) > \frac{1}{2}\underline{\theta}(1-\gamma_i)$ (by simplifying the derivative of (21) with respect to γ_j), a higher γ_j increases the incentives of firm i to include the biomarker test when the rival includes it.

The equilibria in case (b) depend on conditions (19) and (21). Hence, we can state the following:

Proposition 2. *Let us assume that condition* (3) *does not hold. Then, the following equilibria are obtained:*

(i) one of the firms includes the biomarker test if $\Delta R_{ib} > 0$ *and* $\Delta R'_{ib} < 0$*;*

(ii) both firms include the biomarker test if $\Delta R_{ib} > 0$ *and* $\Delta R'_{ib} > 0$*; and*

(iii) both firms exclude the biomarker test if $\Delta R_{ib} < 0$*.*

Proof. See Appendix A.

Proposition 2 states that if condition (19) holds (i.e., $\Delta R_{ib} > 0$), the firms have an incentive to deviate from an equilibrium in which both firms exclude the biomarker test from their clinical trials. As before, the decision to include the biomarker test depends on how much advantage the test provides over the rival and on the characteristics of the drug. The increase in the probability of being chosen over the rival must be sufficiently large to overcome the decrease in expected profit due to having fewer customers. The decision will also depend on the proportion of patients who will benefit from the drug. The larger the fraction of responders is, the greater the interest in including the test in the trial to provide evidence of the quality of the drug.

4.3 Firms' relative incentives

Suppose that $\gamma_1 \geq \gamma_2$, so that drug 1 has more promise ex ante.[11] We now compare the incentives to include the biomarker test for firm 1 with those for firm 2 in case (a):

$$\Delta R_{1a} - \Delta R_{2a} = -(\gamma_1 - \gamma_2)(1 - \overline{\theta} + \underline{\theta}) - (1 - \gamma_1)(1 - \gamma_2)(\rho_2 - \rho_1) \tag{22}$$

and case (b):

$$\Delta R_{1b} - \Delta R_{2b} = -(\gamma_1 - \gamma_2)(1 - \overline{\theta}) - (1 - \gamma_1)(1 - \gamma_2)(\rho_2 - \rho_1) \tag{23}$$

The sign of these expressions will depend on the values of ρ_1 and ρ_2. Suppose that $\rho_1 = \rho_2$; each firm has the same risk of statistically insignificant result when each has a $\underline{\theta}$-drug. However, firm 1 is more likely to develop a drug with $\overline{\theta}$ responders (since $\gamma_1 \geq \gamma_2$). Therefore, firm 2 is less likely to be chosen when it does not include the biomarker, and it has greater incentives to include a biomarker than firm 1. For other relative values of ρ_1 and ρ_2, see Appendix B.

We summarize the above analysis as follows:

Proposition 3. *If firm i is less promising in that it is less likely to develop a drug that benefits a high proportion of responders than its rival firm j and $\rho_i \geq \rho_j$, firm i has stronger incentives than firm j to include a biomarker test in its clinical trial.*

A more promising firm is more likely to be approved when none of the firms includes the biomarker test. Therefore, it will be less eager to include it than the less promising firm. On the other hand, the less promising firm needs the biomarker test to increase its chance of being chosen over its more promising rival.

[11] Trial returns to the firm's experience are positive (Danzon et al., 2005). For example, if the developer of drug 1 has more experience than the developer of drug 2, drug 1 is likely to have a greater success probability. An alternative is to regard the developer of drug 1 as the firm that is more focused (on a therapeutic area), rather than broader experience, which is associated with greater drug and trial success.

4.4 Duopoly vs. monopoly

We will now compare the incentives to include the biomarker under a duopoly with the incentives under monopoly. As before, we distinguish the incentives in the two cases (a) and (b).

Case (a)

Case (a) is the case in which (3) holds. Each firm has a stronger interest in including a biomarker test in its clinical trials when there is competition. We see this by comparing (17) with (15). The gains for firm i from including the biomarker test when its competitor does not – hence, deviating from $(\beta_1 = 0, \beta_2 = 0)$ – are greater than the gains for a monopolist from including the test. The difference between the incentives to include the biomarker test under duopoly and monopoly is given by

$$\Delta R_{ia} - \Delta R_M = \underbrace{\frac{1}{2}\gamma_i\gamma_j + (1-\gamma_i)\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right]}_{\substack{\text{gain from being chosen over rival} \\ \text{due to biomarker}}} - \underbrace{(1-\gamma_i)\rho_i\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right]}_{\substack{\text{gain from increasing the probability} \\ \text{of a statistically significant trial}}} > 0. \quad (24)$$

This expression distinguishes two types of gains from including the biomarker test. The first part represents the gain from being chosen over the rival since the biomarker test makes the drug more appealing to the health authority. The second part represents the gain from increasing the probability of obtaining statistically significant trial results. We can see, however, that it is negative, meaning that the incentive to include the biomarker test to avoid the risk of a statistically inconclusive trial is weaker under competition than under monopoly. Nevertheless, the gain from being chosen over the rival is large enough to overcome this. When each firm excludes the biomarker test, firm i faces the risk that its competitor is chosen by the health authority. Firm i can include the biomarker test to eliminate this risk and ensure that its drug is always chosen. In other words, there is an expected loss from not including the biomarker test when there is competition, which leads to an incentive to include it. Hence, we can state the following:

Lemma 1. *Let us assume that* (3) *holds. Competition increases the interest of each firm in including a biomarker test in clinical trials.*

A proof can be found in Appendix C.

Given that the incentives to include the biomarker test are greater under competition, condition (15) ensures that condition (17) is fulfilled. In other words, a monopoly equilibrium in which the monopolist includes the biomarker test implies a duopoly equilibrium where both firms include the test with the same parameter values.

Case (b)

Case (b) is the case in which (3) does not hold. The effect of competition on the interest in including a biomarker test in clinical trials depends on some characteristics of the drugs and the firms. Here, we compare (19) with (15). The difference between the incentives to include the biomarker test under duopoly and monopoly is given by

$$\Delta R_{ib} - \Delta R_M = \underbrace{\frac{1}{2}\gamma_i\gamma_j + (1-\gamma_i)\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right]}_{\substack{\text{gain from being chosen over rival} \\ \text{due to biomarker}}} - \underbrace{\underline{\theta}\gamma_j(1-\gamma_i)}_{\substack{\text{loss from} \\ \text{rival being chosen} \\ \text{when } \theta_i = \underline{\theta} \\ \text{and } \theta_j = \overline{\theta}}} \tag{25}$$

$$- \underbrace{(1-\gamma_i)\rho_i\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right]}_{\substack{\text{gain from increasing the probability} \\ \text{of a statistically significant trial}}}.$$

The effect of competition in case (b) is lower than in case (a) because the health authority will choose a drug without a biomarker test that is effective for $\overline{\theta}$ patients over a drug with a biomarker test that is effective for $\underline{\theta}$ patients. We can state the following:

Lemma 2. *Let us assume that* (3) *does not hold. Competition will increase the interest of each firm in including the biomarker test in its clinical trials if*
$\underline{\theta}\gamma_j(1-\gamma_i) < \frac{1}{2}\gamma_i\gamma_j + (1-\gamma_i)\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right] - (1-\gamma_i)\rho_i\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right]$.

From (25), we note that when drug i is effecitve for $\underline{\theta}$ patients and drug j is effective for $\overline{\theta}$ patients, firm i incurs a loss, even when it uses the biomarker test, because the rival will be chosen. Nevertheless, if this expected loss, given by $\underline{\theta}\gamma_j(1-\gamma_i)$, is lower than the expected gain in all other combinations of drug i's and drug j's θ, firm i has a stronger interest in including a biomarker test in clinical trials when there is competition than under monopoly.

However, given that the incentives to include the biomarker test under competition in case (b) are not always greater than under monopoly, condition (15) does not ensure that condition (19) is fulfilled. This means that there can be a situation where a monopolist will include the biomarker test, but under competition, there will not be incentives to deviate from an equilibrium in which both firms exclude the test. Hence, if (25) is negative, there is a possibility that a biomarker test will be included in clinical trials under monopoly but excluded under duopoly.

Overall, under competition in both cases (a) and (b), the incentive for firm i to include a biomarker test in clinical trials consists of two factors: the desire to avoid the risk of statistically inconclusive clinical trials and the desire to be chosen over the rival by having the best drug.

The first incentive comes from ρ_i and is present even when the firm does not have a rival.[12] We find that this type of incentive is weaker under duopoly than under monopoly. This is because the rival also faces a risk of statistically inconclusive trial results. This makes the firm more likely to win over its rival, even without a biomarker test. Therefore, the firm is less interested in including the test if the purpose is to increase the probability of trial success.

The second type of incentive only exists under competition and derives from the difference between firm i's profits if it is chosen over its rival and the profits it would make if the rival were chosen.[13] In other words, the private value of including the biomarker test in clinical trials is determined based on the outcome if firm i includes the biomarker test and its rival does not. A firm that includes the biomarker test increases the expected quality of its drug, making it more appealing to the health authority than the rival's drug. Nevertheless, this type of incentive is weaker in case (b) than in case (a) because, when the rival has a higher proportion of responders, it will always be chosen by the health authority, which makes the firm less interested in including the biomarker test in its clinical trials.

We summarize the above discussion as follows:

Proposition 4. *The incentives to include the biomarker test to avoid the risk of statistically inconclusive trial results are lower under duopoly than under monopoly. However, competition creates incentives to include the biomarker test to make the drug more appealing to the health authority than the rival's drug.*

Proposition 4 highlights the fact that the incentive driving the monopolist to include the biomarker (from the probability of not obtaining statistically significant trial results) is actually weaker under competition. However, the existence of competition generates another type of incentive for the firm, which comes from the consideration that the rival may develop a more appealing drug if the firm does not include a biomarker test.

Note that if conditions (17) and (19) are not satisfied, each firm will only have an incentive to include a biomarker test if the price offered for the drug is higher when the biomarker test is used. Since competitive effects can result in greater incentives to include the biomarker test, the drug price when the test is needed to provide incentives can be lower under competition than under monopoly.

[12] This incentive is labeled the "profit incentive" in Beath et al. (1989), which corresponds to the "replacement effect" in Gilbert & Newberry (1982) in the R&D literature.

[13] This type of incentive is labeled "competitive threat" in Beath et al. (1989), which corresponds to the "efficiency effect" in Gilbert & Newberry (1982).

4.5 Welfare implications

Welfare in market equilibrium

Let us now evaluate the welfare effects of the market equilibrium. Welfare consists of the sum of consumers' and firms' utility net of the payments for the drug. As before, we assume that funds to pay the drug price can be raised in a non-distortionary manner, which simplifies the welfare function to the expected gross aggregate consumer utility ex ante. We consider and compare the expected welfare in the three possible equilibria: both firms include the biomarker test in their clinical trials, both exclude it, or only one of the firms includes it in case (b).

We construct the expected social welfare when both firms include the biomarker test in the following way. Patients will benefit from a drug with a high proportion $\overline{\theta}$ of responders if at least one of the firms develops it. Otherwise, only a drug with a low proportion $\underline{\theta}$ of responders will be developed and approved. This yields the following expected social welfare when both include the biomarker test:

$$W^{1,1} = \left[\gamma_1\gamma_2 + \gamma_1(1-\gamma_2) + \gamma_2(1-\gamma_1)\right]\overline{\theta}V + (1-\gamma_1)(1-\gamma_2)\underline{\theta}V \tag{26}$$

Now, let us examine the case in which neither of the firms includes the biomarker. The probability that at least one of the firms develops a $\overline{\theta}$-drug remains the same, but the probability that a $\underline{\theta}$-drug will be developed must take into account the probability that either one or both firms have statistically significant trial results, represented by $(1-\rho_1\rho_2)$. Hence, expected social welfare when neither of the firms includes the biomarker is given by

$$W^{0,0} = \left[\gamma_1\gamma_2 + \gamma_1(1-\gamma_2) + \gamma_2(1-\gamma_1)\right]\left[\overline{\theta}V - (1-\overline{\theta})k\right] + (1-\gamma_1)(1-\gamma_2)(1-\rho_1\rho_2)\left[\underline{\theta}V - (1-\underline{\theta})k\right]. \tag{27}$$

The outcome is $(R_1^{1,1}, R_2^{1,1})$, i.e., both firms include the biomarker test, which can be a unique equilibrium in both cases (a) and (b), as discussed above. We can see that the inclusion of the biomarker test by both firms is more socially beneficial than the exclusion as follows:

$$W^{1,1} - W^{0,0} = (\gamma_1 + \gamma_2 - \gamma_1\gamma_2)(1-\overline{\theta})k + (1-\gamma_1)(1-\gamma_2)\left[(1-\rho_1\rho_2)(1-\underline{\theta})k + \rho_1\rho_2\underline{\theta}V\right] > 0 \tag{28}$$

The benefit in these cases comes from sparing nonresponders' health and from increasing the likelihood of a statistically significant result in clinical trials.

Suppose now that only one of the firms (e.g., firm 1) includes the biomarker test in the clinical trial. In case (b), this is the equilibrium if condition (19) is satisfied and condition (21) is not. Note that the drug with a biomarker test will always be chosen except when it is

effective for $\underline{\theta}$ patients, in which case the alternative without a biomarker test that is effective for $\overline{\theta}$ patients will be chosen. In this case, the expected social welfare is given by

$$W_b^{1,0} = \gamma_1\overline{\theta}V + (1-\gamma_1)\gamma_2[\overline{\theta}V - (1-\overline{\theta})k] + (1-\gamma_1)(1-\gamma_2)\underline{\theta}V. \tag{29}$$

When comparing it with $W^{0,0}$ in (27), we clearly see that it is socially beneficial for one firm to include the biomarker test:

$$W_b^{1,0} - W^{0,0} = \gamma_1(1-\overline{\theta})k + (1-\gamma_1)(1-\gamma_2)(1-\rho_1\rho_2)(1-\underline{\theta})k + (1-\gamma_1)(1-\gamma_2)\rho_1\rho_2\underline{\theta}V > 0 \tag{30}$$

In conclusion, we can state the following:

Lemma 3. *It is more socially beneficial when at least one of the firms includes the biomarker test in clinical trials than when both exclude it.*

Overall, given that conditions (17) and (19) are satisfied, the equilibrium outcome is that both firms will include the biomarker test in case (a) and that either one or two firms will include the biomarker test in case (b). The problem is that if these conditions are not satisfied, neither firm has an incentive to include the biomarker test and deviate from the outcome $(R_1^{0,0}, R_2^{0,0})$, which is less socially beneficial. In this situation, there may be social gains from encouraging one firm (e.g., firm 1) to include the biomarker test, for instance, by offering a higher price for the drug if it uses a biomarker test. This will make the inclusion of the biomarker test the dominant strategy for firm 1, which will lead to the outcome $(R_1^{1,1}, R_2^{1,1})$ in case (a) and to either $(R_1^{1,1}, R_2^{1,1})$ or $(R_1^{1,0}, R_2^{0,1})$ in case (b).

Welfare in duopoly vs. monopoly

Finally, we compare the welfare properties of the equilibria under duopoly with the inclusion of the biomarker test under monopoly. We now restrict attention to the effect of competition on social welfare.

Consider the equilibrium in which both firms include the biomarker test in the duopoly model. In case (a), this is the unique equilibrium if (17) is satisfied, while in case (b), this is the equilibrium if both (19) and (21) are satisfied. For comparison purposes, we assume that the monopolist corresponds to firm 1 under duopoly. The difference in expected social welfare is then given by

$$W^{1,1} - W_M^1 = \gamma_2(1-\gamma_1)V(\overline{\theta} - \underline{\theta}) > 0. \tag{31}$$

This difference is positive because there is a social gain from competition: there is an increase in the probability of a drug that is effective for more responders being developed since two firms are working on it instead of only one.

Let us now consider the equilibrium in which only one firm (e.g., firm 1) includes the biomarker test. This is an equilibrium in case (b) if condition (19) is satisfied and condition (21) is not. The difference in expected social welfare is given by

$$W_b^{1,0} - W_M^1 = \gamma_2(1-\gamma_1)[V(\overline{\theta}-\underline{\theta}) - (1-\overline{\theta}k)] > 0. \tag{32}$$

This difference is positive given that (3) is not satisfied. As before, the gain from competition is due to an increase in the probability that a drug that benefits a high fraction of patients will be developed because there is another firm in the race to develop it. However, that gain comes from the firm that does not include the biomarker test in its trial, which implies a disutility k for the nonresponders.

The above results can be summarized as follows:

Proposition 5. *The social benefit from the inclusion of a biomarker test in clinical trials is greater under duopoly than under monopoly.*

Since there are two firms, rather than one, with the potential to develop a drug that is effective for a high proportion of patients, the social gain from duopoly is given by the increase in expected health benefits for those who respond to that drug.

Consider now the case in which the same parameter values entail a situation where a monopolist includes the biomarker test and an equilibrium where neither firm includes the biomarker test under duopoly, which can occur in case (b). Hence, condition (15) is satisfied, while condition (19) is not. The difference in expected social welfare between a duopoly equilibrium without a biomarker test and a monopoly with a biomarker test is given by

$$\begin{aligned} W^{0,0} - W_M^1 = & \underbrace{\gamma_2(1-\gamma_1)\overline{\theta}V}_{\substack{\text{more likely to} \\ \text{benefit } \overline{\theta}}} - \underbrace{(1-\gamma_1)[1-(1-\gamma_2)(1-\rho_1\rho_2)]\underline{\theta}V}_{\substack{\text{less likely to} \\ \text{benefit } \underline{\theta}}} \\ & \underbrace{-(\gamma_1+\gamma_2-\gamma_1\gamma_2)(1-\overline{\theta})k - (1-\gamma_1)(1-\gamma_2)(1-\rho_1\rho_2)(1-\underline{\theta})k}_{\text{side effects for nonresponders}}. \end{aligned} \tag{33}$$

This difference can either be positive or negative. Here, competition implies a tradeoff. On the one hand, a drug that benefits a $\overline{\theta}$ proportion of patients is more likely to be developed because there is one more firm in the development process. On the other hand, it is less likely that the drug developed benefits a $\underline{\theta}$ proportion of patients due to the risk of a statistically

insignificant trial result, and in either case, the drug is expected to entail side effects for the nonresponders. Therefore, competition in this case may not be more socially beneficial than monopoly if the increase in expected health gains from a $\overline{\theta}$-drug does not overcome the side effects for nonresponders and the lower expected gain from a $\underline{\theta}$-drug.

5 Discussion of the framework

Although we assume that information regarding the inclusion of the biomarker in clinical trials will become public, a pharmaceutical firm may gather private information on the efficacy of a drug with a biomarker-based selection of patients. In other words, the firm could decide whether to apply for marketing approval of the drug with biomarker testing only after the trial determines the efficacy of the drug. This "non-public" version was analyzed by Scott Morton & Seabright (2013) in a monopoly setting, where the firm includes the biomarker test in the clinical trial without being obliged to disclose the efficiency of the biomarker to the health authority. They find that the firm will only reveal the use of the biomarker when the clinical trial results would be statistically inconclusive without it.

The results from Section 4 could change if they were derived in a "non-public" form. In particular, the conditions under which it is profitable to reveal the biomarker would vary depending on the response rate of the drug (θ). It is clear that firm i would still prefer to reveal the use of the biomarker when the clinical trial results would be statistically inconclusive without it since it will never receive marketing approval otherwise. Even in the other cases (i.e., when the response rate is high, $\overline{\theta}$, or when the response rate is low, $\underline{\theta}$, but the trial results are statistically significant without the biomarker test), the threat from a rival is likely to lead to positive expected gains from using the biomarker test under certain conditions. Hence, the reasoning of competition effects from Section 4.4 can apply to a "non-public" version of the model.

To see this, consider the following example. Suppose that firm i includes the biomarker test in the clinical trial and discovers that its drug is effective for $\overline{\theta}$ patients. Then, it faces the decision of whether to apply for drug approval with the biomarker test. The firm does not know whether its rival's drug is effective for $\overline{\theta}$ or $\underline{\theta}$ or whether it will apply with a biomarker test. Consider the situation where the rival does not disclose the use of the test. Firm i's drug will be chosen by the health authority, and firm i will profit $P\overline{\theta}$ if it uses the biomarker test. On the other hand, if firm i does not reveal the use of the biomarker test, its expected profit is given by $P[\gamma_j \frac{1}{2} + (1 - \gamma_j)]$, i.e., each drug is chosen with probability 1/2 when they are the same,

and drug i is chosen with probability 1 when drug j is effective only for $\underline{\theta}$ patients. Hence, it will be profitable for firm i to disclose the inclusion of the biomarker when its drug benefits $\overline{\theta}$ patients if $\overline{\theta} > \gamma_j \frac{1}{2} + (1 - \gamma_j)$. It is clear that if it were not for the threat of a competitor, the firm would not have any incentives to reveal the use of the biomarker test in this case.

However, we assume in the main model that the firms always disclose the inclusion of the biomarker, since drug developers are required to submit all data to the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for approval, including trial protocols, data from successful and failed trials (Omae et al., 2019) and the selection of participants (EU Directive for Human Medicines 2001/83/EC).

Moreover, gathering biomarker-based private information is not costless. First, it would require a firm to conduct two clinical trials, one with biomarker testing and another without, implying additional R&D costs. Second, if the health authority knows that the pharmaceutical firm assessed the drug's efficacy or side effects in a group of patients selected by a biomarker test, concealing the results of that trial is expected to cause skepticism (Gentzkow & Kamenica, 2017c). Hence, it may not be possible for the firm to gather this information and keep it private if it does not have sufficient funds to conduct more than one clinical trial or if the failure to disclose trial results is too risky for its reputation.

6 Concluding remarks

The clinical trial paradigm for new drugs has been changing with the introduction of biomarker tests to select participants who are likely to benefit. While biomarker testing is a way to avoid adverse drug reactions among nonresponders and to reduce trials' size and improve the probability of success, it reduces the size of the market to which the drug can be sold. Nevertheless, previous literature has noted that a monopolist drug manufacturer will not include a biomarker test in the clinical trial for its new drug unless policies, such as an upward adjustment in the drug price, are adopted. In this paper, we study how the presence of a competitor in the race for drug marketing approval affects the incentives of pharmaceutical firms to include biomarker testing in clinical drug trials.

The analysis has shown that the inclusion of a biomarker test in the clinical trial can actually generate an advantage for a firm over its rival by making the drug more appealing to the health authority. A firm under competition can use a biomarker test to improve the quality of its drug, making it more likely to be chosen over the rival's drug. On the other hand, the incentive to include the biomarker test with the aim of improving the probability of a statistically significant

trial is weaker under duopoly than monopoly. Nevertheless, running a trial with a biomarker test in a duopoly setting not only is more socially beneficial but can also be more profitable than in a monopoly setting. Furthermore, the incentives for biomarker test inclusion are greater when the health authority always chooses to approve a drug with a biomarker test, even when this drug benefits a lower proportion of patients than an alternative without a test. Finally, we find that a pharmaceutical firm with less potential to develop a high-efficacy drug has stronger interest in including the biomarker test in the trial than a firm with more potential. Overall, the results suggest that winning the drug marketing approval race over a rival firm by improving the probability of trial success and making the drug more attractive to the health authority through biomarker testing is in some circumstances more important than losing potential drug revenues.

To conclude, competition can encourage the development of personalized medicine without a change in the drug price or with a price increase that is smaller than it would be under monopoly. Therefore, there may be social gains from competition in pharmaceutical R&D, especially for governments with strict budget controls. This highlights the importance of antitrust policies and global competition among a large number of drug developers, including pharmaceutical and biotechnology firms and universities.

Appendix A

Proof of Proposition 1. As shown in Table 2, $R_{ia}^{0,1} = 0$; hence, $R_i^{1,1} - R_{ia}^{0,1} > 0$, which means that it is more profitable for firm i to include the biomarker test when the rival includes it. Therefore, in case (a), there is an equilibrium in which both firms include the biomarker test. Let us now examine how we achieve the equilibria described in points (i) and (ii):

(i) If $\Delta R_{ia} > 0$, it is more profitable for firm i to deviate from an outcome where both firms exclude the biomarker test. Hence, in this case, the outcome $(R_1^{1,1}, R_2^{1,1})$ is a unique equilibrium. Therefore, both firms will include the test.

(ii) If $\Delta R_{ia} < 0$, firm i will not have incentives to deviate from an outcome where both firms exclude the biomarker test. Hence, the outcome $(R_1^{0,0}, R_2^{0,0})$ is also an equilibrium. However, we focus on payoff dominant equilibria, i.e., equilibria that result in a greater payoff. For example, the outcome $(R_1^{1,1}, R_2^{1,1})$ is payoff dominant over $(R_1^{0,0}, R_2^{0,0})$ if $R_i^{1,1} - R_i^{0,0} > 0$ (see Table 2). Then, the question becomes whether we can simultaneously have $\Delta R_{ia} < 0$ and $R_i^{1,1} - R_i^{0,0} > 0$, which implies $R_i^{1,1} - R_i^{0,0} - \Delta R_{ia} > 0$. However, we show that this is not possible as follows:

$$
\begin{aligned}
& R_i^{1,1} - R_i^{0,0} - \Delta R_{ia} \\
& = \gamma_i(\overline{\theta} - 1)\left(1 - \frac{1}{2}\gamma_j\right) + \frac{1}{2}(1-\gamma_i)(1-\gamma_j)\left[\underline{\theta} - (1-\rho_i)(1+\rho_j)\right] \\
& - \gamma_i\left(\overline{\theta} - 1 + \frac{1}{2}\gamma_j\right) - (1-\gamma_i)\left[\underline{\theta} - \frac{1}{2}(1-\gamma_j)(1-\rho_i)(1+\rho_j)\right] \\
& = -\frac{1}{2}\gamma_i\gamma_j\overline{\theta} - (1-\gamma_i)\underline{\theta}\left[1 - \frac{1}{2}(1-\gamma_j)\right] < 0
\end{aligned}
\tag{A1}
$$

Expression (A1) shows that if $\Delta R_{ia} < 0$, the payoff from the outcome $(R_1^{1,1}, R_2^{1,1})$ is lower than the payoff from the outcome $(R_1^{0,0}, R_2^{0,0})$. Therefore, $\Delta R_{ia} < 0$ implies that the outcome $(R_1^{0,0}, R_2^{0,0})$ is payoff dominant. Q.E.D.

Proof of Proposition 2. In the following, we show how each equilibrium described in points (i), (ii) and (iii) is achieved.

(i) If $\Delta R_{ib} > 0$, firm i prefers to include the biomarker test when its rival excludes it. Additionally, if $\Delta R'_{ib} < 0$, firm i has no incentives to include the biomarker test if its rival does not. Hence, there is an equilibrium in which one of the firms includes the biomarker test and the other does not. Furthermore, we show that the conditions for an

equilibrium in which one of the firms includes the biomarker test describe a non-empty set of parameters. The conditions are as follows:

$$\Delta R_{ib} > 0 > \Delta R'_{ib} \tag{A2}$$

which we can rewrite as

$$\begin{aligned} &\gamma_i \left[\overline{\theta} - 1 + \frac{1}{2}\gamma_j\right] + (1-\gamma_i)(1-\gamma_j)\left[\underline{\theta} - \frac{1}{2}(1-\rho_i)(1+\rho_j)\right] > 0 \\ &> \gamma_i \left[\overline{\theta}(1-\frac{1}{2}\gamma_j) - 1 + \gamma_j\right] + \frac{1}{2}(1-\gamma_i)(1-\gamma_j)\underline{\theta} \end{aligned} \tag{A3}$$

For example, we observe numerically that if $\gamma_i = 0.5$, $\gamma_j = 0.2$, $\overline{\theta} = 0.6$, $\underline{\theta} = 0.58$, $\rho_i = 0.75$, and $\rho_j = 0.6$, we have the following:

$$\Delta R_{ib} = 0.5\left[0.6 - 1 + \frac{1}{2}\times 0.2\right] + (1-0.5)(1-0.2)\left[0.58 - \frac{1}{2}(1-0.75)(1+0.6)\right] = 0.002 \tag{A4}$$

which is greater than zero, and

$$\Delta R'_{ib} = 0.5\left[0.6(1-\frac{1}{2}\times 0.2) - 1 + 0.2\right] + \frac{1}{2}\times 0.58(1-0.5)(1-0.2) = -0.014 \tag{A5}$$

which is lower than zero. Thus, condition (A2) defines a non-empty set of parameters. There exists an equilibrium in which one of the firms includes the biomarker test if $\Delta R_{ib} > 0 > \Delta R'_{ib}$.

(ii) If $\Delta R_{ib} > 0$, there are incentives to deviate from an outcome where both exclude the biomarker test. Additionally, if $\Delta R'_{ib} > 0$, there are no incentives to deviate from an equilibrium in which both firms include the biomarker test. Hence, the unique equilibrium is that both include the biomarker test.

(iii) Finally, we show that the firms will exclude the biomarker test if $\Delta R_{ib} < 0$. The firms will not have an incentive to deviate from the outcome $(R_1^{0,0}, R_2^{0,0})$, which will be an equilibrium.

Additionally, let us suppose that $\Delta R'_{ib} < 0$. Then, the firms have an incentive to deviate from an equilibrium in which both include the biomarker test. Hence, both firms excluding the biomarker test, i.e., outcome $(R_1^{0,0}, R_2^{0,0})$, is a unique equilibrium if $\Delta R_{ib} < 0$ and $\Delta R'_{ib} < 0$.

Alternatively, let us suppose that $\Delta R'_{ib} > 0$. Then, the firms will not have an incentive to deviate from an equilibrium in which both include the biomarker test, i.e., the outcome $(R_1^{1,1}, R_2^{1,1})$ is also an equilibrium. However, we focus on payoff dominant equilibria. For

example, the outcome $(R_1^{1,1}, R_2^{1,1})$ is payoff dominant over $(R_1^{0,0}, R_2^{0,0})$ if $R_i^{1,1} - R_i^{0,0} > 0$ (see Table 3). For that to be true, we must check whether we can simultaneously have $\Delta R_{ib} < 0$ and $R_i^{1,1} - R_i^{0,0} > 0$, which implies $R_i^{1,1} - R_i^{0,0} - \Delta R_{ib} > 0$. However, we show that this is not possible as follows:

$$\begin{aligned} & R_i^{1,1} - R_i^{0,0} - \Delta R_{ib} \\ & = \gamma_i(\overline{\theta} - 1)\left(1 - \frac{1}{2}\gamma_j\right) + \frac{1}{2}(1-\gamma_i)(1-\gamma_j)[\underline{\theta} - (1-\rho_i)(1+\rho_j)] \\ & - \gamma_i\left[\overline{\theta} - 1 + \frac{1}{2}\gamma_j\right] - (1-\gamma_i)(1-\gamma_j)\left[\underline{\theta} - \frac{1}{2}(1-\rho_i)(1+\rho_j)\right] \end{aligned} \tag{A6}$$

which we can simplify as

$$-\gamma_i\gamma_j\overline{\theta} - (1-\gamma_i)(1-\gamma_j)\underline{\theta} < 0 \tag{A7}$$

Hence, the payoff from the outcome $(R_1^{1,1}, R_2^{1,1})$ is lower than that from the outcome $(R_1^{0,0}, R_2^{0,0})$. Therefore, $\Delta R_{ib} < 0$ implies that the outcome $(R_1^{0,0}, R_2^{0,0})$ is payoff dominant. Q.E.D.

Appendix B

In the following, we will briefly consider the relative incentives for biomarker test inclusion where $\gamma_1 > \gamma_2$ in the cases in which ρ_1 differs from ρ_2.

Suppose that $\rho_2 > \rho_1$; firm 2 has a higher probability of obtaining a statistically insignificant result when its drug is effective for $\underline{\theta}$ patients when it excludes the biomarker test. Therefore, firm 2 has a stronger interest in including the biomarker test in the clinical trial to eliminate the risk of not receiving market approval.

Suppose that $\rho_1 > \rho_2$ and $(1-\gamma_1)(1-\gamma_2)(\rho_1 - \rho_2) > (\gamma_1 - \gamma_2)(1 - \overline{\theta} + \underline{\theta})$ in case (a) and $(1-\gamma_1)(1-\gamma_2)(\rho_1 - \rho_2) > (\gamma_1 - \gamma_2)(1 - \overline{\theta})$ in case (b). This means that for firm 1, the expected risk of not receiving market approval due to statistically insignificant results in the clinical trial is greater than the gain when the biomarker test is excluded. In that case, firm 1 has stronger incentives to include the biomarker test to eliminate that risk. Otherwise, firm 2 is more interested in including the biomarker test in the clinical trial than firm 1.

Appendix C

Proof of Lemma 1. First, we show that the expression in brackets in (24) is positive:

$$\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right] > 0 \tag{C1}$$

which we can rewrite as

$$2 > (1-\gamma_j)(1+\rho_j) \tag{C2}$$

Given that $0 < \gamma_j < 1$ and $0 < \rho_j < 1$, (C1) holds and the expression in brackets is positive.

Second, we show that expression (24) is positive. Expression (24) can be simplified as follows:

$$\begin{aligned}\Delta R_{ia} - \Delta R_M &= \underbrace{\frac{1}{2}\gamma_i\gamma_j + (1-\gamma_i)\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right]}_{\substack{\text{gain from being chosen over rival} \\ \text{due to biomarker}}} - \underbrace{(1-\gamma_i)\rho_i\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right]}_{\substack{\text{gain from increasing the probability} \\ \text{of a statistically significant trial}}} \\ &= \frac{1}{2}\gamma_i\gamma_j + (1-\gamma_i)(1-\rho_i)\underbrace{\left[1 - \frac{1}{2}(1-\gamma_j)(1+\rho_j)\right]}_{+} > 0.\end{aligned}$$

Given that the expression in brackets is positive, condition (24) holds. We can, therefore, conclude that the expected profit with biomarker testing under duopoly is greater than that under monopoly. Q.E.D.

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