Stanford University • May 2014

SIEPR policy brief

Stanford Institute for Economic Policy Research

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Do Firms Underinvest In Long-Term Research? Evidence From Cancer Clinical Trials

By Eric Budish (Chicago Booth), Benjamin N. Roin (Harvard Law School), and Heidi Williams (MIT and NBER)

Introduction

A survey of drugs approved by the U.S. Food and Drug Administration (FDA) over the past five years reveals that eight new drugs have been approved to treat lung cancer, the leading cause of cancer deaths in the US. All eight of those drugs were approved on the basis of evidence that each generated incremental improvements in survival among patients with the most advanced form of lung cancer. A well-known example is Genentech's drug Avastin, which was estimated to extend the life of late-stage lung cancer patients on average from 10.3 months to 12.3 months. In contrast, no drug has ever been approved to prevent lung cancer, and only six drugs have ever been approved to prevent any type of cancer.

This pattern of drug development could be explained by any number of factors. More patients could be diagnosed with late-stage lung cancer than are diagnosed with early-stage lung cancer, or the scientific challenges associated with treating early-stage lung cancer could be extremely difficult. This brief summarizes the results of a study that investigated an alternative idea: Private firms may invest more in late-stage cancer drugs — and "too little" in treatments for early stage cancers and cancer prevention drugs — because late-stage cancer drugs can be brought to market comparatively quickly, whereas drugs to treat early-stage cancers and to prevent cancers require a much longer time to bring to market.

In our paper, we present a simple theoretical model that clarifies two potential reasons why private firms may underinvest in long-term projects. First, companies may be too "impatient," in the sense of excessively focusing on behaviors with short-run payoffs. This idea has been widely discussed in both policy

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and practitioner circles, as well as in the academic literature, but little empirical evidence exists on whether this problem is quantitatively important in practice. Second, the structure of the patent system may also disincentivize long-term projects. We traditionally think of the patent system as offering a "fixed" period of market exclusivity — e.g., 20 years of patent protection in the United States. However, in practice, many firms face competitive pressure to file patent applications at the time of discovery ("invention") rather than at the time of first sale ("commercialization"). This implies that even though on paper patent terms are fixed at 20 years, in practice effective patent terms vary. Inventions that commercialize at the time of invention receive a full patent term, whereas inventions that have a long time lag between invention and commercialization receive substantially reduced — or, in extreme cases, zero — patent terms. This means that the patent system provides — perhaps inadvertently — very little incentive for private firms to engage in long-term research in cases where firms file patents at the time of discovery. This situation holds in the pharmaceutical industry, where firms face strong incentives to file patent applications early on in the drug development process. Because of the need for subsequent research and clinical trial investments, drugs will not actually be available to patients until many years after patent applications are filed.

Our study: Measuring "Missing" R&D Investments

The idea that firms may underinvest in long-term research — while intuitive — is difficult to test empirically. The key prediction is that there are "missing" private R&D investments on projects with long commercialization lags. In practice, we do not observe the commercialization lags of projects that are never developed, and "missing" R&D is hard to distinguish from alternative explanations such as a lack of demand or a lack of scientific opportunities.

Three features of cancer markets allow us to make progress on quantifying this missing R&D. First, the treatment of cancer patients is organized around the organ (e.g., lung) and stage (e.g., metastatic) of disease, which provides a natural categorization of both observed and potential R&D activity. Second, for each such group of cancer patients we observe a good predictor of how long it would take to commercialize drugs for those patients: the expected survival time of patients diagnosed with a particular kind and stage of disease. Survival time predicts commercialization lags because a firm commercializing a new cancer drug must complete FDA-required clinical trials showing evidence that the drug is safe and effective; and, in cancer, "effective" is usually interpreted as improving survival. Because it takes longer to document evidence that a drug improves survival when patients have a higher baseline survival rate, the survival rate of patient groups can provide a proxy for commercialization lags. Third, cancer markets provide several sources of variation that allow us to construct empirical tests for whether private firms underinvest in long-term projects.

To illustrate, consider two examples of clinical trials for prostate cancer treatments, both published in the *New England Journal of Medicine* in 2011. A first study analyzed a treatment for metastatic prostate cancer (an advanced stage of prostate cancer with a five-year survival rate of around 20 percent). The study tracked patient survival for a median time of 12.8 months, and estimated statistically significant improvements in survival (a gain of 3.9 months of life on average). A second study analyzed a treatment for localized prostate cancer (an early stage of prostate cancer with a five-year survival rate of around 80 percent). The study tracked patient survival for a median time of 9.1 years, estimating statistically significant improvements in survival. As expected, this stark difference in patient follow-up times translates into a large difference in clinical trial length: 3 years for the metastatic patient trial versus 18 years for the localized patient trial. Consistent with the idea that commercialization lags reduce R&D incentives, the study of metastatic cancer patients was funded by a private firm whereas the study of localized cancer patients was funded by the National Cancer Institute.

For our study, we construct data on all such cancer clinical trials from 1973 to 2009, which

we match to data on patient survival times over the same period. Our survival data is drawn from patient-level cancer registry data, which we aggregate to cancer-stage level patient groups (e.g., localized breast cancer, metastatic prostate cancer). Our measure of cancer treatment R&D is newly constructed from a cancer clinical trial registry that has cataloged trials since the 1970s. For example, if we observe a firm initiate a clinical trial enrolling patients with metastatic breast cancer, we "count" the existence of that trial as an indicator of private R&D investment on treatments for metastatic breast cancer patients. These clinical trial counts provide an observable proxy for dollars of R&D investments into treatments for different groups of cancer patients, which is useful because dollars of R&D investments are not directly observable.

Our Findings: Research Investments

Using our newly constructed data, we first document that patient groups with longer commercialization lags (as proxied by higher survival rates) tend to have lower levels of R&D investment. Figure 1 gives a sense of this basic pattern. The horizontal axis plots the average five-year survival rate for each of three cancer stages: metastatic, regional, and localized. The left-hand-side vertical axis plots the number of clinical trials for each group. On average, metastatic cancer patients in our data have a five-year survival rate of around 10 percent, and are eligible to enroll in around 12,000 clinical trials in our data. In contrast, localized cancer patients have a five-year survival rate of around 70 percent, and are eligible to enroll in just over 6,000 clinical trials in our data.

In theory, this correlation between the five-year survival rate and R&D investments could be explained simply by differences in demand for treatments. While our study investigates this possibility through a series of more formal empirical tests, a simple test — illustrated by the right-hand-side vertical axis — suggests that this possibility does not explain the data. Specifically, the number of clinical trials per life-year lost from cancer (a proxy for market demand) shows a very similar pattern.

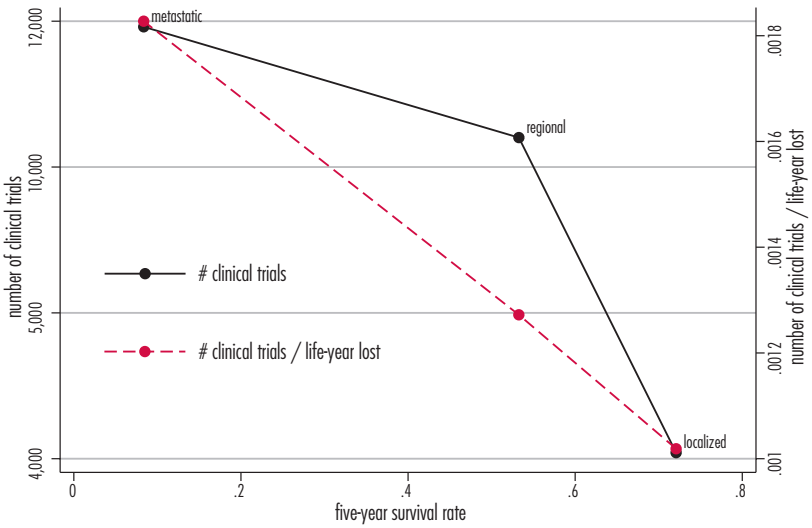
This pattern is even more stark if we contrast recurrent cancers (advanced cancers with very poor survival prospects) and cancer prevention. Fewer than 500 trials in our data aim to prevent cancer, whereas recurrent cancers have more than 17,000 trials.

Note that from a medical perspective, a distortion in R&D away from localized cancer patients could be particularly concerning. Metastatic cancers are most often not curable, whereas localized cancers more often are.

We then present results from two empirical tests that aim to test our hypothesis more rigorously.

First, we document evidence that shortening commercialization lags increases R&D investments. This test takes advantage of the fact that some types of cancers are allowed to use so-called surrogate endpoints. Whereas most clinical trials must test whether a treatment improves survival, trials that are allowed to use surrogate endpoints measure the effectiveness of a drug in terms of a non-survival

Figure 1



outcome that can — in most cases — be observed more quickly than survival would be observed. As an example, clinical trials for leukemia often rely on a "complete response" metric which can be measured via blood and bone marrow samples, and which can provide evidence of whether a treatment is effective in a shorter amount of time than survival improvements can be observed.

Our empirical work takes advantage of the fact that some cancers — specifically, blood-related cancers (leukemias and lymphomas) — are almost always allowed to use surrogate endpoints, whereas other cancers are allowed to use surrogate endpoints less often. Figure 2 illustrates this comparison. As in Figure 1, the horizontal axis orders observations by the five-year survival rate, and the vertical axis orders observations by the number of clinical trials. Here, each observation is a cancer-stage — e.g., localized breast cancer. The gray dashed line is fitted to the data on non-blood related cancers, whereas the red solid line is fitted to the data on blood-related cancers.

The key relationship of interest — the correlation between the five-year survival rate and R&D investments — sharply differs across these two groups of cancers. As predicted by our model, blood-related and non-blood related cancers have similar levels of R&D investments for patient groups with short survival times. Intuitively, the reduction in commercialization lag afforded by a surrogate endpoint is very small for patient groups that would have had very short clinical trials even if survival had been used as the outcome variable. In contrast, for trials enrolling patients with long survival times — which would have required long clinical trials had surrogate endpoints not been used — R&D investments are much higher when surrogate endpoints are allowed.

This pattern suggests that when valid surrogate endpoints are available, allowing firms to use surrogate endpoints not only shortens clinical trial lengths, but also increases R&D investments.

Our second empirical test documents a contrast between public and private R&D investments. The key idea we test is whether private research investments are distorted away from long-term research projects compared to what society would prefer. If we take public research investments as one indication of what R&D allocations society would prefer, we would expect to see that the ratio of private research investments to public research investments is lower for research projects with long commercialization lags. Figure 3 documents evidence consistent with this idea. The share of clinical trials that are privately financed is lower for projects with longer commercialization lags.

As a complement to these empirical analyses, we also provide case study evidence documenting that all six FDA-approved cancer prevention technologies — technologies that should have long commercialization lags, and hence should be "missing" — either relied on the use of surrogate endpoints or were approved on the basis of publicly financed clinical trials. That is, we expect cancer prevention trials to have long commercialization lags, and no cancer prevention technologies have been privately developed without relying on surrogate endpoints. A first example is the drug Tamoxifen, which was FDA approved for several

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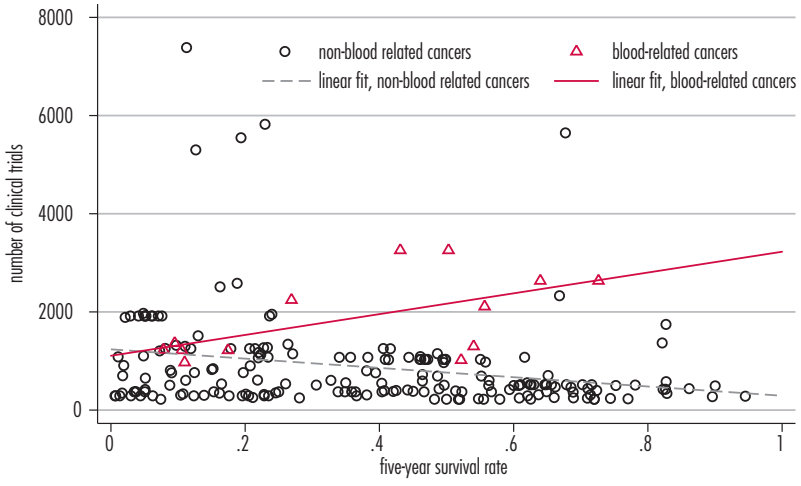
Figure 2



cancer indications while on-patent. Later, a publicly funded clinical trial supported the 1998 FDA approval of Tamoxifen as a chemoprevention agent — preventing breast cancer incidence in high-risk groups. A second example is the recent FDA approval of cervical cancer vaccines, which relied on the use of human papillomavirus (HPV) incidence as a surrogate endpoint for cervical cancer incidence.

Discussion

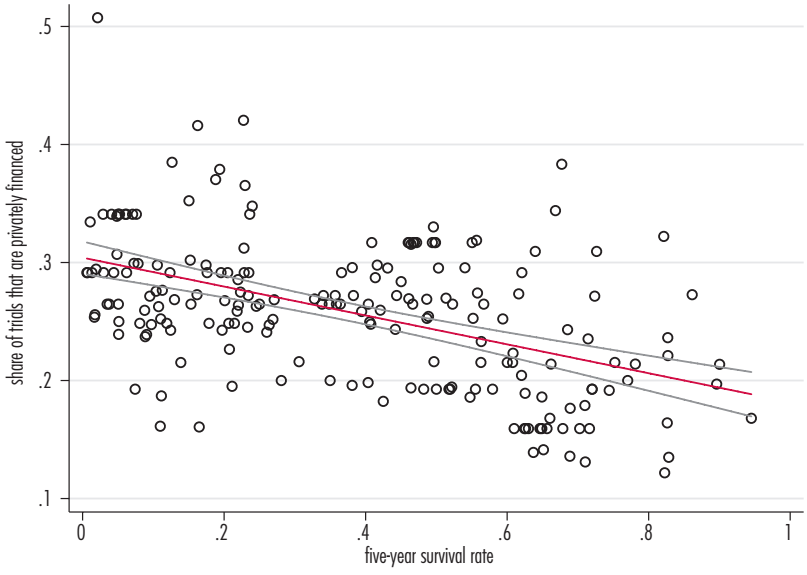
Taken together, our study documents a body of empirical evidence providing support for the idea that commercialization lags distort private R&D investments. In the case of cancer treatments, this suggests that private firms provide "too few" research investments on drugs to prevent cancer or to treat early stage cancers, compared to the amount they invest in treatments for late stage cancers.

While our theoretical analysis is applicable in general, our data and empirical evidence is specific to cancer markets. This is itself of substantive interest because of cancer's tremendous morbidity and mortality burden. In the paper, we do a rough calculation of what improvements in cancer survival rates would have been observed — from 1973 to 2003 — in the absence of this distortion in private R&D. We estimate that among one cohort of patients — U.S. cancer patients diagnosed in 2003 — this distortion resulted in around 890,000 lost life-years. Valued at $100,000 per life-year lost, the estimated value of these lost life-years is on the order of $89 billion.

In the paper, we analyze three policy interventions that could address this distortion: a policy change that would allow firms to rely on (valid) surrogate endpoints in clinical trials, targeted R&D subsidies, and a patent design change that would start the patent clock at commercialization. In practice, the patent design change may be administratively easier to implement through FDA-awarded exclusivity grants, as are currently implemented under existing public policies such as the U.S. Orphan Drug Act, rather than via reforms to the patent system.

Our empirical evidence suggests that at least in the case of blood-related cancers, apparently valid surrogate endpoints were effective in increasing R&D investments on innovations that would otherwise have had long commercialization lags. The resulting increases in R&D appear to have translated (in this case) into real gains in patient health. While much attention has been focused on the risks and costs of using surrogate endpoints that may imperfectly correlate with real improvements in patient health, our analysis is — to the best of our knowledge — the first attempt to use the historical record to quantify how the availability and use of a valid surrogate endpoint affected R&D allocations and patient health outcomes. Our results suggest that research investments aimed at establishing and validating surrogate endpoints may have a large social return.

Figure 3



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Eric Budish, Benjamin N. Roin, and Heidi Williams (2013), "Do fixed patent terms distort innovation? Evidence from cancer clinical trials," NBER working paper #19430.

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366 Galvez Street
Stanford, CA 94305
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A publication of the
Stanford Institute for
Economic Policy Research

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