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Competing with precision:

incentives for developing predictive biomarker tests

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Abstract

We study the incentives of drug producers to develop predictive biomarkers, taking into account strategic interaction between drug producers and health plans. For this purpose we develop a two-dimensional spatial framework that allows us to capture the informational role of biomarkers and their effects on price competition and treatment choices. Although biomarkers increase the information available to prescribers, we identify an anticompetitive effect on the prices set by producers of therapeutically substitutable drugs. We also find that better information about each patient's most therapeutically appropriate drug does not necessarily lead to more efficient treatment outcomes.

Keywords: Pharmaceutical markets; Precision medicine; Therapeutic competition; Predictive biomarkers.

JEL Classification: I11; I18; L13; L65.

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1 Introduction

Although the advancement of medicine offers new treatment opportunities for patients with severe diseases, individual treatment responses often vary substantially. If the average treatment effect of a drug, say measured by gained QALYs, is sufficiently high relative to incremental treatment costs, the traditional approach by many health plans has been to allow physicians to prescribe the drug based on a 'trial and error' basis. Consequently, many patients who receive expensive treatment will not see the health improvements they could hope for, or even experience more serious side-effects than others. According to Antonanzas et al. (2018), over 90% of drugs work for fewer than half of the patients they are prescribed for.

Improvements in the technology for sequencing the human genome have enabled more precise tailoring of treatments within groups of patients sharing the same diagnosis. Increased precision of interventions is achieved by exploring predictive biomarkers, which '*identify individuals who are more likely than similar individuals without the biomarker to experience favourable or unfavourable effects from exposure to a medical product*'.[1] Instead of treating many patients and accepting lower response rates, biomarkers associated with molecular and genetic characteristics are used to narrow down the number of patients that are given a specific treatment. Patients without these biomarkers, can instead be offered other treatment alternatives or no treatment at all, thus avoiding the burden of receiving ineffective treatment.

The potentially large benefit to patients and society of improved precision of medical treatment has been recognised for several decades already, since the start of research efforts to determine the DNA sequence of the entire human genome (Langreth and Waldholz, 1999). Parallel to the race between the two major sequencing projects, The Human Genome project and Celera Genomics, the pharmaceutical industry started to invest in mapping variations in the human genome, referred to as Single Nucleotide Polymorphisms (SNP) Consortium, already then aiming for precision, or personalised medicine (The International SNP Map Working Group, 2001). So far, predictive biomarkers have made most progress in oncology, but other therapeutic areas are also experiencing progress in detecting biomarkers that can provide prescribing physicians with better information about who are likely to respond to a given therapy (see Jørgensen, 2021, for a recent review). Although initial excessive optimism was replaced with a period of dissatisfaction about the progress of personalised medicine (Towse and Garrison, 2013), it is

[1] See the definition offered by the FDA-NIH Biomarker working group (https://www.ncbi.nlm.nih.gov/books/NBK338449/).

expected that we will continue to see research effort into precision medicine, with development of specific biomarkers to inform prescription choices (Stern et al., 2017).

Predictive biomarkers challenge economic regulation and coverage decisions of regulators and health plans. By detecting biomarkers for new and existing therapies, drug producers run the risk of reducing the size of the market since non-responding patients no longer are going to be treated. Unless drug prices are sensitive to improved precision, the incentives to develop biomarkers are weak (see for example Towse and Garrison, 2013, Scott Morton and Seabright, 2013, and Stern et al., 2018).

Despite regulatory challenges being identified and discussed in the literature, the effect of biomarkers and precision medicine on competition in pharmaceutical markets remains under-explored. On the one hand, patent-holding drug producers enjoy market power, giving rise to price setting flexibility. Health plans, on the other hand, enjoy countervailing monopsony power, first and foremost by controlling access to their plans (Lakdawalla, 2018). The decision to develop a biomarker is clearly a strategic choice by drug producers that is likely to affect the dynamics of competition. An illustrating example is the introduction of a biomarker for the immuno-oncology drug Keytruda sold by Merck.[2] This drug faced competition from Opdivo by Bristol-Myers Squibb for treating several types of cancer. While the biomarker reduced the sales of Keytruda due to fewer patients, the efficacy of the drug improved relative to Opdivo not using a biomarker and tested on a broader population. Merck's launch of a biomarker turned out to be a crucial and profitable strategy for the success of Keytruda.

Our paper aims at developing new knowledge about how predictive biomarkers affect the strategic interaction between drug producers and health plans, and how this feeds back to the incentives to develop biomarkers in the first place. By exploring the equilibrium impact of biomarkers on prescription choices, drug prices, and health benefits, the analysis improves our understanding of economic regulatory challenges of precision medicine by identifying potential sources of inefficiency.

We consider a market for prescription drugs that is served either by a monopolist or by two producers supplying different, but therapeutically substitutable drugs. A drug producer can only gain access to the market if the health plan is willing to sign a contract with the producer, and these contractual decisions determine which of the drugs can be prescribed by

[2] See for instance the article 'A pharmaceutical firm bets big on a cancer drug' in the Economist, February 24th 2018.

physicians affiliated with the health plan. Both producers can develop a predictive biomarker that, if included in the plan, will inform prescribing physicians about the therapeutic match between the specific drug and the patient. A drug without a biomarker can still be included in the health plan, but physicians then need to rely on the average performance of the drug, as learned from clinical trials and use, when making treatment choices.

We develop a spatial competition framework with up to two drugs available and a distribution of patients who differ with respect to their therapeutic match with each drug. The two drugs represent alternative treatment options, with different active substances and pharmacodynamics. Our model allows these drugs to have different maximum treatment effects (vertical differentiation) and different treatment effects for given patient characteristics (horizontal differentiation). The insurer decides which drugs to include in the plan, based on total costs and expected health outcomes, and affiliated physicians are delegated the task of choosing among the included drugs when receiving a patient. An important feature of our model is the ability of drug producers to develop biomarkers that, in effect, will inform physicians about the therapeutic match between the drug and the patient. We derive the equilibrium drug prices, profits, market shares and expected overall health outcomes with and without biomarkers, which inform us about the incentives to develop predictive biomarkers in the first place. This is done both for the monopoly case and for the therapeutic competition case with two producers.

Our monopoly case confirms an important mechanism already discussed in the literature by showing that the drug producer will not develop a predictive biomarker if the average treatment effect is sufficiently strong. In the absence of a biomarker, drug treatment is prescribed to all patients if the perceived costs of drug treatment do not exceed the health benefit of the average patient in the population. However, in the presence of such predictive biomarkers the drug is prescribed to all patients only if the costs do not exceed the health benefit of the marginal patient with the weakest response. In other words, the introduction of a predictive biomarker test can cause a drop in demand that makes the development of such a test unprofitable for the monopoly producer.

Assuming instead that the expected health benefit of drug treatment is negative, implying that no patients will be prescribed the drug in the absence of patient-specific information about mismatch costs, the only way for the monopolist to gain access to the health plan is to develop a predictive biomarker test that identifies the patients who have a positive health benefit of drug treatment. Although this represents a direct efficiency gain, by ensuring access for responding

patients, we also show that a monopolist with a biomarker will set a price that leads to under-treatment of patients, implying that the efficiency gains of a biomarker test are partly offset by the monopolist's incentives to price the drug excessively high.

By introducing therapeutic competition, we derive two novel sets of results that expand our understanding of the market effects of precision medicine. First, the introduction of biomarkers affects the intensity of price competition between the producers of therapeutically substitutable drugs. If the qualities of the drugs are sufficiently high to ensure a fully covered market, we show that, perhaps surprisingly, biomarkers have an *anti-competitive* effect. With more precise information about the therapeutic match between a drug and the patient, the competing producer needs to offer a larger rebate to switch the physician's prescription choice, thus making drug demand less price elastic when individual mismatch costs for both drugs are observed by the prescribing physician. However, this is no longer true if drug qualities are sufficiently low, such that some patients are left untreated in equilibrium. In this case, we show (in an extension to our main model) that biomarkers have instead a *pro-competitive* effect by making drug demand more price elastic.

Second, we show that better information about each patient's most therapeutically appropriate drug does not necessarily lead to more efficient treatment outcomes. The intuition for this result can be traced back to the distortion in treatment choices caused by the drug producers' incentives to set different prices with a higher price for the high-quality drug, which means that, all else equal, too many patients will be prescribed the cheaper, less efficient drug. By providing more information to prescribers, this distortion might be reinforced by biomarkers via their equilibrium effects on price setting. We show that such an adverse effect of biomarkers on treatment efficiency occurs if the difference in drug quality between the two competing drugs is sufficiently large.

Overall, a key insight from our analysis is that drug producers' incentives for developing biomarker tests rely crucially on market characteristics, and the analysis allows us to identify and explain several possible equilibrium configurations: (i) A biomarker test will never be developed by a monopoly producer of a high-quality drug, since such a test would lead to a drop in demand. (ii) Biomarker tests will always be developed by a monopoly producer of a low-quality drug or by duopoly producers of drugs with relatively high qualities. In the former case, a biomarker test will be introduced because it is the only way to access the market. In the latter case, a biomarker is also necessary for the low-quality producer to gain access to the health plan,

given the presence of a therapeutically substitutable drug of higher quality. However, because of the previously described dampening-of-competition effect, the best response of the high-quality producer is also to develop a biomarker. (iii) Finally, because the effect of biomarkers turns pro-competitive when the market is not fully covered, a biomarker test for only one of the drugs can be an equilibrium outcome in a duopoly with relatively low drug qualities.

The rest of the paper is organised as follows. In the next section, we discuss the existing literature. In Section 3, we present the model. In Section 4, we analyse the monopoly case, characterising pricing, profit, and total health outcomes with and without a predictive biomarker. In Section 5, we characterise the effects of biomarkers under therapeutic competition. In Section 6 we extend the main analysis to a case in which there are untreated patients in equilibrium. Finally, in Section 7 we provide some concluding remarks.

2 Related literature

Due to the heterogeneity of patients and differences in expected treatment effects between available drugs, the spatial framework, combining horizontal and vertical differentiation, has already shown useful in capturing important features of pharmaceutical markets, with respect to both demand-side and supply-side characteristics (see for example Brekke et al., 2007, Miraldo, 2009, Bardey et al., 2010, Bardey et al., 2016, Brekke et al., 2016, Gonzàles et al., 2016, and Brekke et al., 2022). Among these, the general set-up in our paper relates most closely to the spatial formulation in Miraldo (2009) and Brekke et al. (2022). Like Brekke et al. (2022), we allow the health plan to decide on the market access of the drugs, implying that drug producers compete both for the market and on the market. This assumption is of particular importance for our analysis of biomarkers since improved precision affects both access decisions of health plans and inter-brand competition.

In the standard Hotelling model, which has been extensively used in the above referenced literature, the distribution of patients with respect to their matching with different treatment alternatives is one-dimensional. To capture the informational role of predictive biomarkers, we adapt the standard Hotelling model with a two-dimensional treatment preference structure. This allow us to investigate the drug-specific role of predictive biomarkers. In most cases, a biomarker will be verified for a specific treatment option only, without being able to predict treatment outcomes for all other available drugs within the same therapeutic class. If a producer

succeeds in developing a predictive biomarker for its drug, this will not automatically reveal patients' therapeutic match to other treatment options.

The economic literature on biomarkers is still relatively new (see Towse and Garrison, 2013, and Stern et al., 2017, for reviews of economic issues). One of the main questions addressed concerns the regulatory implications of precision medicine. Scott Morton and Seabright (2013) develop a stylised model in which a monopoly drug producer decides whether to include a biomarker test in the early stages of clinical trial for a new drug. When making this choice, the producer faces a trade-off between the increased likelihood of statistically significant trial results and the reduced market size due to exclusion of non-responding patients. The price is exogenous, and they conclude that a form of pay-for-performance contract is needed to stimulate biomarkers.[3]

Antonanza et al. (2015) investigate the incentives of health authorities to use a predictive biomarker to inform treatment choices. Like in our set-up, two treatments are available, and patients differ with respect to which of these gives the best outcome. They show how the incentives to adopt biomarkers depend on the uncertainty (specificity and sensitivity) of the tests. In their model, treatment costs (drug prices) are exogenous, with no strategic market interaction between producers. Antonanza et al. (2018) explore how a health authority should design a pay-for-performance mechanism to provide incentives to develop biomarkers. The drug price is still exogenous, but health authorities can commit to penalties for treated patients not cured. As in our model, they assume that the drug producer has already received approval for the drug (based on efficacy and risk assessment), and that post-approval predictive biomarkers can be explored for increased precision.[4]

Differently from all of the above mentioned papers, our main contribution to a still underdeveloped literature is that we analyse the strategic effects of biomarkers on drug pricing and show how such effects determine the incentives to develop biomarkers in the first place. We also investigate how the effects of biomarkers on overall treatment efficiency might be crucially shaped by strategic effects via the drug producers' pricing incentives, which is another potentially important issue that has been hitherto ignored in the literature.

[3] See Antonanza et al. (2019) for an analysis of price policies to induce the development of biomarkers in the clinical trials (pre-approval).

[4] A common assumption in the literature is that the individual physician is informed by biomarkers, if these are available. In a recent study, Bardey et al. (2021) investigate physicians' incentives to adopt personalised medicine techniques that require costly effort in clinics. In a laboratory experiment conducted with prospective physicians, they find that payment schemes influence the decision to buy diagnostic tests.

Our paper is also related to the wider IO literature on the competitive effects of (supply-side) information provision, including the literature on informative advertising in differentiated markets. The seminal paper by Grossman and Shapiro (1984) show that firms' provision of ads with information about product characteristics improve the matching of products to consumers, but can be excessive from a welfare perspective.[5] They also show that informative advertising intensifies price competition, as it expands the competitive segment of consumers, implying that the firms are better off with a more costly advertising technology. While there are parallels to this literature, our study differs along several dimensions, including the information technology of biomarkers and the presence of an insurer that decides on market access for the drugs based on expected health benefits and costs. There is also a literature on market transparency in differentiated markets (see, for instance, Schultz, 2004). Similarly to our paper, these studies address the competitive effects of improved information. However, this literature is mainly concerned with government-induced market transparency and many of the papers focus on the trade-off between increased demand elasticity and risk of collusion.[6]

3 Model

Consider a therapeutic class with at most two patented drugs, indexed by $i = 1, 2$, and a unit mass of potential patients. Clinical trials that led to the drugs' approval revealed that they are both vertically and horizontally differentiated, implying that health benefits vary both across drugs and across patients. More specifically, we assume that the health benefit of a patient who is treated with drug i is given by $v_i - tx_i$, where v_i is the quality of the drug and x_i is a measure of the therapeutic match between the patient and the drug, such that a lower value of x_i indicates a better therapeutic match between the drug and the patient. We assume that x_i is a patient-specific random draw from a uniform distribution on $[0, 1]$. The relative importance of the horizontal dimension is reflected by the mismatch cost parameter $t > 0$, which therefore measures (inversely) the degree of therapeutic substitutability between the two drugs. We assume, without loss of generality, that $v_1 \geq v_2$, and we will henceforth refer to drug 1 as the high-quality drug.

[5] There is a long list of papers building on Grossman and Shapiro (1984), including Brekke and Kuhn (2006) and Hamilton (2009).

[6] See for instance the early paper by Albæk et al. (1997).

3.1 Physicians

Physicians prescribe what is considered the most appropriate treatment for the individual patient, which is either one unit of one of the available drugs, or no drug treatment at all. When making the prescription decision, the physician takes into account both the patient's health benefit and the drug prices. More specifically, if one unit of drug i is prescribed to a patient with a known mismatch value x_i, the utility assigned to this choice by the prescribing physician is

$$u_i(x_i) = v_i - tx_i - \beta p_i, \tag{1}$$

where p_i is the unit price of drug i. For each patient, the physician will prescribe the drug that yields the highest utility, as specified by (1), but only if this utility is non-negative. Otherwise, no drug treatment is given. The parameter $\beta \in (0, 1]$ measures how sensitive the physician's prescription decision is to the drug price. In the special case of $\beta = 1$, the physician takes drug prices fully into account and acts as a perfect agent for a third-party purchaser that maximises total health benefits net of purchasing costs. However, in the more general case of $\beta < 1$, health benefits are more important than drug prices for the prescribing physician. Notice that our interpretation of β is sufficiently general to incorporate patient copayments, where a higher copayment rate implies a higher value of β.[7]

3.2 Predictive biomarkers

The information available to the prescribing physician depends on whether predictive biomarker tests are developed. Without predictive biomarkers, the treatment choice can only be based on drug specific information, as revealed by the clinical trials. We assume that the clinical trials provide information about the quality of the drug, v_i, and the distribution of patients responses, $x_i \sim U[0, 1]$. In this case, the prescribing physician must base her treatment choice on the expected mismatch cost, which is $t/2$ for all patients. Thus, in the absence of predictive biomarkers, all patients get the same treatment, either drug 1 or drug 2, depending on quality differences relative to price differences between the two drugs.

On the other hand, if predictive biomarkers are available, the treatment choice can be person-

[7] Consider a patient who is prescribed drug i and pays σp_i, where $\sigma \in (0, 1)$ is the copayment rate. The utility associated with this prescription choice is $v_i - \sigma p_i - tx_i$ from a patient perspective and $v_i - p_i - tx_i$ from a third-party purchaser perspective. If the prescribing physician maximises a weighted average of patient utility and purchaser utility, with a weight α given to the latter, the resulting physician payoff function is identical to (1) for $\beta := \alpha(1 - \sigma) + \sigma$, implying that β is increasing in the copayment rate (σ) and in the weight given to purchaser utility (α).

alised, based on the patient-specific information revealed by the test results. More specifically, we assume that a predictive biomarker test developed for drug i reveals the mismatch value x_i for each patient, implying that the physician learns each patient's exact therapeutic match with drug i.

3.3 The objectives of pharmaceutical firms and insurer

Each drug is produced by a profit-maximising firm. The payment for drug i includes the per-unit price p_i. Assuming a constant marginal cost of drug production, equal for both drugs and normalised to 0, the profit of producer i is given by

$$\pi_i = p_i y_i, \tag{2}$$

where y_i is the demand for drug i, which is derived from drug prescription decisions that maximise (1) for each patient.

The available number of drugs for prescribing physicians are determined by a monopoly purchaser (health plan) who decides whether to include one or both (or potentially no) drugs in its health plan. The objective of the health plan is to maximise its surplus, defined as total health benefits net of drug payments.

The total health benefits and health plan surplus depend on the number of drugs included in the plan. Generally, total health benefits are given by

$$H = \sum_i \left(\int_0^1 (v_i - t x_i) \, f_i(x_i) \, dx_i \right), \tag{3}$$

where f_i is the density of patients with mismatch value x_i being prescribed drug i, such that

$$y_i = \int_0^1 f_i(x_i) \, dx_i. \tag{4}$$

The health plan's total surplus is then given by

$$S = H - \sum_i p_i y_i. \tag{5}$$

3.4 Timing

We consider a game with the following timing:

1. The drug producers simultaneously and non-cooperatively decide whether or not to develop a biomarker test.

2. The drug producers simultaneously and non-cooperatively submit prices p_i.

3. The insurer decides whether to include one or both drugs in the health plan (or none of the drugs if a positive surplus cannot be achieved).

4. Each patient is prescribed a drug from the available choice set (or no prescription if drug treatment does not yield a positive utility).

We assume that each producer commits to a price that is not renegotiable and that is unconditional on the inclusion decisions by the purchaser. As usual, the game is solved by backwards induction to find the subgame perfect Nash equilibrium.

4 Monopoly

We start out by considering the case of a monopoly market, where only one drug exists. Alternatively, we can interpret this case as the quality difference between the two drugs being so large that therapeutic competition is infeasible, effectively turning the market into a monopoly for the high-quality drug. The monopoly producer's problem is to maximise profits under the constraint that the purchaser's surplus is non-negative. The solution to this problem depends on whether or not a predictive biomarker test is developed.

4.1 No biomarker test

Without a predictive biomarker test, the expected mismatch cost is $t/2$ for all patients, which implies that the physician will make the same prescription choice for all patients; the drug is either prescribed to everybody or to nobody. Demand for the drug, if it is included in the health plan, is therefore given by[8]

$$y^N = \begin{cases} 0 & if \quad v - \frac{t}{2} - \beta p < 0 \\ 1 & if \quad v - \frac{t}{2} - \beta p \geq 0 \end{cases}. \tag{6}$$

[8] In monopoly, we use superscripts T and N to distinguish the cases where the drug comes with a biomarker test or not, respectively. Furthermore, to save notation, we drop the drug indicator i on all variables in the monopoly case.

If the drug is prescribed to all patients, the total health benefits are given by

$$H^N = \int_0^1 (v - tx)\, dx = v - \frac{t}{2}. \tag{7}$$

The health plan's surplus is therefore

$$S^N = \begin{cases} 0 & if \quad v - \frac{t}{2} - \beta p < 0 \\ v - \frac{t}{2} - p & if \quad v - \frac{t}{2} - \beta p \geq 0 \end{cases}. \tag{8}$$

Suppose that $v > t/2$, so that $H^N > 0$. When solving its profit-maximisation problem, the producer is constrained by the condition that the offered price must give the health plan a non-negative surplus (i.e., $S^N \geq 0$). Since $\beta \leq 1$, it is straightforward to conclude that the producer can extract the entire surplus of the health plan and still have non-negative demand for the drug. Thus, the condition $S^N \geq 0$ binds at the optimum and the profit-maximising monopoly price is given by

$$p^N = v - \frac{t}{2}, \tag{9}$$

which yields $y^N = 1$ and therefore a monopoly profit of

$$\pi^N = v - \frac{t}{2}. \tag{10}$$

If instead $v < t/2$, so that $H^N = 0$, the drug will not be included in the health plan in the absence of a predictive biomarker test. But regardless of whether the drug is included ($v \geq t/2$) or not ($v < t/2$), the health plan is left with zero surplus, i.e., $S^N = 0$.

Whether or not the absence of a biomarker test leads to efficient treatment decisions depend on the quality of the drug. For sufficiently high drug quality, $v \geq t$, the efficient outcome is that all patients are treated, which is indeed the outcome for $v \geq t$ in the absence of a biomarker test. However, if drug quality is lower, $v < t$, the efficient outcome is that some patients (those with higher mismatch costs) are left untreated, since the treatment effect, $v - tx$, is negative for patients with mismatch values sufficiently close to one. In this case, the absence of a predictive biomarker test implies that either too many or too few patients are treated. All patients are treated if $v \in \left[\frac{t}{2}, t\right)$, which implies overtreatment, while no patients are treated if $v < t/2$, which implies undertreatment.

We summarise the possible outcomes, and their efficiency properties, as follows:[9]

Proposition 1 *Consider a monopoly producer of a drug without a predictive biomarker test.*

(i) If $v < t/2$, this drug will not be included in the health plan, which implies that patients are undertreated.

(ii) If $v \geq t/2$, the drug will be included in the health plan, and the physicians' prescription choices lead to overtreatment if $t/2 \leq v < t$ and efficient treatment if $v \geq t$.

4.2 Biomarker test

If a predictive biomarker test is developed, the physician will be able to personalise the treatment choice to each individual patient, depending on the therapeutic match revealed by the test, and drug treatment will be offered if the value of the patient's treatment effect $(v - tx)$ exceeds the perceived treatment cost (βp). Since x is uniformly distributed on $[0, 1]$, total drug demand is given by

$$y^T = \min\left\{\frac{v - \beta p}{t}, 1\right\}, \tag{11}$$

which yields a total health benefit of

$$H^T = \int_0^{y^T} (v - tx)\, dx = \begin{cases} \frac{(v-\beta p)(v+\beta p)}{2t} & if \quad p < \frac{v-t}{\beta} \\ v - \frac{t}{2} & if \quad p \geq \frac{v-t}{\beta} \end{cases}, \tag{12}$$

and a total surplus for the health plan of

$$S^T = \begin{cases} \frac{(v-(2-\beta)p)(v-\beta p)}{2t} & if \quad p < \frac{v-t}{\beta} \\ v - \frac{t}{2} - p & if \quad p \geq \frac{v-t}{\beta} \end{cases}. \tag{13}$$

The profit-maximising price is either an interior solution where the price is so high that some patients are not treated $(y^T < 1)$ or a corner solution in which physicians prescribe the drug to all patients $(y^T = 1)$. In addition to the physicians' prescription choices, the monopoly producer must also take into account the participation constraint of the health plan, $S^T \geq 0$, when setting the drug price. When considering both types of potential corner solutions, stemming from the prescription decisions and from the participation constraint of the purchaser, it can be shown

[9] The results in Proposition 1 follow directly from the previous analysis and a formal proof is thus omitted.

(see Appendix A for details) that the optimal price is given by

$$p^T = \begin{cases} \frac{v}{2\beta} & if \quad v \leq 2t \text{ and } \beta > \frac{2}{3} \\ \frac{v}{2-\beta} & if \quad v \leq 2t \text{ and } \frac{2(v-t)}{2v-t} < \beta \leq \frac{2}{3}, \\ \frac{v-t}{\beta} & if \quad v > 2t \text{ and } \beta > \frac{2(v-t)}{2v-t}, \\ v - \frac{t}{2} & if \quad \beta \leq \frac{2(v-t)}{2v-t}, \end{cases} \tag{14}$$

The corresponding demand for the drug is given by

$$y^T = \begin{cases} \frac{v}{2t} & if \quad v \leq 2t \text{ and } \beta > \frac{2}{3}, \\ \frac{2(1-\beta)v}{(2-\beta)t} & if \quad v \leq 2t \text{ and } \frac{2(v-t)}{2v-t} < \beta \leq \frac{2}{3}, \\ 1 & if \quad v > 2t \text{ or } \beta \leq \frac{2(v-t)}{2v-t}. \end{cases} \tag{15}$$

We see that a corner solution, in which all patients are prescribed the drug, requires either that drug quality is sufficiently high ($v > 2t$) or that physicians' prescription choices are sufficiently insensitive to changes in the drug price ($\beta < 2\left(v-t\right)/\left(2v-t\right)$). In the former case, the profit-maximising price is set such that physicians are indifferent between prescribing the drug or not to the patients with highest mismatch costs ($x = 1$). In the latter case, the optimal price is set such that the purchaser is indifferent between including the drug or not in the health plan.

The producer's profits and health plan's surplus in the monopoly solution are given by, respectively,

$$\pi^T = \begin{cases} \frac{v^2}{4t\beta} & if \quad v \leq 2t \text{ and } \beta > \frac{2}{3} \\ \frac{2v^2(1-\beta)}{t(2-\beta)^2} & if \quad v \leq 2t \text{ and } \frac{2(v-t)}{2v-t} < \beta \leq \frac{2}{3} \\ \frac{v-t}{\beta} & if \quad v > 2t \text{ and } \beta > \frac{2(v-t)}{2v-t} \\ v - \frac{t}{2} & if \quad \beta \leq \frac{2(v-t)}{2v-t} \end{cases} \tag{16}$$

and

$$S^T = \begin{cases} \frac{v^2(3\beta-2)}{8t\beta} & if \quad v \leq 2t \text{ and } \beta > \frac{2}{3} \\ 0 & if \quad v \leq 2t \text{ and } \frac{2(v-t)}{2v-t} < \beta \leq \frac{2}{3} \\ \frac{(2-\beta)t-2(1-\beta)v}{2\beta} & if \quad v > 2t \text{ and } \beta > \frac{2(v-t)}{2v-t} \\ 0 & if \quad \beta \leq \frac{2(v-t)}{2v-t} \end{cases}. \tag{17}$$

When a biomarker test is available, the profit-maximising price is always set such that drug prescription decisions are characterised by either efficient treatment or undertreatment of patients. If $v \geq t$, the efficient outcome is that all patients are treated, which happens only

in a corner solution with $y^T = 1$, but this requires that the drug quality is sufficiently high or that the price sensitivity of drug prescription choices is sufficiently low. Otherwise, $y^T < 1$ and too few patients are treated. On the other hand, if $v < t$, the efficient outcome is that some patients are left untreated. From (15) it is indeed evident that $y^T < 1$ if $v < t$. However, it is easily confirmed that the price is always set such that too few patients are treated. Thus, in contrast to the case of no biomarker test, overtreatment never occurs.

We summarise the outcome and its efficiency properties as follows:[10]

Proposition 2 *Consider a monopoly producer of a drug with a predictive biomarker test.*

(i) The drug will be included in the health plan for all $v > 0$.

(ii) If $v < t$, too few patients are treated.

(iii) If $v \geq t$, treatment decisions are efficient if $v \geq 2t$ or if $\beta < 2(v-t)/(2v-t)$; otherwise, too few patients are treated.

4.3 Incentives to develop a biomarker test

At the first stage of the game, the monopoly drug producer decides whether or not to launch the drug along with a predictive biomarker test, anticipating how the presence or absence of such a test affects physicians' treatment decisions. Abstracting from development costs, suppose, for simplicity, that such a test will be developed as long as profits are strictly higher with than without a biomarker test. The subgame perfect Nash equilibrium outcome, and its efficiency properties, are then characterised as follows:[11]

Proposition 3 *Consider a monopoly producer of a patented drug.*

(i) If $v < t/2$, the monopoly producer develops a predictive biomarker test and the drug is included in the health plan, but the drug price is such that too few patients are treated.

(ii) If $v \geq t/2$, the monopoly producer chooses not to develop a predictive biomarker test but the drug is still included in the health plan. Too many patients are treated if $t/2 \leq v < t$, while treatment decisions are efficient if $v \geq t$.

In order to understand the intuition behind this equilibrium outcome, consider first the case of $v \geq t/2$. In this case, the key effect of a predictive biomarker test is that it makes prescription choices more sensitive to drug prices, all else equal. In the absence of such a test, and for a

[10] The proof of Proposition 2 is given in Appendix B.

[11] The proof of Proposition 3 is given in Appendix B.

given drug price, drug treatment is prescribed to all patients as long as the perceived costs of drug treatment, βp, do not exceed the health benefit of the *average patient* in the population, given by $v - t/2$. However, in the presence of such a test, the drug is prescribed to all patients only if the costs do not exceed the health benefit of the *marginal patient*, which is lower and given by $v - t$. As long as β is sufficiently high, the profit-maximising price in the absence of a predictive biomarker test is too high to yield full market coverage in the presence of such a test. In other words, the introduction of a predictive biomarker test causes a drop in demand that makes the development of such a test unprofitable for the monopoly producer. On the other hand, if β is so low that the monopoly price is set such that the participation constraint of the health plan binds, demand is the same with and without a predictive biomarker test and developing such a test yields no additional profits. Thus, for $v \geq t/2$, the producer chooses not to develop a biomarker test and the resulting treatment efficiency is given by Proposition 1.

The monopoly producer's incentives are very different if $v < t/2$. In this case, the expected health benefit of drug treatment for a randomly chosen patient is negative, implying that no patients will be prescribed the drug in the absence of patient-specific information about mismatch costs. Thus, the only way for the monopolist to gain access to the market is to develop a predictive biomarker test that can identify the patients who have a positive health benefit of drug treatment. Thus, for $v < t/2$, the producer chooses to develop a biomarker test and the resulting treatment efficiency is given by Proposition 2. Notice that the availability of a biomarker test in this case constitutes a Pareto improvement. The producer benefits from such a test since it helps gaining access to the market, treatment inefficiency is reduced, and the health plan also benefits if drug prescription choices are sufficiently price sensitive, as seen by (17).

5 Therapeutic competition

Suppose now that the health plan has the possibility of including two therapeutically substitutable drugs, with drug 1 being the high-quality drug (i.e., $\Delta v := v_1 - v_2 \geq 0$), and where each patient is characterised by a pair of mismatch costs for the two drugs, tx_1 and tx_2, where x_1 and x_2 are independent draws from a uniform distribution on $[0, 1]$. In this setting, drug pricing involves two types of competition: (i) competition for access to the health plan, and (ii) competition for patients in case both drugs are included in the plan.

In order to facilitate the analysis, we henceforth make the following two assumptions:

A1 $v_i \gg t$, $i = 1, 2$.

A2 $\Delta v < t$.

The first assumption is that drug quality is sufficiently high (for both drugs) such that all patients are given drug treatment in equilibrium. Formally, this requires that $v_i - \beta p_i - t > 0$, $i = 1, 2$, which holds in equilibrium if v_i is sufficiently high. The second assumption is that the drug quality difference is sufficiently low such that the efficient treatment outcome is that each drug has positive prescription volumes. Taken together, these assumptions mean that the question of treatment efficiency is not about whether patients are treated or not, but rather a question of whether each patient is prescribed the most appropriate drug. The first assumption also means that we are now considering the case in which drug producers have no incentives to develop a predictive biomarker test if they are in a monopoly position (cf. Proposition 3). As the subsequent analysis will reveal, these incentives are changed in the presence of therapeutic competition.

5.1 Pricing subgame

There are three different versions of the pricing subgame, depending on whether a predictive biomarker test has been developed by both producers, by only one producer, or by none of the producers. We will consider each case in turn.

5.1.1 No biomarker test

If none of the two drugs come with predictive biomarkers, the expected mismatch cost of each patient, for each drug, is $t/2$. The physician's prescription choice can then only be based on quality levels and prices. Suppose that both drugs are included in the health plan, and define the price difference between the high- and low-quality drugs by $\Delta p := p_1 - p_2$. Since the expected health benefit of prescribing drug i is the same for all patients, and given by $v_i - (t/2)$, the physician will prescribe drug 1 (drug 2) to all patients if $\Delta v \geq (<)\, \beta \Delta p$. This dichotomous nature of the optimal prescription choices implies that the availability of therapeutic substitutes does not enlarge the health plan's surplus if predictive biomarkers are not available. Consequently,

the health plan will only include one drug and chooses drug i if

$$p_i \leq p_j + v_i - v_j, \quad i, j = 1, 2; \quad i \neq j. \tag{18}$$

Because of drug quality differences, the producer of the high-quality drug can always ensure that it wins the competition for access by setting a sufficiently low price (that still yields positive profits for the producer). From (18), a price equal to the quality difference between the two drugs is sufficient to win the competition for access. However, the optimal price is constrained by a price ceiling determined by the health plan's break-even price at $v_1 - (t/2)$. The Nash equilibrium at the price bidding stage is thus given by[12]

$$p_1^{NN} = \min\left\{\Delta v, v_1 - \frac{t}{2}\right\} \quad \text{and} \quad p_2^{NN} = 0, \tag{19}$$

and only drug 1 is included in the health plan. Since the winning bid is a price less than the expected health benefit of drug treatment for each patient, the high-quality drug's demand is given by $y_1^{NN} = 1$, and equilibrium profits are given by

$$\pi_1^{NN} = \min\left\{\Delta v, v_1 - \frac{t}{2}\right\} \quad \text{and} \quad \pi_2^{NN} = 0. \tag{20}$$

The total expected health benefit in this equilibrium is given by

$$H^{NN} = v_1 - \frac{t}{2}, \tag{21}$$

and total expected surplus of the health plan is

$$S^{NN} = v_1 - \frac{t}{2} - \min\left\{\Delta v, v_1 - \frac{t}{2}\right\} \geq 0 \tag{22}$$

Although the absence of biomarker tests leads to a *de facto* monopoly outcome where only the high-quality drug gains access to the market, this equilibrium is different from the previously derived monopoly equilibrium in two different dimensions. First, the presence of two therapeutic substitutes creates competition for access to the health plan, which leads to lower drug prices and thus a positive surplus for the health plan, as long as the quality difference between the

[12] Under therapeutic competition, we use superscripts NN, TN, NT and TT to distinguish cases in which a biomarker test is developed by, respectively, no firm, firm 1, firm 2, or both firms.

two drugs is sufficiently low. In contrast, a monopoly producer of a drug without therapeutic substitutes is always able to extract the entire surplus from the health plan in the absence of a biomarker test.

Second, the existence of a therapeutic substitute means that total health benefits can be increased if the two drugs are optimally allocated across the patient population. More precisely, under assumption A2, total health benefits are maximised by giving the high-quality drug to some patients and the low-quality drug to others, depending on relative mismatch costs. Consider patients with a mismatch value x_i for drug i. Among these patients, optimal drug allocation implies that the ones with mismatch values for drug j given by $x_j > x_i - (v_i - v_j)/t$ should be prescribed drug i, whereas the remaining ones should be prescribed drug j. Thus, maximum total health benefits, denoted by H^* and induced by optimal drug allocation, are given by

$$\begin{aligned} H^* &= \int_0^{\frac{\Delta v}{t}} (v_1 - tx_1)\, dx_1 + \int_{\frac{\Delta v}{t}}^1 \left(\int_{x_1 - \frac{\Delta v}{t}}^1 dx_2 \right) (v_1 - tx_1)\, dx_1 \\ &\quad + \int_0^{1-\frac{\Delta v}{t}} \left(\int_{x_2 + \frac{\Delta v}{t}}^1 dx_1 \right) (v_2 - tx_2)\, dx_2 \qquad (23) \\ &= \overline{v} - \frac{t}{3} + \frac{(\Delta v)^2 (3t - \Delta v)}{6t^2}. \end{aligned}$$

By comparing (21) and (23), it is easily confirmed that $H^* > H^{NN}$. In other words, including only the high-quality drug in the health plan implies a suboptimal drug allocation across patients, since some patients with high mismatch costs for drug i would have been better off with drug j, if they had access to this drug.

We summarise the equilibrium outcome in case of no biomarkers as follows:[13]

Proposition 4 *Suppose that a biomarker test does not exist for any of the two drugs.*

(i) Only the high-quality drug will be included in the health plan.

(ii) The allocation of drugs across patients leads to higher treatment mismatch costs than what is socially efficient.

5.1.2 Only one drug with a biomarker test

If producer i develops a biomarker test, the physician learns the therapeutic match between drug i and the patient. Suppose that both drugs are included in the health plan (the condition

[13] The results in Proposition 4 follow directly from the previous analysis and a formal proof is thus omitted.

for this to be an equilibrium outcome will be derived later). The utility from prescribing drug i, with a certain treatment effect, must then be compared with expected treatment outcome from prescribing drug j. Consider a patient whose mismatch value with respect to drug i is found to be x_i. This patient will be prescribed drug i if $v_i - \beta p_i - t x_i > v_j - \beta p_j - (t/2)$. Let $\widehat{x}_i$ denote the mismatch value for the patient whose physician is indifferent between prescribing drug i and drug j, given by

$$\widehat{x}_i = \frac{1}{2} + \frac{v_i - v_j - \beta\left(p_i - p_j\right)}{t}, \quad i, j = 1, 2, \quad i \neq j. \tag{24}$$

Since x_i is uniformly distributed on $[0, 1]$, demand for drugs i and j are given by $y_i = \widehat{x}_i$ and $y_j = 1 - \widehat{x}_i$, respectively. An intriguing implication of this is that demand for the two drugs is the same, regardless of whether the biomarker test applies to the high-quality or the low-quality drug. In either case, demand for the two drugs are given by

$$y_1^{TN} = y_1^{NT} = \frac{1}{2} + \frac{\Delta v - \beta \Delta p}{t} \quad \text{and} \quad y_2^{TN} = y_2^{NT} = \frac{1}{2} - \left(\frac{\Delta v - \beta \Delta p}{t}\right). \tag{25}$$

When each producer chooses its price to maximise profits, the Nash equilibrium prices are given by

$$p_1^{TN} = p_1^{NT} = \frac{t}{2\beta} + \frac{\Delta v}{3\beta} \quad \text{and} \quad p_2^{TN} = p_2^{NT} = \frac{t}{2\beta} - \frac{\Delta v}{3\beta}. \tag{26}$$

As expected, the high-quality drug is more expensive than the low-quality drug, and the equilibrium price difference is increasing in the quality difference between the two drugs. The resulting equilibrium profits for the two producers are given by

$$\pi_1^{TN} = \pi_1^{NT} = \frac{(3t + 2\Delta v)^2}{36t\beta} \quad \text{and} \quad \pi_2^{TN} = \pi_2^{NT} = \frac{(3t - 2\Delta v)^2}{36t\beta}. \tag{27}$$

If the biomarker test applies to drug i, notice that all patients with a mismatch value for drug i such that $x_i \leq \widehat{x}_i$ will be prescribed drug i, where $\widehat{x}_i$ is given by (24). The remaining $1 - \widehat{x}_i$ patients will be prescribed drug j. Since x_i and x_j are independent draws from a uniform distribution, this means that the value of x_j for the $1 - \widehat{x}_i$ patients who are prescribed drug j is a random draw from $U \sim [0, 1]$. Thus, if the biomarker applies to drug i, total health benefits are given by

$$H^{TN} = H^{NT} = \int_0^{\widehat{x}_i} \left(v_i - ts\right) ds + \int_0^1 \left(v_j - ts\right)\left(1 - \widehat{x}_i\right) ds \tag{28}$$

Furthermore, since $\widehat{x}_j = 1 - \widehat{x}_i$, the health benefits are the same, regardless of which drug that comes with a biomarker. Evaluated at the equilibrium prices, these health benefits are given by

$$H^{TN} = H^{NT} = \overline{v} - \frac{3t}{8} + \frac{5\left(\Delta v\right)^2}{18t}, \tag{29}$$

where $\overline{v} := \left(v_1 + v_2\right)/2$ is the average drug quality. The total surplus of the health plan, when both drugs are included and one of them comes with a predictive biomarker test, is given by

$$S^{TN} = S^{NT} = \overline{v} - \frac{\left(4 + 3\beta\right)t}{8\beta} + \frac{\left(\Delta v\right)^2\left(5\beta - 4\right)}{18\beta t}. \tag{30}$$

The next proposition provides the condition for the above derived outcome to constitute a subgame perfect Nash equilibrium in the subgame that starts at the pricing stage, as well as a characterisation of its efficiency properties.

Proposition 5 *Suppose that a biomarker test exists for one of the two drugs.*

(i) Both drugs will be included in the health plan, with equilibrium drug prices given by (26), if the average drug quality is sufficiently high and if $\beta > \left(8\Delta v\right)/\left(3t + 10\Delta v\right)$.

(ii) Compared to the case of no biomarkers, this outcome leads to more (less) efficient treatment choices if $\Delta v < (>)\left(3/10\right)t$.

The most noteworthy feature of this equilibrium is that the additional patient information obtained through a biomarker test for one of the drugs does not necessarily translate into more efficient treatment choices, compared with the case where no such information is available. There are two counteracting effects here. The additional patient information obtained through a biomarker test implies that both drugs are included in the health plan. Suppose that $\Delta v = 0$, which implies $\Delta p = 0$ in equilibrium. In this case, prescription choices would be purely based on quality differences and expected differences in mismatch costs. Inclusion of a second drug would then unambiguously lead an overall improvement in the therapeutic match between drugs and patients, thus bringing the treatment outcome closer to the efficient solution. Comparing (21) and (29), we see that, for $\Delta v = 0$, inclusion of the second drug would increase total health benefits from $\overline{v} - (t/2)$ to $\overline{v} - (3t/8)$. Since patient information is not perfect (since only one biomarker test is available), the total health benefits are in this case still lower than the maximum level, which from (23) is given by $\overline{v} - (t/3)$.

However, if $\Delta v > 0$, prescription choices would also depend on relative drug prices when

both drugs are included in prescription choice set. All else equal, this creates a distortion in the prescription choices where too many patients are prescribed the low-quality drug because it is cheaper. Since Δp is monotonically increasing in Δv, this price distortion effect increases with the quality difference between the two drugs. Thus, if Δv is above a threshold level, given by $(3/10)\,t$, the price distortion effect dominates the effect of improved patient information, leading to an overall reduction in total health benefits.

5.1.3 Both drugs with biomarker tests

Suppose now that both drugs come with a predictive biomarker test, which implies that each patient's pair of mismatch values, x_1 and x_2, can be observed by the prescribing physician. In order to derive drug demand in this case of perfect patient information, consider a patient with a mismatch value for drug 1 equal to x_1. This patient will be prescribed drug 1 if the same patient's mismatch value for drug 2 satisfies the inequality $x_2 > x_1 - (\Delta v - \beta \Delta p)/t$. Thus, the probability that a patient with a mismatch value x_1 will be prescribed drug 1 is

$$\min\left\{\int_{x_1-(\Delta v-\beta\Delta p)/t}^{1} dx_2, 1\right\} = \min\left\{\left(1 + \frac{\Delta v - \beta \Delta p}{t} - x_1\right), 1\right\}. \tag{31}$$

Suppose that $\Delta v - \beta \Delta p > 0$ (which we will subsequently confirm holds in the Nash equilibrium of the pricing game). The density of patients being prescribed drug 1, as a function of x_1, is then given by

$$f_1(x_1) = \begin{cases} 1 & if \quad x_1 \leq \frac{\Delta v - \beta \Delta p}{t} \\ 1 + \frac{\Delta v - \beta \Delta p}{t} - x_1 & if \quad x_1 > \frac{\Delta v - \beta \Delta p}{t} \end{cases}. \tag{32}$$

By a similar logic, the density of patients being prescribed drug 2, as a function of x_2, is given by

$$f_2(x_2) = \begin{cases} 1 - \frac{(\Delta v - \beta \Delta p)}{t} - x_2 & if \quad x_2 \leq 1 - \frac{\Delta v - \beta \Delta p}{t} \\ 0 & if \quad x_2 > 1 - \frac{\Delta v - \beta \Delta p}{t} \end{cases}. \tag{33}$$

Total demand for each of the two drugs is then given by

$$y_1^{TT} = \int_0^1 f_1(x_1)\, dx_1 = \frac{1}{2} + \left(\frac{\Delta v - \beta \Delta p}{t}\right) - \frac{1}{2}\left(\frac{\Delta v - \beta \Delta p}{t}\right)^2 \tag{34}$$

and

$$y_2^{TT} = \int_0^1 f_2(x_2)\, dx_2 = \frac{1}{2} - \left(\frac{\Delta v - \beta \Delta p}{t}\right) + \frac{1}{2}\left(\frac{\Delta v - \beta \Delta p}{t}\right)^2. \tag{35}$$

Notice that positive demand for both drugs requires $\Delta v - \beta \Delta p < t$, which always holds in equilibrium under assumption A2.

By maximising the profit of each producer with respect to its drug price, and solving the corresponding set of first-order conditions, we derive the following Nash equilibrium prices:

$$p_1^{TT} = \frac{3\phi - 5\left(t - \Delta v\right)}{8\beta} \quad \text{and} \quad p_2^{TT} = \frac{\phi + t - \Delta v}{8\beta}, \tag{36}$$

where

$$\phi := \sqrt{9t^2 - \Delta v\left(2t - \Delta v\right)} \in \left(2\sqrt{2}t, 3t\right) \text{ for } \Delta v \in (0, t)\,. \tag{37}$$

This equilibrium is derived under the assumption that $\Delta v - \beta \Delta p > 0$, which, when evaluated at the candidate equilibrium prices, translates to

$$\Delta v - \beta \Delta p^{TT} = \frac{3t + \Delta v - \phi}{4} > 0. \tag{38}$$

Since $\phi \leq 3t$, this condition always holds for $\Delta v > 0$. We can also easily confirm that, as expected, the drug with higher quality has the higher price in equilibrium:

$$\Delta p^{TT} = \frac{\phi - 3\left(t - \Delta v\right)}{4\beta} > 0 \text{ for } \Delta v \in (0, t)\,. \tag{39}$$

The profits of each producer are given by, respectively,

$$\pi_1^{TT} = \frac{\left(22t^2 + 2\left(2t - \Delta v\right)\Delta v - 2\left(t - \Delta v\right)\phi\right)\left(3\phi - 5\left(t - \Delta v\right)\right)}{256\beta t^2} \tag{40}$$

and

$$\pi_2^{TT} = \frac{\left(t - \Delta v + \phi\right)^3}{256\beta t^2}. \tag{41}$$

The total health benefits are given by

$$H^{TT} = \sum_{i=1}^{2} \int_0^1 \left(v_i - t x_i\right) f_i\left(x_i\right) dx_i, \tag{42}$$

where $f_i\left(x_i\right)$ is given by (32)-(33) for $i = 1, 2$. Evaluated at the equilibrium prices, the health benefits are given by

$$H^{TT} = \overline{v} - \frac{t}{3} + \frac{\Delta v\left(3t + \Delta v - \phi\right)\left(7t - \Delta v + \phi\right)}{48t^2}. \tag{43}$$

Finally, total surplus for the health plan, in equilibrium, is given by

$$S^{TT} = \overline{v} - \frac{\Delta v\,(4\beta - 3)\,(t\,(2\phi - 3\Delta v) - \Delta v\,(\phi - \Delta v)) + t^2\,(33\phi - (51 - 32\beta)\,t + 3\,(15 - 8\beta)\,\Delta v)}{96t^2\beta}. \tag{44}$$

Existence conditions and key properties of the above derived Nash equilibrium are given by the following proposition:

Proposition 6 *Suppose that each of the two drugs has a predictive biomarker test.*

(i) Both drugs will be included in the health plan, with equilibrium drug prices given by (36), if the average drug quality is sufficiently high and β is above some threshold level.

(ii) Compared to the case where only one of the two drugs has a biomarker test, drug prices are higher while treatment choices are more (less) efficient if the drug quality difference is sufficiently low (high).

When we compare the effect of introducing a second biomarker test on the equilibrium outcome, two striking results appear. First, equilibrium drug prices are higher when both drugs have predictive biomarker tests, as long as $\Delta v > 0$. This means, perhaps surprisingly, that increased information about the therapeutic match between patients and drugs has a dampening effect on price competition. This result is caused by the fact that drug demand is less price elastic when individual mismatch costs for both drugs are observed by the prescribing physician. In the case where only one of the drugs, say drug i, has a biomarker test, every patient with an observed mismatch value for drug i given by

$$x_i \leq \frac{1}{2} + \frac{v_i - v_j - \beta\,(p_i - p_j)}{t}$$

will be prescribed drug i, while the remaining patients will be prescribed drug j. In other words, for a certain value of x_i, the density of patients being prescribed drug i is either zero ore one. A marginal increase in the price of drug i will reduce the prescription threshold value of x_i by β/t, and since this threshold is the same for all patients, and the patient distribution of x_i has density equal to one, the corresponding demand reduction for drug i is β/t. On the other hand, if the prescribing physician can observe both x_i and x_j, two different patients with the same value of x_i might be prescribed different drugs. More precisely, there is a range of x_i-values defined by $(\underline{x}_i, \overline{x}_i)$ where, for each $x_i \in (\underline{x}_i, \overline{x}_i)$, a share of patients is prescribed drug i while the remaining share is prescribed drug j. In this case, the effect of a marginal increase in the price

of drug i is that, for each $x_i \in (\underline{x}_i, \overline{x}_i)$, the share of patients being prescribed drug i reduces by β/t, and the corresponding reduction in total demand for drug i is this share reduction, β/t, summed over all $x_i \in (\underline{x}_i, \overline{x}_i)$. If the two drugs have equal quality, $\Delta v = 0$, then $\underline{x}_i = 0$ and $\overline{x}_i = 1$, as can be seen from the density functions in (32)-(33). In this case, the total demand reduction caused by a marginal price increase is β/t, which is similar to the case of only one biomarker. However, as long as $\Delta v > 0$, then $\overline{x}_i - \underline{x}_i < 0$ and the demand reduction caused by a marginal price increase is strictly less than β/t. Thus, the demand of each drug is less price responsive when both drugs have biomarker tests, which in turn leads to higher prices in equilibrium.[14]

The other eye-catching result is that better information about each patient's most therapeutically appropriate drug does not necessarily lead to a more efficient treatment outcome. More specifically, the improved patient information gained by a second biomarker test reduces total health benefits if the quality difference between the two drugs is sufficiently large. This result is similar to the one obtained when comparing the equilibrium outcome under no and one biomarker test, respectively (cf. Proposition 5), and is once more caused by the presence of two different distortionary effects. First, if only one of the drugs in the health plan has a biomarker test, drug allocation is suboptimal because of a lack of information about patients' mismatch costs for the drug without a biomarker test. More precisely, if only drug i has a biomarker test, and both drugs are equally expensive, too many (few) patients with low (high) values of x_i are being prescribed drug i, leading to suboptimally high mismatch costs. Second, a distortion in drug allocation is also caused by the drug producers' incentives to set different prices, with a higher price for the high-quality drug, which means that, all else equal, too many patients will be prescribed the cheaper low-quality drug. Although the first distortionary effect is removed by going from one to two biomarker tests, the second distortion related to drug price differences is *reinforced*. This can be seen by comparing the equilibrium price differences in the two cases, which, from (26) and (39), yields

$$\Delta p^{TT} - \Delta p^{TN} = \frac{\Delta v + 3\phi - 9t}{12\beta} > 0 \text{ for } \Delta v \in (0, t)\,. \tag{45}$$

[14] Using (34)-(35), the price responsiveness of demand for drug i is

$$\frac{\partial y_i^{TT}}{\partial p_i} = -\left(\frac{\beta}{t} - \frac{\beta}{t^2}\left|\Delta v - \beta \Delta p\right|\right), \quad i = 1, 2.$$

Thus, a second biomarker test increases the equilibrium price difference between the drugs, and more so the larger the difference in drug quality. If Δv is sufficiently large, the increased distortion caused by a larger drug price difference more than outweighs the effect of improved patient information, causing an overall reduction in patients' health benefits.

5.2 Incentives to develop biomarker tests

What are the incentives to develop biomarker tests when each producer faces competition from a producer of a therapeutic substitute? Once more ignoring the cost of developing a biomarker test, a comparison of producer profits across the previously analysed cases yields the following result:

Proposition 7 *Consider a game between the producers of two therapeutically substitutable drugs. If the average drug quality is sufficiently high, and if demand responds sufficiently strongly to drug prices, the unique subgame perfect Nash equilibrium is that both producers develop a predictive biomarker test, with drug prices and total health benefits given by (36) and (43), respectively.*

The key insight from this analysis is that, in contrast to the case of a monopoly drug producer, therapeutic competition yields strong incentives for the competing producers to develop predictive biomarker tests. The producer of the high-quality drug might prefer a scenario without any biomarkers, since this will help gaining the producer monopoly access to the health plan. However, this is never an equilibrium outcome, since the producer of the low-quality drug has an incentive to develop a biomarker test in order to gain access to the health plan. And given that one of the producers develops a test, the best response of the other producer is also to develop a test. The reason for this is that increased information about patients' mismatch costs (going from one to two biomarkers) makes prescription decisions less price sensitive and thus enables the producers to charge higher drug prices, as previously explained. In other words, biomarker tests work as instruments to dampen price competition between producers of therapeutically substitutable drugs, and the producers' incentives to develop such tests are driven by this dampening-of-competition effect.

Notice, however, that these incentives do no necessarily lead to more efficient treatment outcomes, as shown by Propositions 5 and 6. If the difference in drug quality is sufficiently large, the introduction of biomarker tests leads not only to higher drug prices, but also to lower

total health benefits due to the prescription distortions created by an increased price difference between the two drugs, where too many patients are prescribed the low-quality drug.

6 Extension: Untreated patients in equilibrium

The above analysis of therapeutic competition relies on the underlying assumption (A2) that drug quality is high enough for all patients to be treated in equilibrium; i.e., we have assumed that

$$v_i - \beta p_i - t > 0 \tag{46}$$

in equilibrium for $i = 1, 2$. In this section we investigate how our main result might be affected if this condition does not hold. More specifically, suppose that the parameters of the model are such that the following condition holds in all equilibria where at least one drug has a biomarker test:

$$\frac{t}{2} < v_i - \beta p_i < t,\ i = 1, 2. \tag{47}$$

This means that, for each drug, the net utility of drug prescription is positive for the patients with *average* mismatch costs (equal to $t/2$) but negative for the patients with highest mismatch costs (equal to t). If this condition holds in equilibrium, the previously derived equilibria are the same as long as at least one drug comes without a predictive biomarker test. In these cases (with either zero or one test), the market is fully covered in equilibrium and each patient gets drug treatment. However, in the perfect information case where both drugs have a biomarker test, the Nash equilibrium outcome is different and has a partially covered market, where some patients (with high mismatch costs for both drugs) are being left untreated.

If both drugs have a biomarker test, and drug qualities and drug prices are such that some patients are left untreated, demand for drug i is given by

$$\widetilde{y}_i^{TT} = \int_0^{\frac{v_i - \beta p_i}{t}} f_i\left(x_i\right) dx_i, \quad i = 1, 2, \tag{48}$$

where $f_i\left(x_i\right)$ is given by (32) and (33) for $i = 1$ and $i = 2$, respectively. More explicitly, the demand functions for the two drugs are

$$\widetilde{y}_1^{TT} = \frac{v_1 - \beta p_1}{t} - \frac{\left(v_2 - \beta p_2\right)^2}{2t^2} \tag{49}$$

and

$$\widetilde{y}_2^{TT} = \frac{v_2 - \beta p_2}{t} - \frac{(v_2 - \beta p_2)\left(2\left(v_1 - \beta p_1\right) - \left(v_2 - \beta p_2\right)\right)}{2t^2}. \tag{50}$$

The profits of producer i are thus given by $\widetilde{\pi}_i^{TT} = p_i \widetilde{y}_i^{TT}$, $i = 1, 2$. In the pricing subgame, the candidate Nash equilibrium is given by pair of prices, $\left(\widetilde{p}_1^{TT}, \widetilde{p}_2^{TT}\right)$, that solve the following set of first-order conditions:

$$\frac{\partial \widetilde{\pi}_1^{TT}}{\partial p_1} = \frac{2t\left(v_1 - 2\beta p_1\right) - \left(v_2 - \beta p_2\right)^2}{2t^2} = 0, \tag{51}$$

$$\frac{\partial \widetilde{\pi}_2^{TT}}{\partial p_2} = \frac{\left(v_2 - 2\beta p_2\right)\left(2\left(t - \left(v_1 - \beta p_1\right)\right)\right) + \left(v_2 - \beta p_2\right)\left(v_2 - 3\beta p_2\right)}{2t^2} = 0. \tag{52}$$

This system is analytically solvable for the special case of equal drug qualities, $v_1 = v_2$, in which case

$$\widetilde{p}_i^{TT} = \frac{\sqrt{2}\sqrt{t\left(2t - v_i\right)} - \left(2t - v_i\right)}{\beta}, \quad i = 1, 2. \tag{53}$$

To see the effect of biomarkers on the intensity of price competition in the case of a partially covered market, it is instructive to compare these equilibrium prices with the equilibrium prices in the case of only one biomarker test, given by (26). Due to continuity, we can establish the following price ranking in the neighbourhood of the symmetric equilibrium:

Proposition 8 *Suppose that drug qualities are so low that some patients are being left untreated if the prescribing physician has perfect information about patients' mismatch costs. In this case, and if the quality difference between the two drugs is sufficiently small, equilibrium drug prices are lower if both drugs have biomarker tests than if such a test exists only for one of the drugs.*

If we compare this result with the equivalent price comparison made in the main analysis (cf. Proposition 6), it is evident that the answer to the question of whether biomarker tests are pro-competitive or anti-competitive depends crucially on whether the market is fully or partially covered in the perfect information equilibrium. If drug qualities are sufficiently high, such that the market is fully covered in equilibrium, our analysis in Section 4 revealed that additional biomarker tests make demand less price-elastic (as long as drug qualities are different), thus leading to higher drug prices. On the other hand, Proposition 8 shows that if drug qualities are sufficiently low, so that the market is only partially covered in equilibrium, the opposite result occurs, at least if the quality difference between the drugs is sufficiently small. In this case, additional biomarker tests make demand *more* price-elastic and thus have a *pro-competitive*

effect on drug prices.

In order to explain this result, notice first that $\partial \widetilde{y}_i^{TT}/\partial p_i = -\beta/t$ when evaluated at the symmetric equilibrium, as can easily be verified from (49)-(50). This is the same price sensitivity of demand as under full market coverage with either one or two biomarker tests when $v_1 = v_2$, as can be seen from (25) and (34)-(35), respectively. The result in Proposition 8 is therefore explained by the demand drop resulting from more precise information about patients' mismatch costs. If only one drug has a biomarker test, all patients are given one of the drugs as long as the net utility of drug prescription for the average patient is non-negative, which is true when (47) holds. However, biomarker tests for both drugs allow for the identification of patients whose mismatch costs for both drugs are so high that they will no longer be given drug treatment. As long as the drug quality difference is sufficiently small, this implies a demand drop for both drug producers, which makes demand more price-elastic and therefore leads to lower drug prices.

In order to make a more complete comparison of the cases of full versus partial market coverage under perfect information, we resort to numerical simulations. In Table 1 we present two different numerical examples where we vary the quality difference between the two drugs. Whereas the average drug quality remains constant, the difference in drug quality is relatively small in Panel A ($\Delta v = t/10$) and relatively large in Panel B ($\Delta v = t/2$). The parameter configurations are chosen such that the condition in (46) is violated for the equilibrium prices given by (36), while the condition in (47) holds for the equilibrium prices implicitly given by (53), thus ensuring the existence of the latter equilibrium. We have also confirmed that the inclusion of both drugs in the health plan (in the presence of biomarkers) is an equilibrium outcome. See Appendix C for further details.

Table 1: Partially covered market under perfect information

Panel A: Small quality difference ($v_1 = 2.6$, $v_2 = 2.4$; $\Delta v = t/10$)

	p_1	p_2	y_1	y_2	π_1	π_2	H	S
Two biomarkers	1.28	1.14	0.51	0.44	0.65	0.49	1.80	0.65
One biomarker	1.33	1.17	0.53	0.47	0.71	0.54	1.76	0.50
No biomarkers	0.2	0.00	1.00	0.00	0.20	0.00	1.60	1.40

Panel B: Large quality difference ($v_1 = 3$, $v_2 = 2$; $\Delta v = t/2$)

	p_1	p_2	y_1	y_2	π_1	π_2	H	S
Two biomarkers	1.63	0.94	0.65	0.29	1.06	0.27	1.93	0.59
One biomarker	1.67	0.83	0.67	0.33	1.11	0.28	1.89	0.50
No biomarkers	1.00	0.00	1.00	0.00	1.00	0.00	2.00	1.00

Other parameter values: $t = 2$, $\beta = 0.8$

In the case of small quality differences (Panel A), we see that going from one to two biomarker tests reduces the price of both drugs, thus confirming the result stated in Proposition 8. The price drop is also larger for the high-quality drug, thus contributing to a smaller drug price difference, which all else equal improves the allocational efficiency of drug prescriptions and which contributes to the observed increase in total health benefits.

If the quality difference between the two drugs is larger (Panel B), we see that the price effects of introducing a second biomarker test are heterogeneous across the two drugs. The price of the high-quality drug decreases, while the price of the low-quality drug goes up. This leads to an unambiguous decrease in the drug price difference, which once more is beneficial for allocational efficiency.

Regarding the drug producers' incentives to develop biomarker tests, it is easily verified that the unique Nash equilibrium outcome in each of the two examples in Table 1 is that only one of the producers develop a test. If quality differences are small, none of the producers have incentives to develop a second test because of the resulting price reduction. In the case of larger quality differences, if the high-quality drug already has a biomarker test, the producer of the

low-quality drug will be able to enjoy a price increase by also developing test. However, the corresponding drop in demand (since more precise patient information shifts demand in direction of the high-quality drug) is large enough to make this unprofitable. Thus, compared with the main analysis, we see that the drug producers have weaker incentives to develop biomarker tests when drug qualities are so low that the market is only partially covered under perfect patient information.

As in the main analysis, notice that the presence of biomarker tests does not necessarily improve efficiency in drug prescriptions. In the case of small quality differences (Panel A), the most efficient outcome is that both drugs have a biomarker test. However, if quality differences are larger (Panel B), the most efficient outcome is achieved in the absence of biomarker tests. As in the main analysis, this is explained by the allocative distortion caused by larger drug price differences in the presence of biomarker tests. Since $\Delta v < t$, the optimal drug allocation in both of our examples would be to prescribe the low-quality drug to some patients. But in the equilibrium with either one or two biomarker tests, too many patients are prescribed the low-quality drug because of the price difference between the two drugs, and a larger quality difference aggravates this problem. Thus, in our example in Panel B, total health benefits are higher if every patient is prescribed the high-quality drug, which is the equilibrium outcome in the absence of biomarker tests.

Notice also that, in both of our examples in Table 1, the private incentives to develop biomarker tests fail to produce the most efficient outcome, as measured by the total health benefits. When quality differences are small, the producers have insufficient incentives to develop biomarker tests, while in the case of larger quality differences, these incentives are too strong.

7 Concluding remarks

This paper is a first study of the impact of biomarkers on the dynamics of competition in pharmaceutical markets. A key focus is on the strategic incentive for drug producers to develop a (predictive) biomarker for a given drug therapy and the corresponding effects on market outcomes and social welfare. The set-up is a four-stage game where drug producers decide on the development of biomarkers at stage 1 and submit price bids at stage 2, a purchaser decides whether to include the drugs in the health plan at stage 3, and affiliated physicians select which of the approved drugs to prescribe to patients in the plan at stage 4. Since patients respond

differently to alternative drug treatments, the physicians' prescription choices can only be based on the expected (average) treatment effect in the patient population in absence of a biomarker. However, a biomarker provides information about how individual patients respond to the drug therapy, enabling the physicians to personalise prescriptions of the drugs to their patients.

We study the impact of biomarkers under two different market structures, namely monopoly and imperfect competition (duopoly). A key lesson from our analysis is that more information (via biomarkers) does not necessarily improve market outcomes or social welfare due to the strategic responses from rival drug producers and/or the purchaser. Under monopoly, the drug producer has an incentive to develop a biomarker only if drug quality is so low that the expected treatment effect is negative and the insurer rejects access to the health plan. In this case, a biomarker facilitates access to the health plan by identifying patients with a good therapeutic match and is thus welfare improving. However, due to monopoly pricing by the drug producer, too few patients are treated even when the insurer includes the drug in the health plan. However, if the drug quality is so high that the expected treatment effect is positive, the drug is always included in the health plan, and the monopoly drug producer has no incentive to develop a biomarker test due to the demand-reducing effect of such a test.

Competition changes incentives and outcomes radically. Indeed, drug producers have stronger incentives to develop a biomarker when facing competition than under monopoly. For a low-quality drug producer it is always a dominant strategy to develop a biomarker. Otherwise, the insurer will not include the drug in the health plan due to the expected treatment effect being negative. A high-quality drug producer prefers no biomarkers on the market, as this implies a *de facto* monopoly position, but this is never an equilibrium since the low-quality drug producer develops a biomarker. In this case, the best response for the high-quality drug producer is to also develop a biomarker as demand becomes less price sensitive and thus dampens competition. In an extension, we show that this result can be reversed if the drug quality is sufficiently low so that some patients remain untreated in equilibrium (uncovered market).

The development of a biomarker by the low-quality drug is welfare improving as this switches the market from monopoly to duopoly by facilitating access for the low-quality drug to the health plan. This is not necessarily true with a biomarker for the high-quality drug due to the dampening-of-competition effect described above. Indeed, we show that there is generally not an efficient treatment outcome even though there is perfect information about treatment effects with both drug producers developing a biomarker. This is due to the strategic price responses

induced by the biomarkers that distorts the physicians' prescription decisions away from the socially optimal allocation.

By way of conclusion, let us point at some limitations and scope for future research. First, our study focuses on the incentive for drug producers to develop a biomarker. An alternative could be to consider development of biomarkers by third parties (e.g., universities, research institutes, biotech companies, etc.) for commercial reasons or subsidised by insurers to facilitate improved treatment and/or cost savings. While the incentives of third-parties and insurers to introduce biomarkers are different than for drug producers, our study has investigated in detail the effects of biomarkers (for one or more drugs) on the competition among drug producers. This analysis is valid irrespective of who (the producers, third parties or purchasers) is making the decision to develop a biomarker.

Second, in order to focus on the competitive effects of biomarkers on drug producers' pricing decisions, we assumed that there is one health plan with a given set of patients and thus abstracted from modelling the insurance market. An insurer that limits the availability of drugs in its plan may risk losing individuals to another insurer with a more generous plan if the premia are not fully accounting for such differences. While modelling an insurance market would certainly make the analysis richer, we do think such an extension has limited relevance partly because individuals choose a health plan based on the whole portfolio of drugs in the plan and not single therapies (where biomarkers may be relevant). The choice of health plan is also usually an *ex ante* decision that is taken before individuals know which drug treatments they would need in the future.

Finally, our study has not investigated the impact of biomarkers on the incentives for drug innovation. Instead we have focused on drugs that are already discovered. While it is beyond the scope of this paper to include an innovation stage to the game, let us make one remark before concluding. Innovation incentives are usually increasing in the (expected) profits from a drug discovery. In the paper we show that a biomarker is generally improving the profitability of low-quality drugs, while the high-quality drug producer is generally better off in a market with no biomarkers. A speculative conjecture is thus that biomarkers may distort the drug producers to expend relatively more effort on me-too (low-quality) drug therapies and relatively less effort on radical (high-quality) drug therapies. However, a more comprehensive analysis of the effect of biomarkers on innovation incentives is left for future research.

Appendix

A. Monopoly pricing in the presence of a biomarker test

If the drug is included in the health plan and has a biomarker test, demand is given by (11). If the health plan's participation constraint does not bind, the profit-maximising monopoly price is given by

$$p^T = \begin{cases} \frac{v}{2\beta} & if \quad v \leq 2t \\ \frac{v-t}{\beta} & if \quad v > 2t \end{cases}, \tag{A1}$$

where $y^T < (=) \, 1$ if $v < (\geq) \, 2t$.

The next step is to check what is required for the purchaser's participation constraint to hold. As a function of p^T, this constraint is given by

$$S^T = \left(v - p^T - \frac{ty^T}{2} \right) y^T \geq 0. \tag{A2}$$

Consider first the case of $v < 2t$, for which the unconstrained monopoly price satisfies the health plan's participation constraint if

$$S^T = \frac{(3\beta - 2)\, v^2}{8t\beta} \geq 0. \tag{A3}$$

It follows that $S^T \geq 0$ if $\beta \geq 2/3$. On the other hand, if $\beta < 2/3$, the monopoly producer's price setting is constrained by the condition that the health plan's surplus must be non-negative. In this case, the optimal (constrained) price solves

$$\left(v - p^T - \frac{ty^T}{2} \right) y^T = 0, \tag{A4}$$

where y^T is either an interior solution given by $y^T = (v - \beta p)/t$, or a corner solution given by $y^T = 1$. The optimal (constrained) price that implements an interior solution is therefore given by

$$p^T = \frac{v}{2 - \beta}, \tag{A5}$$

whereas the price that implements a corner solution is

$$p^T = v - \frac{t}{2}. \tag{A6}$$

By a simple comparison of profits, we find that the optimal price is given by (A5) if $\beta \geq 2(v-t)/(2v-t)$ and by (A6) if $\beta < 2(v-t)/(2v-t)$.

Consider next the case of $v > 2t$, which implies a fully covered market in the profit-maximising solution. Setting $p^T = (v-t)/\beta$ and $y^T = 1$ in (A2), the purchaser's participation constraint is given by

$$S^T = \frac{t(2-\beta) - 2(1-\beta)v}{2\beta} \geq 0, \tag{A9}$$

which holds if $\beta \geq 2(v-t)/(2v-t)$. On the contrary, if $\beta < 2(v-t)/(2v-t)$, the producer must offer the purchaser a lower price. In this case, we have already found that the highest price that the purchaser is willing to accept is the price given by (A6).

B. Proofs

Proof of Proposition 2

(i) The result follows directly from (17)

(ii) The health benefit of drug treatment is positive for patients with mismatch costs that satisfy $v - tx > 0$. Thus, if $v < t$, efficiency requires that v/t patients are treated with the drug, while $1 - (v/t)$ patients are left untreated. If a predictive biomarker test is available and $v < t$, it follows from (15) that the number of patients treated is given by $v/2t$ if $\beta > 2/3$ and $2(1-\beta)v/(2-\beta)t$ if $\beta < 2/3$. It is straightforward to verify that

$$\max\left\{\frac{v}{2t}, \frac{2(1-\beta)v}{(2-\beta)t}\right\} < \frac{t}{2}, \tag{B1}$$

implying undertreatment.

(iii) If $v > t$, the health benefit of drug treatment is positive for the patients with highest mismatch costs ($v - t > 0$) and thus positive for all patients, which implies that treating all patients is the efficient outcome. By (15), the equilibrium outcome in the presence of a biomarker test i $y^T = 1$ only if v is sufficiently large or β is sufficiently small. Otherwise, $y^T < 1$, which implies undertreatment.

Proof of Proposition 3

(i) If $v < t/2$, the drug is not included in the health plan in the absence of a biomarker test, thus yielding zero profits for the producer, while in the presence of such a test, profits are strictly

positive for all $v > 0$, as evidenced by (16). Thus, the producer develops a biomarker test and the results regarding health plan inclusion and treatment efficiency are given by Proposition 2.

(ii) If $v \geq t/2$, monopoly profits with and without a biomarker test are different in three out of four parameter sets, as defined by (16):

(1) In the parameter set characterised by $v \leq 2t$ and $\beta > \frac{2}{3}$, the profit change resulting from the development of a biomarker test is given by

$$\pi^T - \pi^N = \frac{v^2}{4t\beta} - \left(v - \frac{t}{2}\right) = \frac{v^2 - 2t\beta\,(2v - t)}{4t\beta}. \tag{B2}$$

It is easily confirmed that this expression is convex in v and reaches a minimum at $v = 2\beta t \leq 2t$. Thus, in the relevant interval of v, given by $[t, 2t]$, the maximum value of the profit change is either at $v = t$ or at $v = 2t$. At the lower bound, $v = t$, the numerator is $t^2\,(1 - 2\beta) < 0$ for $\beta > 2/3$, while at the upper bound, $v = 2t$, the numerator is $2t^2\,(2 - 3\beta) < 0$ for $\beta > 2/3$. Thus, $\pi^T - \pi^N < 0$ in the relevant parameter set.

(2) In the parameter set characterised by $v \leq 2t$ and $2\,(v - t)\,/\,(2v - t) < \beta \leq 2/3$, the profit change resulting from a predictive biomarker test is

$$\pi^T - \pi^N = \frac{2\,(1 - \beta)\,v^2}{t\,(2 - \beta)^2} - \left(v - \frac{t}{2}\right) = \frac{(2\,(v - t) + t\beta)\,(2\,(1 - \beta)\,v - (2 - \beta)\,t)}{2t\,(2 - \beta)^2}. \tag{B3}$$

The sign of this expression is determined by the sign of $2\,(1 - \beta)\,v - (2 - \beta)\,t$, which is negative for $\beta > 2\,(v - t)\,/\,(2v - t)$, implying that $\pi^T - \pi^N < 0$ in the relevant parameter set.

(3) In the parameter set characterised by $v > 2t$ and $\beta > 2\,(v - t)\,/\,(2v - t)$, the profit change resulting from a biomarker test is

$$\pi^T - \pi^N = \left(\frac{v - t}{\beta}\right) - \left(v - \frac{t}{2}\right) = \frac{2\,(1 - \beta)\,v - (2 - \beta)\,t}{2\beta} < 0 \text{ for } \beta > \frac{2\,(v - t)}{2v - t}. \tag{B4}$$

Thus, the monopoly producer does not develop a predictive biomarker test if $v > t/2$, and the results regarding health plan inclusion and treatment efficiency are given by Proposition 1.

Proof of Proposition 5

(i) If both drugs are included, the health plan's surplus is given by (30), and this surplus is the same regardless of which drug that comes with a biomarker test. From (30) we see that $S^{TN} = S^{NT} \geq 0$ if $\overline{v}$ is sufficiently high. Given that $S^{TN} = S^{NT} \geq 0$, the alternative is to

include only one of the drugs. If only drug 1 is included, total health benefits are $v_1 - (t/2)$ and total surplus at the candidate equilibrium price chosen by the producer of drug 1 is given by

$$S_1^{TN} = S_1^{NT} = v_1 - \frac{(1+\beta)\,t}{2\beta} - \frac{\Delta v}{3\beta}, \tag{B5}$$

and this surplus is non-negative if v_1 is sufficiently high. Given that drug 1 is included, the additional surplus from also including drug 2 is given by

$$S^{TN} - S_1^{TN} = \frac{(3t - 2\Delta v)}{72}\left(3 - \frac{2\,(5\beta - 4)\,\Delta v}{t\beta}\right) > 0 \text{ for } \Delta v \in (0, t)\,. \tag{B6}$$

Thus, if it is profitable to include drug 1, it is also profitable to include drug 2.

Alternatively, the health plan could include only drug 2. The health plan's net benefit of including only drug 2 instead of only drug 1 is given by

$$S_2^{TN} - S_1^{TN} = \frac{(2 - 3\beta)\,\Delta v}{3\beta} > (<)\,0 \text{ if } \beta < (>)\,\frac{2}{3}. \tag{B7}$$

Thus, if $\beta < 2/3$, including only drug 2 gives the health plan a higher surplus than if only drug 1 is included. If only drug 2 is included, the additional inclusion of drug 1 increases the health plan's surplus by

$$S^{TN} - S_2^{TN} = \frac{(3t + 2\Delta v)}{72}\left(3 + \frac{2\,(5\beta - 4)\,\Delta v}{t\beta}\right). \tag{B8}$$

This expression is positive if

$$\beta > \frac{8\Delta v}{3t + 10\Delta v}. \tag{B9}$$

Notice that this threshold value of β is less than $2/3$ for $\Delta v < t$. Thus, if the condition in (B9) is satisfied, the inclusion of both drugs is the optimal decision of the health plan.

(ii) The change in total health benefits, compared with the equilibrium outcome when no biomarker exists, is given by:

$$H^{TN} - H^{NN} = \overline{v} - \frac{3t}{8} + \frac{5\,(\Delta v)^2}{18t} - \left(v_1 - \frac{t}{2}\right) = \frac{(3t - 10\Delta v)\,(3t - 2\Delta v)}{72t}. \tag{B10}$$

It is straightforward to verify that $H^{TN} - H^{NN} > 0$ if $\Delta v < (3t/10)$ and $\Delta H < 0$ for $\Delta v \in (3t/10, t)$.

Proof of Proposition 6

(i) If both drugs are included, the health plan's surplus is given by (44), which is non-negative if $\overline{v}$ is sufficiently high. Given that $S^{TT} \geq 0$, the alternative for the health plan is to include only one of the drugs. If only drug 1 is included, the health plan's surplus, evaluated at the candidate equilibrium price of drug 1, is given by

$$S_1^{TT} = v_1 - \frac{t}{2} - \frac{3\phi - 5\left(t - \Delta v\right)}{8\beta}. \tag{B11}$$

The additional surplus obtained by also including drug 2 is then given by

$$S^{TT} - S_1^{TT} = \frac{\Delta v^2\left(4\beta - 3\right)\left(3t + \phi - \Delta\right) - 9t^3 - t\Delta\left(2\phi\left(4\beta - 3\right) + t\left(24\beta - 15\right)\right) + t^2\left(3\phi + 16t\beta\right)}{96t^2\beta}. \tag{B12}$$

The sign of this expression is given by the sign of the numerator, which we denote μ, and which depends on the parameter β as follows:

$$\frac{\partial \mu}{\partial \beta} = 4\left(4t^3 + \left(\Delta v\right)^2\left(\phi - \Delta v\right) - t\Delta v\left(6t + 2\phi - 3\Delta v\right)\right). \tag{B13}$$

The sign of this expression is *a priori* indeterminate, but notice that it does not depend on β. Thus, μ is either monotonically increasing or monotonically decreasing in β, depending on the values of t and Δv. Evaluating μ at the lower and upper bounds of β, respectively, yields

$$\lim_{\beta \to 0} \mu = 3t^2\left(\phi - 3t\right) + 3t\Delta v\left(5t + 2\phi - 3\Delta v\right) - 3\left(\Delta v\right)^2\left(\phi - \Delta v\right) > 0 \text{ for } \Delta v \in \left(0, t\right), \tag{B14}$$

$$\lim_{\beta \to 1} \mu = t^2\left(7t + 3\phi\right) - t\Delta v\left(9t + 2\phi - 3\Delta v\right) + \left(\Delta v\right)^2\left(\phi - \Delta v\right) > 0 \text{ for } \Delta v \in \left(0, t\right). \tag{B15}$$

This implies that $\mu > 0$ and therefore that $S^{TT} - S_1^{TT} > 0$ for all $\Delta v \in (0, t)$. In other words, it is always more beneficial for the health plan to include both drugs rather then only drug 1.

However, although drug 1 has higher quality than drug 2, the latter drug is cheaper in the candidate equilibrium. Thus, the health plan might potentially benefit from including only drug 2. If drug 1 is replaced by drug 2 as the only drug in the health plan, the increase in the health plan's total surplus is given by

$$S_2^{TT} - S_1^{TT} = -\frac{3t - \phi + \left(4\beta - 3\right)\Delta v}{4\beta}. \tag{B16}$$

It is easy to see that $S_2^{TT} - S_1^{TT} > 0$ if $\beta < \beta_0$, where

$$\beta_0 := \frac{\phi - 3(t - \Delta v)}{4\Delta v}. \tag{B17}$$

If $\beta < \beta_0$, the health plan prefers to select drug 2 if only one drug is included. In this case, the increase in the health plan's surplus from also including drug 1, is given by

$$S^{TT} - S_2^{TT} = \frac{\Delta v(4\beta - 3)(\Delta v(\phi - \Delta v) - t(2\phi - 3\Delta v)) + t^2(63t + 16t\beta - 21\phi) - 3t^2\Delta v(19 - 24\beta)}{96t^2\beta}. \tag{B18}$$

The sign of this expression is given by the sign of the numerator, which we denote by η, and which depends on β in the following way:

$$\frac{\partial \eta}{\partial \beta} = 4\left(t\Delta v(18t - 2\phi + 3\Delta v) + 4t^3 + (\Delta v)^2(\phi - \Delta v)\right) > 0 \text{ for } \Delta v \in (0, t). \tag{B19}$$

Thus, η is monotonically increasing in β. It is also relatively straightforward to verify that $\eta = 0$ for a value of β that lies strictly between 0 and 1. This threshold value, denoted by β_1, is given by

$$\beta_1 := \frac{t^2(21\phi - 63t) + 3(\Delta v)^2(3t + \phi - \Delta v) + t\Delta v(57t - 6\phi)}{4(\Delta v)^2(3t + \phi - \Delta v) + 16t^3 + t\Delta v(72t - 8\phi)}. \tag{B20}$$

Thus, $S^{TT} > (<)\, S_2^{TT}$ if $\beta > (<)\, \beta_1$. Furthermore, by comparing (B17) and (B20) we can verify that

$$\beta_0 - \beta_1 = \frac{4t^3(\phi - 3t) + (\Delta v)^2\phi(\phi - \Delta v) + t\Delta v\left(21t^2 + 3t(\phi - 4\Delta v) + 3(\Delta v)^2 - 2\phi^2\right)}{4v\left(4t^3 + t\Delta v(18t - 2\phi + 3\Delta v) + (\Delta v)^2(\phi - \Delta v)\right)} > 0 \tag{B21}$$

This implies that the equilibrium described in Proposition 6, in which both drugs are included in the health plan, exists if $\beta > \beta_1$. Notice that the scope for this condition to hold is larger when drug quality differences are smaller, with $\lim_{\Delta v \to 0} \beta_1 = 0$.

(ii) Comparing (26) and (36), the equilibrium change in the price of drug 1 when both drugs (instead of only one) has predictive biomarker test, is given by

$$p_1^{TT} - p_1^{TN} = \frac{7\Delta v + 9(\phi - 3t)}{24\beta} > 0 \text{ for } \Delta v \in (0, t), \tag{B22}$$

and

$$p_2^{TT} - p_2^{TN} = \frac{5\Delta v + 3(\phi - 3t)}{24\beta} > 0 \text{ for } \Delta v \in (0, t). \tag{B23}$$

The corresponding effect on total health benefits is given by a comparison of (29) and (43), yielding

$$H^{TT} - H^{TN} = \frac{t\left(6t^2 + \Delta v\left(63t - 12\phi - 28\Delta v\right)\right) - 3\Delta v\left(\phi - \Delta v\right)^2}{144t^2}. \tag{B24}$$

The sign of this expression is *a priori* indeterminate. Notice however that

$$\frac{\partial\left(H^{TT} - H^{TN}\right)}{\partial \Delta v} = -\frac{\left(\begin{array}{c} 108t^3 + 3(\phi - \Delta v)\left(\phi(\phi + \Delta v) + 6(\Delta v)^2\right) \\ -t\left(\phi(63t - 50\Delta v) + 18\Delta v(8t - 3\Delta v)\right) \end{array}\right)}{144t^2\phi} < 0 \text{ for } \Delta v \in (0, t). \tag{B25}$$

Thus, $H^{TT} - H^{TN}$ is monotonically decreasing in Δv. Evaluating the health benefits difference at the lower and upper limits of Δv yields, respectively,

$$\lim_{\Delta v \to 0}\left(H^{TT} - H^{TN}\right) = \frac{t}{24} > 0 \tag{B26}$$

and

$$\lim_{\Delta v \to 1}\left(H^{TT} - H^{TN}\right) = \left(\frac{7}{72} - \frac{1}{12}\sqrt{2}\right)t < 0. \tag{B27}$$

Thus, $H^{TT} > (<)\, H^{TN}$ if Δv is sufficiently small (large).

Proof of Proposition 7

If the conditions stated in Proposition 5 are satisfied, we know from Propositions 4 and 5 that only the high-quality drug will be included in the health plan in the case of no biomarkers, while both drugs will be included if one of the drugs has a biomarker test. Thus, if the high-quality drug does not have a biomarker test, the best response of the producer of the low-quality drug is to develop a biomarker test. This means that an outcome with no biomarker test for any of the drugs cannot be a Nash equilibrium.

The only possible Nash equilibria are therefore that either one or both firms develop a test. To confirm whether such equilibria exist, we need to compare the equilibrium profits of each firm in the cases of one and two biomarker tests. Define $\Delta\pi_1 := \pi_1^{TT} - \pi_1^{NT} = \pi_1^{TT} - \pi_1^{TN}$.

Using (27) and (40), we find that

$$\Delta\pi_1 = \frac{9t\left(\phi\left(38t - 3\phi - 4\Delta v\right) - 87t^2\right) + 7t\Delta v\left(3t + \Delta v\right) + 9\Delta v\left(\phi - \Delta v\right)\left(5\Delta v + 3\phi\right)}{1152t^2\beta}. \quad \text{(B28)}$$

We can determine the sign of this expression by first deriving

$$\frac{\partial^4\left(\Delta\pi_1\right)}{\partial\left(\Delta v\right)^4} = 6912t^4\frac{\left(11t - 8\Delta v\right)t + 4\left(\Delta v\right)^2}{1152t^2\beta\phi^7} > 0, \quad \text{(B29)}$$

which implies that

$$\frac{\partial^3\left(\Delta\pi_1\right)}{\partial\left(\Delta v\right)^3} = -\frac{3\left(77t^5 + \phi^5 - \left(\Delta v\right)^5 - t\Delta v\left(30t\left(\Delta v\right)^2 - 70t^2\Delta v + 121t^3 - 5\left(\Delta v\right)^3\right)\right)}{32t^2\beta\phi^5} \quad \text{(B30)}$$

is monotonically increasing in Δv. Evaluating this expression at the upper bound of Δv yields

$$\lim_{\Delta v \to t}\frac{\partial^3\left(\Delta\pi_1\right)}{\partial\left(\Delta v\right)^3} = -\frac{3}{32t^2\beta} < 0, \quad \text{(B31)}$$

which implies that $\partial^3\left(\Delta\pi_1\right)/\partial\left(\Delta v\right)^3 < 0$ for all $\Delta v \in (0, t)$, which in turn implies that

$$\frac{\partial^2\left(\Delta\pi_1\right)}{\partial\left(\Delta v\right)^2} = \frac{t\left(1575t^3 - 37\phi^3\right) - 27\Delta v\left(\phi^3 - 2t\Delta v\left(9t - 2\Delta v\right) + 28t^3 - \left(\Delta v\right)^3\right)}{288t^2\beta\phi^3} \quad \text{(B32)}$$

is monotonically decreasing in Δv. Evaluating this expression at the lower and upper bounds of Δv yields, respectively,

$$\lim_{\Delta v \to 0}\frac{\partial^2\left(\Delta\pi_1\right)}{\partial\left(\Delta v\right)^2} = \frac{2}{27t\beta} > 0 \quad \text{(B33)}$$

and

$$\lim_{\Delta v \to t}\frac{\partial^2\left(\Delta\pi_1\right)}{\partial\left(\Delta v\right)^2} = \frac{153\sqrt{2} - 256}{1152t\beta} < 0, \quad \text{(B34)}$$

which, together with the fact that $\partial^3\left(\Delta\pi_1\right)/\partial\left(\Delta v\right)^3 < 0$ for $\Delta v \in (0, t)$, means that $\partial\left(\Delta\pi_1\right)/\partial\left(\Delta v\right)$ is a concave function of Δv on the interval $\Delta v \in (0, t)$ and reaches a maximum on this interval for a value of Δv that lies strictly between 0 and t. Evaluating $\partial\left(\Delta\pi_1\right)/\partial\left(\Delta v\right)$ at the lower and upper bounds of Δv yields, respectively,

$$\lim_{\Delta v \to 0}\frac{\partial\left(\Delta\pi_1\right)}{\partial\left(\Delta v\right)} = \frac{1}{12\beta} > 0 \quad \text{(B35)}$$

and

$$\lim_{\Delta v \to t} \frac{\partial (\Delta \pi_1)}{\partial (\Delta v)} = \frac{29}{288\beta} > 0. \tag{B36}$$

This implies that $\partial (\Delta \pi_1) / \partial (\Delta v) > 0$ for all $\Delta v \in (0, t)$. In other words, $\Delta \pi_1$ is monotonically increasing in Δv. Evaluating $\Delta \pi_1$ at the lower bound of Δv yields

$$\lim_{\Delta v \to 0} \Delta \pi_1 = 0, \tag{B37}$$

which implies that $\Delta \pi_1 > 0$ for $\Delta v \in (0, t)$.

Now define $\Delta \pi_2 := \pi_2^{TT} - \pi_2^{NT} = \pi_2^{TT} - \pi_2^{TN}$. Using (27) and (41) we find

$$\Delta \pi_2 = \frac{9 (\phi - \Delta v) \left(\phi (\Delta v + \phi) + 4 (\Delta v)^2 \right) + t \left(27\phi (t - 2\Delta v) + 148 \Delta v (3t - \Delta v) - 324 t^2 \right)}{2304 t^2 \beta}. \tag{B38}$$

The sign of $\Delta \pi_2$ can be determined by a similar procedure as we determined the sign of $\Delta \pi_1$. We start out by deriving

$$\frac{\partial^4 (\Delta \pi_2)}{\partial (\Delta v)^4} = \frac{90 t^4}{\beta \phi^7} > 0, \tag{B39}$$

which means that $\partial^3 (\Delta \pi_2) / \partial (\Delta v)^3$ is monotonically increasing in Δv, and since

$$\lim_{\Delta v \to t} \frac{\partial^3 (\Delta \pi_2)}{\partial (\Delta v)^3} = -\frac{3}{32 t^2 \beta} < 0, \tag{B40}$$

we can conclude that $\partial^3 (\Delta \pi_2) / \partial (\Delta v)^3 < 0$ for all $\Delta v \in (0, t)$. Since

$$\frac{\partial^2 (\Delta \pi_2)}{\partial (\Delta v)^2} = \frac{37 t (3t - \phi) \left(\phi (3t + \phi) + 9 t^2 \right) - 27 \Delta v \left(\phi^3 + 28 t^3 - \Delta v \left(18 t^2 - \Delta v (4t - \Delta v) \right) \right)}{288 t^2 \beta \phi^3} \tag{B41}$$

is monotonically decreasing in Δv and

$$\lim_{\Delta v \to 0} \frac{\partial^2 (\Delta \pi_2)}{\partial (\Delta v)^2} = 0, \tag{B42}$$

we can conclude that $\partial^2 (\Delta \pi_2) / \partial (\Delta v)^2 < 0$ for all $\Delta v \in (0, 1)$. Furthermore, since

$$\frac{\partial (\Delta \pi_2)}{\partial (\Delta v)} = \frac{3 t^2 (37\phi - 63t) + \Delta v (t (243t - 74\phi) - 27 \Delta v (3t - \Delta v + \phi))}{576 t^2 \beta \phi} \tag{B43}$$

is monotonically decreasing in Δv and

$$\lim_{\Delta v \to t} \frac{\partial (\Delta \pi_2)}{\partial (\Delta v)} = \frac{5}{288\beta} > 0, \tag{B44}$$

we conclude that $\partial (\Delta \pi_2) / \partial (\Delta v) > 0$ for all $\Delta v \in (0, t)$, which in turn means that $\Delta \pi_2$ is monotonically increasing in Δv. Since $\lim_{\Delta v \to 0} \Delta \pi_2 = 0$, it follows that $\Delta \pi_2 > 0$ for all $\Delta v \in (0, 1)$.

Since $\pi_1^{TT} > \pi_1^{NT} = \pi_1^{TN}$ and $\pi_2^{TT} > \pi_2^{NT} = \pi_2^{TN}$, this means that, if one of the firm develops a test, the best response of the other firm is to develop a test as well. Thus, the unique subgame perfect Nash equilibrium is that both firms develop a test.

Proof of Proposition 8

From (36), the equilibrium prices for equal drug qualities, and where only one of the drugs has a biomarker test, are given by

$$p_1^{TN} = p_2^{NT} = \frac{t}{2\beta}. \tag{B45}$$

A comparison with (53) yields

$$p_i^{TN} - \widetilde{p}_i^{TT} = \frac{5t - 2v_i - 2\sqrt{2}\sqrt{t\,(2t - v_i)}}{2\beta}, \quad i = 1, 2. \tag{B46}$$

The sign of this expression depends on the sign of the numerator. The first- and second-order derivatives of the numerator with respect to v_i are, respectively,

$$\frac{\partial \left(5t - 2v_i - 2\sqrt{2}\sqrt{t\,(2t - v_i)}\right)}{\partial v_i} = -2\left(1 - \frac{1}{2}\left(\frac{\sqrt{2}\sqrt{t\,(2t - v_i)}}{2t - v_i}\right)\right) \tag{B47}$$

and

$$\frac{\partial^2 \left(5t - 2v_i - 2\sqrt{2}\sqrt{t\,(2t - v_i)}\right)}{\partial v_i^2} = \frac{t\sqrt{2}}{2\,(2t - v_i)\sqrt{t\,(2t - v_i)}} > 0. \tag{B48}$$

Thus, the numerator in (B46) is convex in v_i and reaches a minimum at the value of v_i for which the first-order derivative in (B47) is zero. It is easily confirmed that the first-order derivative is zero for $v_i = (3/2)\,t$, and that the numerator is also zero at this value of v_i. Since this is a minimum, it follows directly that (B46) is positive, thus $p_i^{NT} > \widetilde{p}_i^{TT}$, for the entire parameter set that ensures existence of the symmetric Nash equilibrium given by (53), i.e., $v_i < (3/2)\,t$. Due to continuity, this price difference must remain positive also in the neighbourhood of the

symmetric equilibrium; i.e., when the difference in drug quality is sufficiently small.

C. Supplementary analysis for the numerical examples in Table 1.

Suppose that v_i and t are such that (47) holds in all equilibria where at least one drug has a biomarker test.

In the case where no drug has a biomarker test, the equilibrium outcome is given by (19)-(22), and the parameter values in Table 1 are such that $\Delta v < v_1 - (t/2)$, implying $S^{NN} > 0$.

In the case where only one drug has a biomarker test, the equilibrium outcome is given by (26)-(30), regardless of which drug the biomarker test applies to. The only difference from the main analysis is that the condition (47) changes the outside option of the health plan. Given that $S^{TN} \geq 0$, both drugs will be included if $S^{TN} \geq \max\left\{S_1^{TN}, S_2^{TN}\right\}$, evaluated at the prices given by (26). Now given the condition in (47), if the health plan includes only the drug without a biomarker test, the surplus is the total health benefit net of purchasing costs from a fully covered market. On the other hand, if the health plan includes only the drug with a biomarker test, the surplus is the total health benefit net of purchasing costs from a partially covered market. Thus, if drug i comes with a biomarker test and drug j does not, the outside options are

$$S_i^{TN} = \int_0^{\frac{v_i - \beta p_i^{TN}}{t}} (v_i - t x_i)\, dx_i - p_i^{TN} \left(\frac{v_i - \beta p_i^{TN}}{t}\right) \tag{C1}$$

and

$$S_j^{TN} = \int_0^1 (v_1 - t x_j)\, dx_j - p_j^{TN}. \tag{C2}$$

It is straightforward to verify that $S^{TN} \geq 0$ and $S^{TN} \geq \max\left\{S_1^{TN}, S_2^{TN}\right\}$, and that (47) holds, in each of the numerical examples in Table 1.

In the case where both drugs have a biomarker test, the Nash equilibrium prices, denoted $\widetilde{p}_i^{TT}$, are implicitly given by (51)-(52), with equilibrium demand given by (49) and (50). Profits are given by $\widetilde{\pi}_i^{TT} = \widetilde{p}_i^{TT} \widetilde{y}_i^{TT}$, while total health benefits are

$$\begin{aligned}
\widetilde{H}^{TT} \;=\; & \int_0^{\frac{\Delta v - \beta\left(\widetilde{p}_1^{TT} - \widetilde{p}_2^{TT}\right)}{t}} (v_1 - t x_1)\, dx_1 + \int_{\frac{\Delta v - \beta(\widetilde{p}_1 - \widetilde{p}_2)}{t}}^{\frac{v_1 - \beta \widetilde{p}_1}{t}} (v_1 - t x_1) \left(1 + \frac{\Delta v - \beta\left(\widetilde{p}_1 - \widetilde{p}_2\right)}{t} - x_1\right) dx_1 \\
& + \int_0^{\frac{v_2 - \beta \widetilde{p}_2}{t}} (v_2 - t x_2) \left(1 - \frac{\left(\Delta v - \beta\left(\widetilde{p}_1 - \widetilde{p}_2\right)\right)}{t} - x_2\right) dx_2,
\end{aligned} \tag{C3}$$

and the total surplus of the health plan is

$$\widetilde{S}^{TT} = \widetilde{H}^{TT} - \sum_{i=1}^{2} \widetilde{p}_i^{TT} \widetilde{y}_i^{TT}. \tag{C4}$$

Both drugs are included in the health plan if $\widetilde{S}^{TT} \geq 0$ and $\widetilde{S}^{TT} \geq \max\left\{\widetilde{S}_1^{TT}, \widetilde{S}_2^{TT}\right\}$, where

$$\widetilde{S}_i^{TT} = \int_0^{\frac{v_i - \beta\widetilde{p}_i}{t}} (v_i - t x_i)\, dx_i - \widetilde{p}_i \left(\frac{v_i - \beta\widetilde{p}_i}{t}\right), \quad i = 1, 2. \tag{C5}$$

It is straightforward to verify that $\widetilde{S}^{TT} \geq 0$ and $\widetilde{S}^{TT} \geq \max\left\{\widetilde{S}_1^{TT}, \widetilde{S}_2^{TT}\right\}$, and that (47) holds, for each of the numerical examples in Table 1.

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