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Research into biomarkers: how does drug procurement affect the design of clinical trials?

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Abstract

This paper examines incentives for pharmaceutical firms to invest in biomarkers that predict which groups of sufferers from a certain medical condition will respond well to a particular treatment. We show that when pricing of the treatment is imperfectly responsive to effectiveness, firms undertaking clinical trial have an incentive to expand the relevant treatment population in order both to increase the probability of a statistically significant result, and to increase future revenues. Firms may fail to include potentially promising biomarkers in clinical trials, may include such biomarkers without disclosing them in the public protocol, and may fail to disclose the relevance of clinically predictive biomarkers. We show how many existing pricing and procurement schemes create adverse incentives of this kind, and discuss various mechanisms that may help to mitigate such effects.

JEL codes: I12, I13, I18, L65

Keywords: clinical trials, biomarkers, pharmaceuticals, medical procurement.

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1. Introduction

The efficacy of many healthcare treatments - both drugs and clinical devices - varies substantially across the population of treated patients. The reasons why some patients respond well to treatment and others do not can often remain mysterious, but modern medical techniques hold open the possibility that explanations may be found in genetic or other characteristics of patients that affect their probability of responding to treatment (such characteristics are generally known as "biomarkers"). It is tempting to think that research into biomarkers will be like research into other forms of medical treatment, and that, making due allowance for the imperfections of intellectual property rights, the private profitability of such research will be reasonably positively correlated with its social value. In this paper we show that this presumption is mistaken. Research into biomarkers will often be unprofitable precisely when it would be most socially valuable, and for a simple reason: biomarkers typically have social value because they reduce the numbers of patients who will take expensive but ineffective medical treatments. Unless the revenues accruing to firms that provide effective treatments reflect the increase in effectiveness that biomarkers make possible, expecting firms to devote optimal amounts of resources to biomarker research is expecting them to invest actively in reducing their markets.

This is not merely a theoretical possibility. In March 2011 the *New York Times* described the approval by the FDA of Yervoy, a Bristol Myers Squibb drug that treats skin cancer (melanoma)[1]. According to the article, the drug prolongs life for an average of four months over the baseline of six months achievable with existing treatments. However, 20% of patients in the trial lived eighteen months or more (above baseline) upon receiving the drug. Elementary calculations therefore suggest that the other 80% gained an average of approximately two weeks or less of additional life over baseline. The article said "There is no way at present to predict which patients will benefit from the drug."

It seems eminently clear, though, that Bristol Myers Squibb has no incentive to try to find out. The article goes on to say that there are 68,000 new cases of melanoma in the US every year, which implies that the drug could earn up to $6 billion dollars of revenue per year. If a biomarker for the benefit could be found, BMS' revenue would potentially drop by 80%, as the patients who found out they would not benefit from the drug stopped purchasing it. This problem could be fixed with a five-fold increase in the price of the drug. However, it seems unlikely that the amount BMS could charge for the drug would be raised in consequence, first because there are political costs to doing so, but secondly, because BMS is *already* pricing the drug according to its benefits for the 20% most fortunate. The price of the drug is $120,000 per patient per year. This yields a cost per QALY measure of $360,000, which is far above the conventional threshold of about $100,000. For those who live an additional 18-plus months, the cost of an additional year is below $80,000, which is in the typical range used by health economists. The empirical regularity that firms cannot change the US prices of their drugs after launch, or face large costs of doing so, is a theme to which we will return repeatedly in this paper. If finding a biomarker would only cut BMS's revenue, we can safely predict that no such research will be undertaken (by BMS at least).

[1] "Approval for Drug that Treats Melanoma" New York Times, March 26, 2011, page B1.

A specific example of the case of falling revenue comes from the case of Erbitux (cetuximab) in the United States. This drug, originally patented in 1989 by Rhone-Poulenc-Rorer[2] and now manufactured and distributed in the US by Bristol-Myers-Squibb and Eli Lilly, is used to treat cancer of the colon, and others. If the cancer cells have a mutated KRAS gene, cetuximab does not bind to the cancer, whereas when the gene is not mutated, the medication binds to the cancer cells and stops them multiplying. As a result of a genetic test for the mutation in the KRAS gene developed by the German company Qiagen, about 40% of patients discovered the drug would not work for them. Quantity sold dropped sharply as a result -- while price remained constant. The discovery of an effective biomarker therefore caused a large fall in revenue from the drug. The example shows that biomarker research can be undertaken effectively and with large benefits in costs saved, but it is notable that the company that developed the drug was not the company that invented it, and the biomarker was not developed until more than two decades after the original drug. Another similar example was the drug Herceptin which appeared at launch to have a marginal average effects on breast cancer patients. After the gene generating HER2 was identified as the biomarker for effectiveness, the drug could be given only to the approximately 20% of women for whom it would work.

Of course, reducing the numbers of patients who take an ineffective treatment is not the only benefit of biomarkers. Sometimes biomarkers also enable clinical effectiveness to be more precisely distinguished from statistical noise. This makes it important to model carefully the trade-offs between the benefits of research into biomarkers and its costs, and to do so in a way that distinguishes between private and social benefits and costs. This is our task in this paper. We model a decision whether or not to include a test for a biomarker in a clinical trial for a new treatment. The efficacy of the treatment must be discovered via clinical trial and varies across patients. Average efficacy of the drug is unknown *ex ante*, as well as which subgroups most benefit from the treatment. We model the case where the firm may have private information about efficacy among subgroups, and also runs the clinical trial and chooses its design.[3] We show in this setting that there is potential for information discovery to be sub-optimal. Firms may fail to test for biomarkers in clinical trials even though there would be a strong social benefit in their doing so. Alternatively, they may include such tests privately (without incorporating them in the formal protocol of the trials) and fail to disclose the analysis of such tests even when doing so would create large benefits for patients and health care providers. Many of the tradeoffs we analyze apply to research into biomarkers that might occur after the treatment is approved. While we focus on the incentives to invest in biomarkers in clinical trials, we also have in mind that our results will apply to incentives for *ex post* biomarker research.

Whether private and social incentives can be aligned depends importantly upon the detail of medical procurement schemes. Procurement schemes vary across jurisdictions, and we discuss some of the main features of this variation below. As will be clear, the procurement scheme affects not only government expenditure on healthcare treatments, but also the incentive of the innovator to invest in knowledge about which groups are most helped by the drug. There are also

[2] The patent was subsequently successfully challenged by Yeda Research in 2006, see http://usatoday30.usatoday.com/money/industries/health/drugs/2006-09-14-imclone-usat_x.htm

[3] An interesting example of the problems generated by firms designing clinical trials in the antidepressants market is contained in Kirsch (2010). Beckman (2010) considers a similar problem to ours with focus on the science of biomarkers.

spillover effects between procurement schemes in different jurisdictions. Prices across jurisdictions are not completely independent; they are linked because it is politically costly to set a much higher price in one country relative to prices in other similar-income countries. Firms would like to choose very different prices across countries because the institutional setting and willingness to pay between, for example, the US and France, is very different. In particular, the United States puts no limits on the price of a pharmaceutical or device. By contrast, many European countries evaluate the cost effectiveness of products before they are included in the national insurance scheme.

The paper is structured as follows. In section 2 we develop a simple stylized model in which a firm engaging in a clinical trial for a treatment must decide whether or not to include a biomarker that it suspects will identify patients who will respond to the treatment. In section 3 we summarize the features of medical procurement systems across countries and discuss how they may mitigate or aggravate the discrepancy between private and social benefits of research into biomarkers. Section 4 concludes.

2. A model of clinical trials including biomarkers

There are n sufferers from a condition.

A drug exists that the firm knows to be effective for at least some sufferers, but it does not know how many. We abstract from uncertainty about the size of the benefit for each sufferer, which would complicate the algebra without adding to the insight. Specifically, it believes with probability π that the drug will produce benefits V in a proportion b_H of these sufferers and with probability $(1-\pi)$ will produce these benefits in a proportion $b_L < b_H$ of sufferers. If the proportion is b_H we shall say the drug is "High-Efficacy". If the proportion is b_L we shall call it "Low Efficacy"; a special case of this is if $b_L = 0$, when the drug has no efficacy at all. It will also produce average side effects k in all sufferers; susceptibility to side effects is assumed to be independent of any other feature affecting the sufferers' benefits from the drug. The marginal cost of producing the drug is c.

The firm also has private information suggesting that a particular biomarker M, found in proportion m of the subjects, may be a useful predictor of the individuals who benefit from the drug. We presume that $m > b_H$ as it is simpler to treat the case where possession of the marker is a necessary condition for responding to the treatment (since then patients responding negatively to the biomarker will not take the treatment). More complex relations between possession of the biomarker and responsiveness to the treatment would be unlikely to change the main trade-offs we examine in this paper.

Specifically, with probability γ the effect of the drug is positive only in bearers of M, while with probability $(1-\gamma)$ there is no effect of the biomarker. It costs s to test individual patients for the presence of M. We can measure the precision of the biomarker by $1/m$, the inverse of the proportion of patients who bear the marker.

The question arises whether the firm should run a clinical trial including or excluding the biomarker, and whether it will be privately profitable for it to do so. The trial contains *t* subjects. Suppose that, given t, if the drug does in fact benefit proportion b_H of sufferers it is almost certain that the trial will show this, but that if it benefits the smaller proportion b_L, there is a probability ρ of an insignificant result when viewing the average outcome. However, in the b_L case, if the biomarker is included and is in fact relevant, then it is almost certain that the trial will show a significant benefit for the subjects with the biomarker.

We consider first the social benefit and then the private profitability of including the biomarker in the trial. We do so under the assumption that the results of the trial will become publicly known, leaving until later the possibility that the firm may be able to avoid revealing the results of including the biomarker if it chooses not to do so. There may be regulations in a jurisdiction that require the firm to disclose studies of biomarkers in its clinical trials. Our model in this paper is designed to reflect a situation where knowledge of the biomarker and its effects are limited and uncertain. Even if researchers at the firm have a conjecture, the firm can tell the regulator that it does not have definite results to disclose. We set up the problem the firm faces: should it invest in a formal declaration of the biomarker and analysis of its effects, or instead choose not to pursue the biomarker, even if scientists at the firm have a hypothesis concerning a potential relationship?

The extra cost of the trial if the biomarker is included will be *s.t.*, and this will be a factor in the calculation of both private and social benefit. With probability (1-γ) the biomarker is ineffective so there is no compensating benefit. The alternative, that the biomarker is effective, occurs with probability γ. In this case we can divide the benefits from including the biomarker into two categories:

1) First, there are the benefits from giving the drug in future to a smaller group of patients, thereby saving on marginal costs and sparing other patients who would not benefit from the side-effects.
2) Secondly, there are the benefits from making it more likely that the trial will reveal a statistically significant result.

The first benefits occur if the trial would find a statistically significant result for the whole population regardless of the inclusion of the biomarker. This can occur either if the drug is High-Efficacy (probability π) or if the drug is Low-Efficacy but the trial would find a result anyway: the combined probability is therefore π + (1-π)(1 - ρ)). The net benefit for each patient in the general population of patients who is thereby spared an ineffective treatment is (*k*+*c*), which occurs for proportion (1-*m*) of patients; all patients however, need to be tested, at a cost of *s* per patient.

The second benefits occur if the trial would not find a statistically significant result for the whole population but does find one for the subjects with the biomarker: conditional on the efficacy of the biomarker, this occurs with probability (1-π)ρ. The social benefit is equal to the number of patients with the biomarker who are thereby enabled to take the drug, multiplied by their expected benefit from taking the drug, net of both side effects and marginal production costs.

Thus it is socially beneficial to include the biomarker in the trial if the sum of these two benefits exceeds the cost of the test, which is s per subject multiplied by the number of subjects t.

(1) $$n.\gamma\,[\,(\pi + (1-\pi)(1-\rho))((1-m)(k+c) - s) + (1-\pi)\rho\,(m((V.b_L/m) - k - c) - s)] > s.t$$

We compare this with the private profitability of including the biomarker. As with the social benefit this occurs only if the biomarker is indeed validated by the trial. The private profitability has three components: any increase in the price of the drug that may be possible from the use of the biomarker, any saving in the marginal cost of the drug from avoiding giving the drug to patients without the biomarker, and any additional revenue from the drug due to a reduction in the probability of a statistically inconclusive test. We assume here that the cost of testing for the biomarker in the whole population if it is found to be relevant is borne by the procurer (the individual, the insurer, or the health authority as appropriate) and that the firm makes neither a loss nor a profit on that part of the treatment. It would be straightforward to incorporate alternative assumptions, but these would complicate the algebra for no additional insight.

In order to calculate this benefit explicitly we need to specify the price of the drug under various outcomes of the trial. Let P be the price of the drug if it is shown to have a statistically significant benefit for either proportion b_H or proportion b_L of sufferers, when either the biomarker is not included or it is included and proves ineffective. Recall that the per patient benefit, should it exist, is V for all patients regardless of population effectiveness. Let P' be the corresponding price when the biomarker is indeed shown to be effective. Then we can write the condition under which it is privately profitable to include the biomarker in the trial as

(2) $$n.\,\gamma\,[\,(\pi\,((P')m - (P) + c(1-m)) + (1-\pi)(1-\rho)\,((P')m - (P) + c(1-m))) + ((1-\pi)\rho\,m(P'-c)\,] > s.t$$

Comparing equations (1) and (2) is instructive. Each equation has the general form

(i) $$n.\,\gamma\,[\pi\,A^i + (1-\pi)(1-\rho)\,B^i + ((1-\pi)\rho\,C^i\,] > s.t \qquad \text{for } i=1,2$$

We can note that $A^1=B^1= (1-m)(k+c) - s$: when the trial would yield a significant result even without the biomarker, the social gains from the biomarker are just the marginal costs and the side effects avoided by no longer giving the drug to patients for whom it would be ineffective, less the cost of treating the whole population for the biomarker. By contrast, A^2 and B^2 both contain the term $c(1-m)$, indicating that the private firm internalizes only the marginal cost saving but not the avoidance of side effects. In addition, A^2 and B^2 both contain the term $(P')m - (P)$, which is just the net effect on revenue per sufferer in the population of using the biomarker. These terms will be negative unless the price for the drug when given to patients with the biomarker is raised to compensate for the greater precision of treatment with the biomarker. In particular, the new price must at least equal the price without the biomarker multiplied by $1/m$, which is the precision of the biomarker.

As for the terms C^i, we can note that if $C^1 = C^2$ this implies that $P' = (V.b_L/m) - k - sn/m$, meaning that the price is equal to the expected value of the treatment per patient treated with the biomarker, net of side effects and net of the per patient cost of treating the whole population of

sufferers for the biomarker. Once again this implies that for efficiency, the price if the biomarker is validated needs to reflect the greater precision of treatment made possible by the biomarker.

Overall, therefore, there are two main reasons why a private firm may have a weaker interest in including a promising biomarker in its clinical trials. First, it does not directly internalize the benefits to patients who are spared taking an ineffective drug with potential side effects, unless these benefits are reflected in the price of the drug. Secondly, the fact that the biomarker makes it possible to treat a more precise sub-population of patients will directly reduce firm revenues unless the price of the drug increases in proportion to the precision of the biomarker.

We now consider how the firm's incentives might change if it has the opportunity to include the biomarker in the trial without being obliged to disclose the effectiveness of the biomarker. It is evident that it will always choose to include the biomarker provided the benefits from avoiding the risk of a statistically inconclusive trial are large enough to outweigh the additional costs of testing the patients. These costs may be almost zero, if the biomarker is a characteristic (like age or gender) information about which will be collected automatically in the course of the trial. They may be positive but still low if testing for the biomarker is just a matter of subjecting a blood or tissue sample to an additional procedure.[4] They may be significant if testing for the biomarker involves subjecting the *patient* (rather than the sample) to an additional procedure, such as a genetic analysis of additional tissue (for instance, an RNA analysis).

However, if the firm has the option of including the biomarker without the obligation to disclose the result, the risk of losing revenue from a reduction in the number of patients treated will no longer be a disincentive. The firm can always choose not to disclose the relevance of the biomarker if this results in lost revenue. However, the increase in the efficiency of the firm's incentives to include the biomarker in the trial does not mean that there is an increase in efficiency as a result, because the firm now has inefficient incentives to disclose the result of the trial, notably if the biomarker is relevant but its disclosure would result in a revenue loss.

The calculation becomes more interesting if there are costs of including the biomarker in a "non-public" form. One potential cost is that if the biomarker does appear to be relevant and the firm wishes to demonstrate this to the authorities, it may need to bear the supplementary cost of a proper follow-up trial. For instance, there might be an informed-consent obligation for publicly performing certain tests, which would be incurred in a comprehensive trial but would be avoided if the firm wished to retain the non-disclosure option. Call this cost C for each member of the afflicted population that bears the biomarker (it might seem more natural to define it as the cost per patient enrolled in the trial, but the real costs include the delay in realizing revenue for each of the patients who subsequently purchase the treatment). Then the condition for it to be privately profitable to include the biomarker can be written

$$(3) \qquad n.\gamma \ [\pi \max[A^2,0] + (1-\pi)(1 - \rho) \max[B^2 ,0] + ((1-\pi)\rho \ m(P' - c - C) \ ] > s.t$$

Comparing (3) with (2) shows that including the biomarker in a private form will be more attractive than including it in a public form if the option value of not revealing the result of the test (given by the first two terms, and valuable only if the trial shows a statistically significant

[4] See Trusheim et al (2007) for more information about biomarkers and their use.

result without the biomarker) exceeds the greater expected cost of the follow-up study in the event that the firm chooses to use the biomarker.

To summarize, the perverse incentives embodied in the system of procurement prices for drugs may induce firms to engage in three types of undesirable behavior from the point of view of public welfare:

1) They may fail to include potentially promising but costly biomarkers in clinical trials (since the firm does not internalize the benefits to patients of reduced side effects, and since a successful biomarker may reduce the firm's revenue by diminishing the pool of patients who purchase the treatment).

2) They may include potentially promising biomarkers in trials without disclosing them in the public protocol, thereby requiring further costs to be incurred in follow-up studies to demonstrate their relevance if the firm decides to use them to establish statistical significance of the trial.

3) They may fail to disclose the relevance of biomarkers that have been shown to be relevant if the firm decides that these would not increase the chance of regulatory approval, but would diminish the pool of potential patients.

The first two types of perverse incentive are likely to be important only for a subset of biomarkers that are either costly to include in a clinical trial, or costly to include in a "non-public" form, as when they involve biomarker-specific informed consent. However, the third type of perverse incentive may occur for any kind of biomarker, however low its cost, if its inclusion might lower the revenues received by the firm. More generally, in the absence of carefully designed payment mechanisms, insufficient incentives to disclose the relevance of biomarkers would seem potentially to characterize a large number of fields of pharmaceutical research.[5]

Other settings to which these results apply include, for example, studies of the effects of drugs that have lost patent protection. A generic treatment may be widely used for a condition the FDA has not approved ("off-label" prescribing). Patients would be better off if prescribers knew whether the drug were indeed efficacious and what the appropriate dose might be. Similar arguments can be made for pediatric or obstetric indications. However, no party has the financial incentive to undertake such a study because there are no property rights left in the treatment. Of course, a government could undertake to provide this public good. If taxpayers did not want to fund the research, there are limited options in a 'free market' pharmaceutical system. A single-payor system could, for example, impose a fee on users of the generic drug that could be used to fund the acquisition of information through a trial. Note that the disincentive in this example is only the lack of an increase in sales; the biomarker problem we focus on in this paper is the strong disincentive to engage in research due to a projected *drop* in sales.

Our very stylized model abstracts from a number of real-world issues, such as the fact that in reality the size of the trial may not be fixed. For instance, there may be a trade-off between the number of patients enrolled in the trial and the inclusion of the biomarker as far as the effect on

[5] See Trusheim et al (2011) for a discussion of other factors related to the use of biomarkers in clinical trials.

the probability of finding a statistically significant result is concerned. Additionally, it might be possible for a diagnostic firm to have the right incentive to develop a test for a biomarker after the drug is launched.[6] Insurance companies would likely be willing to pay for such a test if it produced a significant savings in drug costs. Notice, however, that it is very likely that the original innovator has a greater capability in developing tests for biomarkers for its own product. Third parties are likely to be less skilled or slower, or both, so relying on them to solve this problem could involve social costs. Nevertheless, the model illustrates quite simply the challenge for those involved in devising mechanisms for pharmaceutical procurement created by the fact that firms have significant private information about the existence of potential biomarkers that affect the size of the potential patient pool.

3. Medical procurement schemes: an international comparison

The model above illustrates three inefficiencies that come about due to the firm's design of its clinical trial. The root cause of the inefficiencies is the inability of the firm to adjust the price of the drug to its realized efficacy in the population. (We exclude from our definition of "price adjustment" the annual price increases, usually small, but sometimes as large as 15%, that pharmaceutical companies routinely undertake.) In principle, it seems as if this could be possible; why shouldn't a firm alter its price by a large amount as it discovers significant new information about its product, for example? Many product prices fluctuate widely with supply and demand. The difference in our setting is that pharmaceutical prices are set in a political environment as well as an economic one. Healthcare costs are primarily borne by the government in most developed countries. Since governments rarely have as many resources as they desire, and healthcare is a large budget item, the cost of healthcare is often the subject of public debate and scrutiny. The price of pharmaceutical products is typically very visible; prices are often paid at least in part by patients, and typically a large proportion of citizens consume one or more pharmaceutical products. A firm setting price in such an environment faces both the formal regulation in each jurisdiction as well as the general threat of a political response should prices become "too" high. Furthermore, regulators and politicians around the world regularly compare the prices paid in their country to the cost of that same medication in other countries of similar income. Therefore, a firm that engages in price discrimination across developed countries may be creating political difficulties for itself. These forces make it costly to adjust price to match efficacy in some jurisdictions.

We should make it clear that the critical assumption in our model is the firm's inability to raise price after new information about efficacy is discovered. There are, of course, differences across countries in the level of prices, with the US being the outlier in its willingness to pay very high prices for pharmaceutical treatments.[7] This high willingness to pay is known by firms when they set the initial launch prices of their drugs, as is the high cost of later raising the drug's price.

[6] Intellectual property rights held by the innovator might be a constraint on this strategy.

[7] We are aware of no QALY (or similar) standard for a major payor in the United States. Furthermore, we know of no case where a firm's product was rejected by Medicare or an insurer due to its price level. (Indeed, Medicare is prevented by law from imposing such a standard.)

Both factors likely contribute to the high US launch prices of pharmaceutical products, but they are separate mechanisms.

Nevertheless, there are some jurisdictions that, at least in principle, allow such dynamic re-pricing in response to new information. In 2009 England adjusted its pharmaceutical pricing scheme (PPRS) to allow firms to change their proposed prices in response to new positive studies of efficacy or additional indications. In return for being able to raise price in response to better clinical outcomes, the regulator is also permitted to lower a drug's price in response to poorer trial results. The basic methodology of NICE (National Institute for Clinical Effectiveness) is to use data on clinical effectiveness to calculate an incremental quality effectiveness ratio. This ratio represents the net gain per additional net cost of the new treatment. The numerator is the price difference between the two treatments (including the price of complementary medications, nursing, etc), while the denominator is the difference in QALYs between the two treatments. If a product has an incremental price per QALY that is below a threshold level (the threshold is officially not disclosed by NICE but commonly believed to be about £30,000) then the agency issues a positive recommendation and all health authorities must provide the treatment. By contrast, drugs with a high incremental price per QALY are not recommended for use, though local health authorities and physicians may provide those treatments if they choose and can afford to pay for them out of their global budgets.

One can immediately see in this setting that a firm has an incentive to choose a price close to the threshold employed by NICE. If the firm's best guess of the threshold is £30K, and it knows its drug produces 0.1 additional QALY more than the next best alternative product on average, then in the simplest possible model the firm will want to submit a price of £3,000. (Note that in this simple example we completely abstract from uncertainty over the comparator, the data being used, and other more sophisticated aspects of the game between firm and regulator.) The beauty of this type of rule is its flexibility. Suppose the firm discovers a biomarker in the clinical trial population, and suppose further it determines that the entire positive effect of the drug is being driven by 10% of the patients with the biomarker. If use of the drug were restricted to this 10%, the total social gain to patients would be unchanged since the total number of life years saved would remain constant. If the total revenue offered to the firm was *ex ante* efficient, then there would be no reason to alter it due to the discovery of the biomarker and consequent limiting of the use of the drug. *Ex post*, the drug would be consumed by one tenth of the patients that were previously taking it, but the firm would charge a price that was ten times higher. The price per QALY would be unchanged, as both the numerator and denominator increase by a factor of 10.

A scheme with a procurement price that is flexible in response to efficacy means that, in theory, the discovery of a biomarker and the consequent focusing of the use of the medication on responsive patients need not lower revenue to the innovating firm. Moreover, the medication can continue to pass a QALY test when taking into account both the new price and the new usage.

Other examples of novel pricing from England come from the relatively new "Patient Access Schemes" which are *ad hoc* performance-based contracts and arrangements to share risk with the manufacturer that need special government approvals and are relatively rare. For example, if the treatment does not perform as expected, the manufacturer may have to forfeit revenues. A good example related to our model is the pricing scheme adopted by Johnson & Johnson's Velcade

(whose generic name is bortezomib). This cancer drug was effective in a minority of patients, and achieved complete remission in approximately 15%. The remaining patients were not helped at all, and significant side-effects were reported in some[8]. At the time there was no known attribute to help physicians predict who would benefit from this treatment, and like our motivating example in the introduction, the drug was expensive. Due to its high price and poor efficacy (diluted by the low response rate), Velcade would have failed the NICE test and would therefore have had zero sales in England. However, J&J proposed a novel pay-for-performance scheme: NHS would administer the drug to all indicated patients, but would only pay for the drug in the cases where there was a clinical result (a 50% reduction in Serum M levels). This result was expected to occur in about half of all patients.

One can immediately see that this would lower the price per QALY by a factor of two, since the effective price would drop to approximately one half of its previous level. Using this pricing plan, NICE gave Velcade a positive recommendation and cancer patients in England were able to benefit from it at a lower price. Because the marginal cost of the medication was low, the absence of a known biomarker was not a barrier to a scheme that required delivering the medication to all affected patients. In a setting where there is a procurement scheme that permits price adjustment in response to efficacy through either a QALY methodology or a pay-for-performance methodology, the firm's incentive to search for viable biomarkers may be preserved (though the firm still may not internalize side effects or the cost of testing, depending on institutional details).

While pay-for-performance schemes such as these can solve many problems, an immediate difficulty that suggests itself is that performance may not always be easily verifiable.[9] Lack of verifiability can create potential incentives for distorted reporting of patient outcomes, especially when these are not a matter of mortality but of less easily verifiable symptoms. However, where outcomes can be verified with reasonable reliability, pay-for-performance contracts have other virtues besides giving incentives for research into biomarkers. First, they may arbitrage differences of opinion between insurers and pharmaceutical companies. A company that is optimistic about the efficacy of a treatment in a particular case will estimate that a contract is more lucrative than an insurer with forecasts informed by the less positive clinical literature. This difference in beliefs may make pay for performance contracts especially desirable between firms and insurers. Secondly, under some circumstances it might be desirable to pass some of the sensitivity of price to performance on to patients. In normal circumstances, uncertainty in prices will be bad for risk-averse patients, but uncertainty in drug pricing can be positively desirable if the price is positively correlated with the patient's ability to repay. A drug that the patient need only pay for on the condition that she is restored to health will bring her higher utility than a drug with the same expected, but fixed, price.

Other nations have systems that also consider price in relationship to efficacy, though none has a system that is quite as well designed as England's. Australia's approval process has a cost-effectiveness track for firms with new treatments that have clinical evidence of efficacy.[10] The

[8] ttp://en.wikipedia.org/wiki/Velcade
[9] See Raftery (2010) for an example.
[10] Owen et al (2008) describes a new scheme in Australia for evaluating effectiveness and adjusting price accordingly.

Pharmaceutical Benefits Pricing Authority then sets a reimbursement price, which depends on the strength of the clinical evidence and other factors. If the drug's sales are higher than anticipated, the government negotiates a special rebate, which brings the total payment closer to a lump sum than a linear pricing scheme. However, the (effective) price adjustment is not in response to additional clinical evidence concerning realized effectiveness in particular groups. Germany has a very strong reference price system that does not allow for new information to reclassify a drug into a different reference group. France bases its prices on the lowest price available in a group of other European countries, and therefore indirectly price is loosely based on cost-effectiveness. Increased expenditure can lead to negotiations for special rebates. Neither system appears to encourage investment in learning about biomarkers.

An environment that does not consider cost effectiveness at all can be found in the United States, the single most important market for new pharmaceutical products in the world (with 40% of global pharmaceutical revenue). Launch prices for new medications are completely unregulated in the United States; the firm is free to set any price it feels the market will bear. Many patients are insured in a way that makes them somewhat indifferent to the cost of the medication. As shown by Berndt (FIND CITE) when consumers are generously insured, the optimal profit-maximizing price of the drug increases dramatically. Importantly, a significant fraction of demand in the United States is managed by Pharmacy Benefit Managers, or PBMs, whose job it is to create elasticity of demand. The PBM bargains with manufacturers over the price of the drug and steers its patients to those that offer the best price-quality tradeoff. So one can think of the PBM as roughly analyzing price per QALY, and demanding products accordingly. The PBM also tends not to "deny" coverage of medications due to their failure to fall under a price per QALY threshold. Rather, medications that are not cost effective have a much higher co-payment for the consumer. This financial incentive, in addition to education to physicians and pharmacists, drives demand to the preferred product. However, there are drugs that have very poor substitutes for which the PBM cannot create price competition; the insurer typically must cover these drugs despite their cost. These are novel drugs, drugs that treat frail patients, drugs that treat fatal illnesses and so on. Many biologics fall in this category. The forces constraining the manufacturer's price for such medications are not primarily due to the existence of substitute products, but rather will be both economic and political.

Medicare enrollees must pay 20% of the cost of physician-administered drugs. However, many Medicare and other patients in the US carry supplemental insurance that in turn covers co-payments (e.g. Medicaid). Privately insured patients without such supplemental coverage may be fully covered by their primary insurer, or may pay significant co-insurance (e.g. 30%) of the cost of any "specialty" drug. The very high prices of many biologics means that 30% co-insurance results in a significant payment relative to median family income. Many of the biologics currently on the market are for dire diseases, and so consumer willingness to pay could be high. However, there are many consumers whose income is not sufficient to pay the co-insurance, even if they are 'insured.' A number of manufacturers offer financial assistance to such patients. If such a patient would otherwise drop out of the market, the clear financial incentive for the manufacturer is to preserve demand by forgiving the patient's 30% co-payment while collecting the 70% co-payment from the insurer. Of course, such 'financial aid' undoes any incentive effects of the co-insurance.

List prices play an important role in the pricing of pharmaceuticals in the US. A general theory of list prices is unfortunately lacking in the economics literature. One potential role the

list price may play in the context of pharmaceuticals is to allow the firm to commit up front to a price consistent with the most optimistic forecasts of demand (efficacy). We assume that raising price is costly to the firm in terms of publicity about the brand, political scrutiny, potential regulation, etc. Thus the firm prefers a pricing scheme that does not require it to increase price after a product is launched. If maximum demand is realized, the list price ensures that firm has not foregone any profit by choosing a price *ex ante*. If demand turns out to be lower, the firm may choose to offer discounts off the list price to all or certain of its customers, effectively lowering the price to match the realized quality of the product. Discounts of this type are used in the retail fashion industry with great frequency in order to match supply with realized demand.

The advantages of a list price to a pharmaceutical firm are several. First, as noted, the firm does not have to face the cost of raising prices in the event that the maximum benefit turns out both to be realized and also to be common among patients. The only potential price alteration it will make is downward. Second, a high US list price serves as a useful benchmark price, or reference, for pharmaceutical regulators in other countries. Discounts off list price are often confidential and tailored to individual customers. Thus the list price is the most public and transparent price available to foreign regulators who are looking for comparisons. Third, a list price set at the maximal outcome allows for perfectly targeted discounts that may change over time according both to the clinical trial outcomes of the drug, any competing drugs that might be introduced, and differences across customers in willingness to pay, or views on the substitutability of the drug.

In many contexts, therefore, the firm will choose a list price that represents the maximum benefit the drug provides – across all clinical trials and patients – given the competitive environment at launch. For example, the firm could choose a price representing the QALY benefits experienced by the patient with the best outcome in the clinical trial. Such a patient's experience has face validity in a political setting, which is useful. Furthermore, for that patient, the medication will have a price per QALY that falls in the standard range. However, to the extent there is heterogeneity in outcomes in the patient population, there will be many patients whose price per QALY is much higher. The example of the drug Yervoy, discussed in the introduction, illustrates this perfectly: for the 80% of patients who obtain a two week increase in life expectancy the effective cost per QALY is $3.12 million. Other examples about which we know very little at present are Alzheimer's drugs. These drugs have small average impacts on the progression of the disease and are very expensive, but seem to significantly benefit a small subset of patients.[11]

We want to emphasize that the specifics of the pricing regime drive the inefficiency of the firm's research decision. The formal model above demonstrates this point. If the firm may not adjust price upwards upon discovery of a biomarker, the model shows that it will not have a financial incentive to reveal it, let alone invest in studies to confirm its accuracy. Unfortunately, the US, a jurisdiction with 40% of global demand, is likely to have one of the worst distortions concerning research into biomarkers due to its pricing regime.

4. Conclusions

In summary, a firm in an environment where price is fixed has perverse incentives in the design of a clinical trial. To use the language of economics rather loosely, the firm wants the trial to

[11] Communication with medical staff at Kaiser Permanente May 29, 2013.

contain as many types of patients as possible conditional on achieving a t-statistic of 2. If the medicine does not have a significant effect (t-statistic of 2) then sales are zero because the regulator does not approve the drug. If the trial is restricted to only the type of patient that the firm thinks will respond, significance will be high but sales will be low. If the trial can be made larger, so that it includes patients with marginal or zero benefit and yet the medicine still has a significant effect in aggregate, approval is still achieved and sales are larger. It is this last case that we analyze in our model. Does the firm want to spend money to research a biomarker that will distinguish patients with a strong response from those with no response? If the price of the drug is fixed, and currently both groups purchase it, doing so can only reduce firm revenue.

A policy conclusion we draw from this research is that purchasers of pharmaceuticals, whether private insurers or government agencies, might gain from additional use of pay-for-performance contracts or prices based on "updatable" QALYs, particularly for expensive drugs with outcomes that vary across patients. These contracts, and perhaps others we do not know about, help mitigate the significant incentive problems against researching biomarkers that we describe in this paper. They could also help fix gaps in research more generally, such as those in generic drugs or natural remedies. Our very simple model has shown that failure to adjust pricing to clinical efficacy – or fixed prices more generally – could have significant negative implications for research into biomarkers. The rapid growth in expenditures on biologic drugs and in our knowledge of the role of genetics suggests that these issues will take on increasing importance in the future.

References:

Beckman, Robert, Jason Clark and Cong Chen (2011): "Integrating predictive biomarkers and classifiers into oncology clinical development programmes," *Nature Reviews: Drug Discovery* (10): 735-748.

Kirsch, Irving, (2010), *The Emperor's New Drugs: Exploding the Antidepressant Myth*, Basic Books, Philadelphia.

Owen, A.J. et al (2008) "A new model to evaluate the long-term cost effectiveness of orphan and highly specialised drugs following listing on the Australian Pharmaceutical Benefits Scheme: the Bosentan Patient Registry", *Journal of Medical Economics*, Vol. 11, No. 2, Pages 235-243.

Raftery, James (2010) Multiple sclerosis risk sharing scheme: a costly failure" *British Medical Journal* 2010; 340.

Trusheim, Mark, Ernst Berndt and Frank L. Douglas (2007): "Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers", *Nature Reviews: Drug Discovery* (6): 1-7.

Trusheim, Mark R et al (2011) Quantifying factors for the success of stratified medicine, *Nature Reviews Drug Discovery* **10**, 817-833.

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