NBER WORKING PAPER SERIES

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Working Paper 20889
http://www.nber.org/papers/w20889

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
January 2015

We acknowledge the financial support of the National Science Foundation through its SciSIP Program (Award SBE-0738142). We are grateful to Jason Abaluck, David Autor, Jim Bessen, Alex Frankel, David Genesove, Ben Jones, Naomi Hausman, Kelly Shue, Scott Stern, John Van Reenen, Heidi Williams, and numerous seminar participants for helpful comments and suggestions. Azoulay and Graff Zivin are currently supported by the NIH for a project examining life cycle events, innovation, and the evolution of scientific fields (P01-AG039347). Azoulay, Graff Zivin, and Sampat are all prior recipients of NIH funding. Azoulay and Li have a current special volunteer agreement with NIH to facilitate access to peer review data. All errors are our own. The views expressed herein are those of the authors and do not necessarily reflect the views of the National Bureau of Economic Research.

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NBER Working Paper No. 20889
January 2015, Revised September 2015
JEL No. O3,O33,O38

ABSTRACT

We quantify the impact of scientific grant funding at the National Institutes of Health (NIH) on patenting by pharmaceutical and biotechnology firms. Our paper makes two contributions. First, we use newly constructed bibliometric data to develop a method for flexibly linking specific grant expenditures to private-sector innovations. Second, we take advantage of idiosyncratic rigidities in the rules governing NIH peer review to generate exogenous variation in funding across research areas. Our results show that NIH funding spurs the development of private-sector patents: a $10 million boost in NIH funding leads to a net increase of 2.3 patents. Though valuing patents is difficult, we report a range of estimates for the private value of these patents using different approaches.

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1 Introduction

The pharmaceutical firm Novartis made use of decades of publicly-funded research in the development of Gleevec, a remarkably effective treatment for chronic myelogenous leukemia (CML). Between the 1960s and 1980s, numerous studies elucidated the causes of CML, documenting the role of a specific gene mutation that leads tyrosine kinase, a common cell signaling molecule, to become overactive. This understanding pointed to an approach for treating CML—develop compounds to inhibit tyrosine kinase—which Novartis scientists then pursued (Pray 2008).

Annual public-sector expenditures in biomedical research total more than $30 billion in the United States alone. While the example of Gleevec is frequently invoked to support the claim that these investments spur private-sector innovation (e.g., Relman [2003]), its history also illustrates the pitfalls that accompany attempts to test this claim empirically. The synthesis of *imatinib mesylate*, the chemical compound eventually marketed as Gleevec, was the culmination of both public and private research investments not only in cancer, but also in the areas of gene mutation, cell signaling, and vascular disease (Hunter 2007). This complicated genealogy means that attempts to isolate the causal role of public funding in developing this—or any other—medical treatment must (i) track the unpredictable and often convoluted path between initial R&D investments and final commercial products; (ii) account for the possibility that public investments may crowd out industry efforts; and (iii) isolate variation in public investment that is uncorrelated with the factors that drive private investments. This paper makes progress on each of these issues.

We analyze the impact of biomedical research funding by the National Institutes of Health (NIH) on patenting by private sector firms, from 1980 through 2005. Our first contribution is to construct improved measures of the commercial output associated with publicly funded research. The most recent work in this area, Blume-Kohout (2012), Toole (2012), and Manton et al. (2009), examines the effects of funding for a disease on outcomes relevant for that same disease, using a pre-specified lag structure. This strategy, however, misses any potential impact on other diseases or with other time lags. Our paper takes a different approach. We construct a new dataset that uses bibliometric information to explicitly link NIH grants with the publications that they support and the patents that cite those publications. By letting the data reveal the relevant linkages, we are able to identify patents that build on NIH-funded research without making a priori assumptions

about the diffusion of scientific knowledge over time and across disease areas. This strategy allows us to trace the often circuitous path from NIH funding to patented innovations.

In addition to uncovering direct linkages between public funding and private-sector patenting, we develop a novel method that combines citation information with a measure of research similarity to identify the set of private-sector patents intellectually related to a given NIH research area—even if these patents do not build explicitly on NIH-funded work. This is important because NIH funding may crowd out private investments. By identifying private-sector patents in areas potentially influenced by NIH funding, we are able to measure the overall impact of public-research investments on private-sector innovation, accounting for the possibility of crowd-out.

Our final contribution relates to identification. Public investments may target research areas with the most potential for follow-on innovation, for example those where disease burden is rising (Acemoglu and Linn 2004) or scientific opportunities are increasing (Lichtenberg 2001). If this were the case, we could observe a correlation between public funding and private patenting even if public investments were unproductive. To address concerns about the endogeneity of public investments, our paper begins with the observation that scientists do not simply propose research on "cancer." Instead, they typically propose research on specific scientific questions that may, at some later date, become useful in the search for cancer therapies. This means that NIH funding for an entire disease may not necessarily coincide with the actual set of resources available for private-sector researchers to build upon. For example, funding for a cancer researcher using a mouse model to study the physiology of tumors is unlikely to be useful for a cancer researcher using high-throughput sequencing techniques to study gene expression. By recognizing that biomedical research has both a science and disease component, we are able to construct a finer-grained measure of public investment at the "disease/science" level.

This level of granularity helps our analysis in two ways. First, we use fixed effects to control for time-varying unobservables related to disease burden or scientific potential. Second, we take advantage of idiosyncrasies in NIH funding at the disease/science level. Consider a grant application related to a specific disease/science area, say cancer/cell signaling. One might decide whether to fund this application by comparing it with other cell-signaling applications (i.e., science rank) or by comparing it with other cancer applications (disease rank). The NIH does neither. Instead, it

decides whether to fund an application based on how its science rank compares with the science ranks of other applications in the same disease area. By requiring that applications be funded on the basis of this "rank of ranks," NIH funding rules often lead to cases in which disease/science areas with similar innovative potential receive different amounts of funding. We develop an instrument to take advantage of funding variation determined by procedural rigidities rather than by conscious efforts to direct resources to areas with more unobserved potential (see Section 3.4 for more details and an example). To the best of our knowledge, with the exception of Moretti, Steinwender, and Van Reenen (2014), no papers in this area have attempted to take advantage of plausibly exogenous variation in public investments.

Our results show that NIH funding increases total private-sector patenting. Our preferred empirical specification suggests that an additional $10 million in NIH funding for a research area generates 2.3 additional private-sector patents in that area, or roughly 1 patent for every 2 to 3 NIH grants. Of course, not all patents are equally valuable; the distribution of patent value is in fact highly skewed (Harhoff, Scherer, and Vopel 2003). In a series of back-of-the envelope calculations (Section 5.3 and Table 8) we report a range of estimates for the private value of these patents using different approaches.

Our results also help in understanding the path through which NIH investments influence private sector innovation by developing estimates of the cross-disease spillover effects of NIH funding. We show that fully half of the patents resulting from NIH funding are for disease applications distinct from the one that funded the initial research. The size of this effect underscores the importance of our approach to linking patents with funding: by looking only within the same disease area when measuring impact, the prior literature in this area would miss almost half of the total impact of basic research funding.

Finally, we consider the possibility that changes in NIH funding can lead firms to reallocate resources to or from other projects. We show that firms which work in an area of increased NIH funding produce more patents in that area, with no commensurate decreases in patenting in other areas of their portfolio. This suggests that NIH funding spurs private patenting by either increasing total firm R&D expenditure or increasing the efficiency of these expenditures.

We proceed as follows. In Section 2, we discuss institutional background and the various effects that NIH funding may have on private patenting. We describe our empirical strategy in Section 3; Sections 4 and 5 present our data and main results, respectively. We discuss the impact of NIH funding on reallocation of firm R&D investments in Section 6, and Section 7 concludes. Robustness checks and alternative specifications can be found in Appendices E, G, H, I, and J.

2 Institutional Background

The NIH is the largest single supporter of biomedical research in the United States, responsible for funding 28 percent of U.S. medical research in 2008. This compares to the 37 percent of research funded by pharmaceutical firms, 15 percent by biotechnology firms, and 7 percent by medical device firms (Dorsey et al. 2013).[1]

The bulk of NIH funding is for "basic" research that aims to extend the frontiers of medical understanding. About one-third of NIH funding is for clinical research (including patient-oriented research, clinical trials, epidemiological and behavioral studies, as well as outcomes and health services research) that is more applied in nature. The agency also supports a range of training grants that help develop the U.S. scientific and medical workforce.

2.1 Possible Effects of NIH Funding

Though many new therapies have intellectual roots in publicly-funded, academic laboratories (Sampat and Lichtenberg 2011, Cockburn and Henderson 1998), most NIH grants yield neither patented innovations nor novel treatment modalities. Yet, NIH funding may have the effect of encouraging firms to make complementary investments in R&D. This may occur if firms underinvest in foundational research because of scientific uncertainty, the high fixed costs of R&D, or the difficulty of appropriating basic scientific knowledge. In this case, NIH investments may increase the expected returns to private investment by generating knowledge that clarifies opportunities for developing new therapies, as in the case of Gleevec. We refer to this possibility as NIH investments "crowding-in" private sector investments.

[1] Other funders include foundations, accounting for 4 percent, other federal funders, about 5 percent, and state and local governments, also about 5 percent.

It is also possible that NIH investments "crowd-out" private-sector efforts. This could happen for a variety of reasons. Public funds could simply be subsidizing the cost of a firm's existing research. Alternatively, they could lower the costs of entry for competitors, reducing the firm's ability to reap market rewards from its R&D investments. This concern is especially salient in the life sciences, since the organization of drug discovery research in the biopharmaceutical industry has been greatly transformed to mimic that of academic labs in terms of size, intellectual autonomy granted to researchers, and rewards linked to the production of high-impact publications (Henderson 1994). Many biomedical scientists also search for positions in academe and industry simultaneously (Stern 2004), and the patterns of mobility between the private and the public sector have been extensively documented (Zucker, Darby, and Torero 2002).

We develop outcome measures that directly test whether NIH funding is useful for firms. In addition, we examine the impact of NIH funding on total private-sector innovation in a given research area, taking into account the possibility that NIH investments may simultaneously encourage some private investments in a research area while crowding out others.

2.2 A Primer on NIH Peer Review and Funding Decisions

The NIH comprises 27 Institutes or Centers (ICs) that are typically organized around body systems (e.g., the National Heart, Lung, and Blood Institute), or disease areas (e.g., the National Cancer Institute). Each Institute receives its own Congressional appropriation and is responsible for funding research that is potentially relevant to its mission. Scientific evaluation of grant applications, by contrast, occurs primarily in approximately 200 standing review committees known as study sections. Each study section is organized around a scientific topic (for example, "Behavioral Genetics and Epidemiology" or "Cellular Signaling and Regulatory Systems") and is responsible for evaluating the quality of applications in its area. Study sections review grant applications from multiple disease areas with similar scientific underpinnings. In turn, ICs fund applications evaluated by multiple study sections.

Study sections assign each application a raw score. During the timespan covered by our data, these ranged from 5.0 (worst) to 1.0 (best). This raw score is meant to be a summary statistic for the study section's assessment of the quality of that application. Raw scores are then normalized within a

study section and converted into a percentile. We call this normalized score the application's "science rank." Once a study section has evaluated an application, the NIH's funding rule is mechanical: an IC must fund the applications it is assigned in order of their science rank until its budget has been exhausted. The worst score that is still funded is known as that IC's "payline." In summary, the peer review process at NIH generates three separate scores for each application: (i) the "raw score" given by the study section; (ii) the within-study section "science rank" immediately derived from the raw score; and (iii) the within-IC ranking of science ranks. It is this final "rank of rank" that determines whether an application is funded. As alluded to in the introduction, the structure of the NIH and its funding rules will play an important role in our empirical work. Section 3.4 details how we exploit these features to isolate exogenous variation in NIH investments across research areas. Appendix A provides more details about the NIH and NIH funding rules.

2.3 Measuring Biomedical Innovation Using Patents

Our main outcome variable is patenting by private sector biopharmaceutical firms (see Appendix B for more details on these patents). Patents may appear a surprising choice; researchers studying medical innovation have typically focused on outcomes that are more immediately welfare-relevant, such as reductions in mortality and morbidity (Manton et al. 2009), drugs entering clinical trials (Blume-Kohout 2012), or new drug approvals (Toole 2012). However, these outcomes cannot be readily linked to variation in public research expenditures without restrictive assumptions. By contrast, biomedical patents can be linked to specific grant expenditures using the bibliographic references they contain. Moreover, securing patents is the principal way that biopharmaceutical firms appropriate the returns from their R&D investments (Cohen, Nelson, and Walsh 2000).

Since our analyses focus on the patented outcomes stemming from NIH-funded research—thereby excluding effects on clinical practice, health behaviors, and unpatented surgical innovations—they cannot provide the foundation for a complete welfare calculation.[2] Another issue is that it is difficult to know the private or social value of individual patents. For the very small subset of

[2]Note that clinical or epidemiological findings may subsequently inspire drug development strategies followed by private firms, possibly resulting in patents that our analysis will capture. In a celebrated case, the patents granted to Eli Lilly concerning recombinant activated Protein C for the treatment of sepsis all refer to a clinical study correlating mortality in a small sample of severely septic patients with depressed levels of Protein C in these patient's bloodstream (Fourrier et al. 1992). This correlation provided the impetus for Lilly's attempt to synthesize a recombinant version of this protein. This product was ultimately withdrawn from the market in 2011 after new evidence emerged regarding the bleeding risks associated with the use of this drug.

patents pertaining to FDA-approved biopharmaceuticals (1,999 of the 315,982 patents in our sample), we can use estimates from the literature to calculate implied drug sales for the impacts of NIH funding in dollar terms—a rough estimate of the private value of these patents.

3 Empirical Strategy

We examine the impact of public R&D investments on private-sector patenting by estimating a regression of the form:

$$Patents_{\widetilde{dst}} = \alpha_0 + \alpha_1 Funding_{dst} + Controls_{dst} + \varepsilon_{dst} \quad (1)$$

The unit of analysis is a disease/science/time (DST) combination. Biomedical research typically involves a set of scientific questions applied toward a particular disease area. Scientists may study, for instance, the role of cell signaling in cancer or gene expression in diabetes. A disease/science classification can be thought of as a "research area" whose projects share a similar disease target and benefit from an understanding of similar scientific methods and mechanisms. We follow these research areas over time.

Our outcome variable, $Patents_{\widetilde{dst}}$, describes the set of private-sector patents that we can associate with NIH funding for disease d, science area s at time t. As further detailed below, these patents need not be confined to the same disease area d or science area s as the original funding source, nor do they need to be issued in the same year t.

The first step in our analysis is to assign NIH funded research projects to specific DSTs. Ordinarily, this task would not be straightforward because grant proposals often have titles—such as *"Impact of Type II Glucocorticoid Receptor Impaired Function in Transgenic Mice"*—that would not enable an outsider to the field to identify either a disease or a science area. In our setting, however, we are able to infer a grant's DST because the NIH requires all grant applicants to specify a funding institute and a study section that will evaluate the application.[3] Therefore, we assign NIH funding to DSTs using the NIH's own categorization: the Institute that funds a grant tells us

[3] A maintained assumption for the empirical exercise is that grant applicants cannot game NIH peer review by choosing to submit their applications to a committee which they expect will be more richly funded. Appendix A provides qualitative and quantitative evidence consistent with this assumption.

its disease area and the study section that evaluates a grant tells us its science area. $Funding_{dst}$ is thus the total amount of NIH support for grants assigned to a particular Institute and evaluated by a particular study section in a particular year.

3.1 Why use DSTs as our Unit of Analysis?

We focus on DSTs as our unit of analysis for two reasons. First, DSTs represent coherent research areas and therefore capture a unit of funding variation that is policy-relevant. A more disaggregated level of analysis, such as the individual grant, has a different interpretation. To see this, consider an analogous regression at the grant level:

$$Patents_{\widetilde{g}} \quad = \quad \alpha_0 + \alpha_1 Funding_g + Controls_g + \varepsilon_g \tag{2}$$

In Equation (2), α_1 captures the impact of changes in funding for grant g on patenting outputs related to g (the comparison is implicitly to a grant g' that receives less funding). Since we typically only observe outcomes for funded grants, α_1 captures the intensive margin effect of budget increases for already funded grants, but would not incorporate any extensive margin impacts of funding additional grants.[4]

To capture the impact of NIH funding at the extensive margin, one would need to examine patenting outcomes related to all grant applications, both funded and unfunded. This is challenging because unfunded applications do not generate acknowledgement data, making it difficult to track downstream outcomes using bibliometric linkages (we describe how we use these linkages at the DST level in Section 3.3). Jacob and Lefgren (2011) circumvent this issue by studying the impact of NIH funding on the publication output of individual scientists. By focusing on the individual, they are able to link publications to scientists using authorship information rather than grant acknowledgements.

In our setting, however, estimating the impact of funding on individual scientists is of less policy interest. Fundamentally, policy makers care about overall innovation in a research area, not about

[4]This is problematic because the NIH has a stated policy of funding the anticipated cost of an accepted research proposal, regardless of its peer review score. As as result, there is relatively less scope for increases in a grant's budget, conditional on being funded, to affect its innovative potential. More likely, when the NIH provides more funding for a research area, this funding is used to support additional grant applications that would not have been funded otherwise. These grants go on to produce publications that, in turn, later inspire commercial applications.

whether a given applicant is funded. If an individual applicant is able to produce more research as a result of being funded, it does not necessarily generate more innovation in a research area because funding for one applicant may simply come at the expense of funding for other applicants with similar ideas: α_1 may therefore misstate the impact of NIH funding on overall innovation in a research area.

By aggregating to the level of a research area, we eliminate the concern that we simply identify the advantage that funded individuals have over unfunded ones. While it is still the case that funding for one DST could come at the expense of funding for other DSTs, this variation is more likely to impact the substantive content of innovation, relative to funding variation at the investigator level. This is because different D-S combinations correspond to different intellectual areas and are therefore less likely to support overlapping research ideas.[5]

Policy makers are perhaps more interested in the impact of funding at the disease level, rather than the disease/science level. Our second reason for examining DSTs is that it is important for our identification strategy. As will be discussed in more detail in Section 3.4, funding for a DST is a byproduct of funding decisions for diseases—made at the Congressional level—and scientific evaluations for individual grant applications—made by peer reviewers. Because no one explicitly allocates funding to a DST, we are able to exploit funding rules that generate incidental variation in funding across research areas. Before delving into the role that rigidities in funding rules play in our analysis, we first detail the construction of patenting outcomes at the DST level.

3.2 Measuring Outcomes Associated with NIH Funding: Traditional Challenges

It is difficult to predict whether and how funding for a given DST will spur private-sector patenting: funding for one research area can have impact on other research areas, with varying time lags. The most direct way of assessing the impact of public funds, then, is to examine its impact on patenting in all research areas, in all subsequent years. With sufficient data and variation, one would be able to estimate all the cross-elasticities—across research areas and over time—associated with changes in public R&D investments.

[5]This does not address the concern that public funds may crowd out private investment. We discussed this form of crowd out in Section 2.1. Section 3.3 discusses how we address this issue empirically.

In practice, however, the literature has traditionally assumed that public investments may only impact private innovation in the same research area, within a well-defined time horizon. Toole (2012), for instance, regresses patenting in a given disease-year on 12 years of lagged funding for that same disease. A generic concern with this type of approach is that it fails to capture any benefits of medical research that cannot be anticipated in advance. These benefits may accrue both to seemingly unrelated research areas and with unexpected time lags; for example, much of the research underlying the development of anti-retrovirals used in the treatment of HIV infection in the 1990s was originally funded by the National Cancer Institute in the 1950s and 1960s, at a time when research on the causes of cancer centered on viruses.[6] In Appendix G, we compare estimates using our approach, described below, to the traditional *ex ante* approach applied to our data.

3.3 Linking Patents to NIH Funding: Novel Solutions

Our approach does not make *ex ante* assumptions about where and when public R&D investments may impact patenting. Instead, we develop new data and metrics to explicitly track this process using bibliometric data. Using this approach, we construct $Patents_{\widetilde{dst}}$ in two different ways. Figure 1 provides an overview of this process and Appendix F provides a detailed description.

Patents citing NIH-funded research. NIH funding may spur private-sector patenting by producing research that firms subsequently build on. The belief that such knowledge spillovers is an important mechanism for productivity growth has been a feature of policy debates since the end of World War II (e.g., Bush 1945), and has also figured prominently in economic scholarship on technological change (Nelson 1982; Cockburn and Henderson 1998). We assess this claim directly by identifying the number of private-sector patents that explicitly cite NIH-funded research.

[6] Gleevec provides another example: Varmus (2009) recounts that that Ciba-Geigy was working with scientists of the Dana Farber Cancer Institute to find drugs that would block the action of a tyrosine kinase that contributes to atherosclerosis in blood vessels, a disorder that is very different from CML. The development of Gleevec also relied heavily on knowledge about the genetic causes of CML that was established in the 1960s and 70s (e.g., Nowell and Hungerford 1960). In this case, the availability of treatment lagged behind basic research by over forty years. In other settings, basic research percolates almost immediately into applied work, such as when publications and patents are released in tandem (Murray 2002).

To do this, we first link NIH grants to the publications they support using grant acknowledgement data.[7] Second, we link those publications to patents that build on their findings (Figure 1, second column). To accomplish this second task, we find and standardize all the publication citations in patents granted by the USPTO. Because publications, rather than patents, are the main output of scientific researchers, this approach represents an advance over the more commonly used patent-to-patent citation data because it allows us to more reliably document how firms draw on scientific findings (Cohen and Roach 2013). Further, the vast majority (over 90%) of patent-to-article citations come from applicants rather than examiners and are thus more plausibly indicators of real knowledge flows than patent-to-patent citations, for which only 60% of citations are applicant generated (Lemley and Sampat 2012).[8]

In previous work, Sampat and Lichtenberg (2011) looked at marketed drugs citing NIH publications, finding that over 40 percent of the drugs approved between 1988 and 2005 cite an NIH-funded publication. This paper builds on the strategy of linking drugs to patents to publications to grants, but extends it in several ways. Most importantly, rather than a retrospective approach examining what share of drug development can be linked back to NIH funding, our analysis is prospective, examining how variation in NIH funding relates to subsequent innovation. This approach allows for "failure" (grants that don't generate any innovation), and is the relevant question for policy makers considering changes to NIH funding.

Taking the acknowledgment and citation data together, we define $Patents_{\widetilde{dst}}$ as the set of patents that cite publications that in turn acknowledge funding from that DST. These patents need not target the same disease as the original source of NIH funding which with they are linked. For example, if a patent related to cardiovascular stents cites research funded with money allocated to diabetes, we would associate this cardiovascular patent with diabetes funding.

This approach has two important drawbacks. First, relying on direct publication-to-patent citations limits the type of intellectual influences we can account for. We would not, for instance, credit NIH funding if it lead to patenting through more complicated citation patterns (e.g., a patent

[7] This is relatively straightforward because *PubMed* started capturing this information systematically starting in 1980. Appendix C1 provides more detail, and discusses the issues that may arise in our design if researchers inflate their publication accomplishments to improve their odds of getting a grant renewed.

[8] We acknowledge that even citations to non-patent prior art can be made for legal and strategic reasons, and are therefore noisy indicators of intellectual influence. We briefly return to this issue in the conclusion. Details of the matching process are discussed in Section 4 and Appendix C2.

that cites a publication that cites a publication that acknowledges the NIH), informal interactions (e.g., two researchers meet and exchange ideas at a conference supported by NIH funding), or the hiring of NIH-funded trainees by private-sector firms. Omitting these channels may lead us to underestimate the impact of NIH funding.

Second, by accounting only for patents that explicitly cite NIH-funded research, this measure treats patents that do not exist and patents that do exist but which cite only privately-funded research in the same way—neither are linked to a DST. As a result, if increased DST funding led to an additional linked patent, we could not tell whether this patent would otherwise have existed or not, i.e., whether private firms would have funded the necessary research instead. In other words, this first outcome measure asks whether NIH-funded research is useful to private firms. While informative, this is not the same as asking whether NIH funding increases *total* private-sector innovation in a research area.

Patents related to NIH-funded research. Our second outcome identifies *all* patents in the intellectual vicinity of an NIH funding area, whether or not these patents actually cite NIH-funded research. This allows us to account for a richer set of channels through which NIH funding may impact private-sector patenting. These patents, hereafter referred to as simply "related patents," may be linked to NIH funding via a longer citation chain or belong to NIH-trained scientists who join a private-sector firm. Crucially, these related patents may also be the result of private sector investments in related research areas; they need not be financially dependent on NIH at all. Capturing the total number of private sector patents in an intellectual area is important because it allows us to take into account the possibility that NIH funding may crowd out private investments. If this were the case, then we would not expect NIH funds to increase the total number of patents in a given research area: it would simply change the funding source for those patents. If, instead, NIH funding lead to the development of patents that would not have otherwise been developed, then we should see an increase in the total amount of innovation in a research area. The impact of NIH funding on total innovation in a research area thus captures the net effect of potential crowd-in and crowd-out.

To construct this measure, we define a patent to be *related* to an NIH funding area if it cites research *similar* to research that is actually funded by that area. In particular, we match each NIH

grant in our sample to publications that acknowledge its support and then link these publications to a set of intellectually similar publications using a keyword-based similarity measure developed by the National Library of Medicine.[9] The final step in our matching process is to identify the set of patents that cite this broader set of publications (see column 3 of Figure 1). The set of patents linked to a DST in this way can be thought of as "related," in the sense that they are part of the same intellectual area as that DST.

3.4 Identification

We address the potential endogeneity of public investments in R&D in two ways.

Fixed Effects Estimation. Our main OLS specification is

$$Patents_{\widetilde{dst}} = \alpha_0 + \alpha_1 Funding_{dst} + \beta' X_{dst} + \delta_{ds} + \gamma_{dt} + \nu_{st} + \varepsilon_{dst} \quad (3)$$

Equation (3) includes pairwise disease/science, disease/year, and science/year fixed effects that account for many common sources of endogeneity. Diseases that affect more people may receive more public and private interest. Some research topics may be more tractable than others; the genetics of breast cancer, for instance, can be studied using a variety of animal models, whereas the same is not true for the genetics of schizophrenia (Nestler and Hyman 2010). We control for time-invariant differences in innovative potential among disease/science areas (δ_{ds}). We also account for changes in the innovative or commercial potential of disease and science areas over time. Disease/year fixed effects γ_{dt} control for potential confounders such as shifting disease burden or public perceptions of disease salience. NIH funding may also respond to scientific advances. The introduction of new DNA-sequencing technologies in the late 1990s, for instance, may have increased both public and private research funding for diseases with a genetic component. We include science/year fixed effects, ν_{st}, to control for this type of variation. Finally, in our most detailed specification, we also include fixed effects for the number of applications that a DST receives. These indicator variables proxy for time-varying interest in a particular research area that may not be captured by our other controls. In our main specifications, this regression is weighted by the average size of a DST, that

[9] The *PubMed* Related Article (PMRA) algorithm analyzes keywords and keyword combinations that are assigned to all life-science publications by the National Library of Medicine and defines similarity on the basis of how many of these keywords overlap. This is discussed in detail in Appendix D.

is, the average yearly number of grants in a disease/science area.[10] To account for serial correlation, standard errors are clustered at the disease/science level.

The remaining funding variation in equation (3) comes from within-disease/year or within-science/year changes. Why is it, for instance, that cancer/cell signaling may receive more funding in 1995 than cancer/tumor physiology? After saturating our specifications with fixed effects, our identifying assumption is that NIH funding for a specific DST is not correlated with changes in the innovative or commercial potential for specific disease/science combinations.

This assumption would be violated if either Congress or NIH administrators allocated funding to DSTs on the basis of their potential. In response to the success of Gleevec, for example, the National Cancer Institute may have decided to devote a greater proportion of its budget toward the study of cell signaling or gene expression, scientific topics that are particularly relevant for targeted cancer therapies. If private firms were behaving similarly, then equation (3) would not be able to identify the impact of public funding, because we would expect changes in patenting for this area even in the absence of additional funds.

In practice it is difficult for the NIH to direct funding to DSTs on the basis of their evolving potential. As discussed in Section 2.2, applications are funded in order of their science ranks. This means that if cell signaling was a particularly "hot topic" in a given year, the NCI could not decide to fund the top 20 cancer-related cell-signaling applications without first funding the top 19 cancer-related applications in all other science areas. Most likely, it would not have the budget to do so.[11] The rigidity of this system was cited in an NIH-commissioned report from 2000, urging reform:

> *"...Researchers perceive that...applications describing some of the most productive, highest impact work may be assigned to too few study sections, causing too much of the 'best science' to compete with itself; that the scope of some study sections is restricted to research with relatively low impact, resulting in undeserved 'entitlements'..."*[12]

Instrumental Variables Estimation. Even if the NIH cannot direct funding to specific DSTs, $Funding_{dst}$ would still be endogenous if study section reviewers assign higher science ranks to applications from DSTs with more potential. If, for instance, the cell-signaling study section decides

[10] Unweighted results are presented in Appendix I, Table I1.

[11] The main way that ICs get around these rules is to either fund an application out of scoring order or to issue a request for proposals (RFPs) or applications (RFAs) on a specific topic. RFPs and RFAs account for only a small portion of NIH grant spending. Grants responding to these are evaluated in specially empaneled study sections, which we exclude from our analysis. See Appendix H for a discussion of out-of-order grant funding.

[12] "Recommendations for Change at The NIH Center For Scientific Review," Final Phase 1 Report, Jan 14, 2000.

to give higher science ranks to cancer-related applications after the discovery of Gleevec, then funding for the cancer/cell signaling DST would reflect this unobserved enthusiasm.

We construct an instrument for DST funding that is not correlated with a DST's potential. Our instrument works by isolating variation in DST funding coming from differences in the within-disease ranking of science ranks ("rank of rank") assigned to otherwise equally meritorious grant applications. Figure 2 illustrates how grant applications with the same quality may have different funding outcomes. Differences in grant-level funding then translate into differences in DST level funding.

In this example, there are two ICs: the National Cancer Institute (NCI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). They are responsible for funding grant applications from two study sections: Cell Signaling and Tumor Physiology. Each row corresponds to a grant application.

The top two panels display the raw scores that each study section assigns to the applications that they review, as well as the normalized "science rank" that these raw scores imply.[13] The bottom two panels of Figure 2 display how science ranks translate into rank of ranks within an IC, using raw scores as tie breakers. The solid line is the payline: applications with rank of rank above the payline are funded; those with rank of rank below are not. In Figure 2, Grant ID G6 is associated with the cancer-tumor physiology DST and receives a raw score of 7.6, while Grant ID G7 is associated with the cancer/cell signaling DST and also receives a raw score of 7.6. Despite receiving the same raw scores, these grants have different funding outcomes. The cancer/cell signaling application, G7, is not funded because diabetes/tumor physiology grants are relatively weak; this gives cancer/tumor physiology applications a high science rank, which in turn leaves less NCI funding for cancer/cell signaling. The additional funding that cancer/tumor physiology receives from this grant can be thought of as "windfall" funding because it is not related to the innovative or commercial potential of that DST.

Our IV strategy compares DSTs that have the same number and quality of grant applications near an IC's payline, but which receive different amounts of windfall funding. Specifically, we estimate:

[13] To aid intuition, in Figure 7 lower scores correspond to grants with poor prognosis for funding, even though, in practice, the NIH scoring system assigns lower scores to the "better" grants.

$$Patents_{\widetilde{dst}} = \alpha_0 + \alpha_1 Funding_{dst} + \Upsilon(\#Applications_{dst}) + \Phi(RawScores_{dst}) + \Psi(ScienceRanks_{dst}) + \delta_{ds} + \gamma_{dt} + \nu_{st} + \varepsilon_{dst} \quad (4)$$

instrumenting $Funding_{dst}$ with

$$WindfallFunding_{dst} = \sum_{g \in \mathbf{G}_{dt}} F_{gdst} \quad (5)$$

$WindfallFunding_{dst}$ is the amount of funding for a DST that comes from the set of grants, $\mathbf{G}_{dt}$, that are within a window around its IC's payline. In our main specifications, we define $\mathbf{G}_{dt}$ to be the set of 25 grant applications on either side of the funding threshold for disease area d in year t; we construct the windfall funding amount to be the sum of funding for grants within this set that are actually funded. On average, windfall funding accounts for 5.6% of a DST's total funding in that year. The median IC receives 750 applications in a given year (the mean is 1,100), making this a relatively tight window. Our results are robust to a variety of other bandwidths.

In general, $WindfallFunding_{dst}$, as currently defined, may still be endogenous. This is because what we call windfall funding is simply the marginal funding that a DST barely gets. Better DSTs may have more applications that are highly scored and those DSTs would have a greater representation of grants in the set $\mathbf{G}_{dt}$ of applications near an IC's payline; if this were the case, these better DSTs would also be likely to have more funded grants within this set. Similarly, even if two DSTs have the same number of grant applications near an IC's payline, applications from better DSTs may justifiably receive higher scores and, as a result, better DSTs may have a greater number of grants that are actually funded.

To address these concerns, we use $WindfallFunding_{dst}$ as an instrument for $Funding_{dst}$ only after including additional variables controlling for the quality of a DST's applications. Specifically, Equation (4) includes a full set of indicator variables for the number of grant applications any given DST has near the threshold set $\mathbf{G}_{dt}$ (i.e., the function Υ in equation (4)), as well as separate cubics in the average raw score and average science ranks of all DST applications within the threshold set $\mathbf{G}$ (i.e., the functions Φ and Ψ in equation (4)). Controlling for both the raw score and science rank

accounts for any differences in quality among applications, meaning that the remaining variation comes only from how science ranks translate into rank of ranks.[14]

In our IV specification, our identifying assumption is that there are no systematic differences in innovative potential among DSTs with (i) the same number of marginal applications, (ii) the same average raw scores, and (iii) the same average science ranks. In Appendix H, we show that a DST's windfall funding, controlling for these variables, is uncorrelated with non-windfall funding, previous and future windfall funding, and other measures of DST output.

4 Data Construction and Descriptive Statistics

Our analysis combines data from several primary sources: (i) Administrative data on NIH funded grants from the IMPAC II database; (ii) publication data from *PubMed* including information on grant acknowledgements; (iii) patent data from the USPTO; and (iv) information on patents related to FDA-approved drugs from the FDA's "Orange Book" and IMS-Health. Our final analytic sample captures linkages between the universe of NIH-funded grants from 1980-2005 at both the individual grant and DST levels, and the universe of biomedical patents granted between 1985 and 2012.[15]

4.1 Grant-level Patent Match

We begin with data on all 153,076 NIH grants from 1980-2005 that were evaluated in chartered study sections (those that are associated with a specific science area, rather than convened on an *ad hoc* basis). These grants were evaluated by 624 such study sections and funded by 17 Institutes.[16]

[14] Jacob and Lefgren (2011) investigate the impact of receiving NIH funding on the publication output of individual scientists using a regression discontinuity design and compare outcomes for grant applications just above and just below an Institute's payline. We cannot use the same design because the running variable—rank of rank—applies to individual grants but not to DSTs. There is no DST-level discontinuity. Instead, we compare DSTs with similar quality applications as judged by their raw and science rank scores, but which receive different levels of windfall funding.

[15] A patent is part of our universe if (i) it is in a relevant patent class and (ii) cites at least one article indexed by *PubMed*. The relevant patent classes are the 92 classes belonging to categories 1 and 3 in the NBER USPTO database (see Appendix B for a complete list). Note that in practice, the second requirement is almost always satisfied for patents in these classes.

[16] The list of the included Institutes is described in Appendix A, Table A1. Briefly, we exclude three small ICs (the National Institute on Minority Health and Health Disparities, the National Institute of Nursing Research, and the National Library of Medicine), as well as six NIH centers which serve mainly administrative functions. Our primary analyses do include three ICs that are not oriented towards a particular disease: the National Institute

The characteristics of these grants are described in Table 1. In total, we have grant-level data that aggregate up to the activities of 14,085 DSTs. This is a only a small fraction of the $624 \times 17 \times 25 = 265,200$ potential DSTs. Appendix E provides extensive detail on the unbalanced structure of our panel dataset. The overwhelming majority of the "missing DSTs" are not missing, but rather do not exist because the corresponding D-S combination is intellectually incoherent.[17]

The average award size for grants in our sample is approximately $1.6 million. Seventy four percent of grants are R01s—the R01 is a renewable, project-based grant that constitutes the majority of NIH's grant spending—and most (60%) are for new research projects (as opposed to renewals of existing projects).

Table 2 describes the life-sciences patents in our sample and show how they are linked to NIH funding. We begin with the universe of 315,982 life-science patents granted by the USPTO between 1980 and 2012. Of these, 232,276 (74%) are private-sector patents and 83,394 (26%) are what we call public-sector patents, meaning those assigned to governments, universities, hospitals, and other institutions (see Appendix B for a description of patent types and definitions). Despite the large number of patents we examine, Table 2 shows that only 4,718 private-sector patents (2%) are associated with advanced drug candidates—drugs and biologics in Phase III trials and beyond—and even fewer, 1,999 (<1%) are associated with FDA-approved new chemical entities and new biological entities.

We find overwhelming evidence that NIH funding is relevant for organizations seeking life-science patents. Forty-four percent of life-science patents in our sample directly cite NIH-funded research. Among the subset of private-sector patents, this figure is 39%. For public-sector patents, this figure is 57%. We further document a greater role of NIH-funded research in the development of high value patents; 50% of patents associated with advanced drug candidates—those that have entered clinical trials—cite NIH-funded research (Sampat and Lichtenberg 2011).

of General Medical Sciences (NIGMS), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and the National Human Genome Research Institute (NHGRI). Note, however, that these Institutes review grant applications from several study sections, which is all that our identification strategy requires. In a robustness test, show that our results are robust to including only disease or body-system specific ICs.

[17] For instance, the National Institute of General Medical Sciences (NIGMS)—an institute which supports research devoted to understanding fundamental biological processes—unsurprisingly never funds applications evaluated in a committee such as the "Community Influences on Health Behavior" (CIHB) study section. As a result, there are no observations in our data set for the intellectually incongruous NIGMS/CIHB pairing, as well as many others. Appendix E provides an exhaustive taxonomy of existing and "missing" DST types, and presents evidence that our analysis account for all DST combinations at risk of receiving research funding.

Table 2 also shows that the vast majority of life-science patents—265,741 patents or about 84% of the universe—cite research that is similar to research funded by an NIH DST. This is true, moreover, for private- and public-sector patents, as well as high value patents, and those from both large and small firms.

According to Table 1, 66,085 or 43% of the NIH grants in our sample produce a publication that is directly cited by a patent. This figure is a lower bound because our publication and patent data are truncated in 2012. Figures 3, 4, 5 and 6 describe the lag times between NIH funding and follow-on patenting. Each figure displays a cumulative hazard curve where the risk being modeled is that of a grant supporting a publication that is cited by a patent. This provides a graphical way to examine the diffusion of knowledge stemming from NIH expenditures, and how this diffusion process varies over time and across diseases.

Figure 3 documents substantial variation in the relevance of NIH funding for patenting across diseases. Approximately 15 years after funding, almost 60% of grants funded by the National Institutes for Allergy and Infectious Diseases have produced research that has been cited by a patent. By contrast, this is true of only 20% of grants funded by the National Institutes of Mental Health. These differences should not be interpreted as comparisons of the efficacy of NIH funds, as they also reflect differences in the ease of biomedical innovation across disease areas and the types of research funded by different Institutes.

Figure 4, meanwhile, shows that time-to-patent has been decreasing over time. Only 20% of grants awarded between 1980 and 1985 produced research that is relevant for a patent in the ten years following. For grants awarded between 1991 and 1995, this figure was almost 40%. One interpretation of this finding is that NIH administrators' efforts to encourage "translational research" have been successful. An alternative view is that patentability has steadily moved upstream along the biopharmaceutical R&D value chain, consistent with other evidence (Eisenberg and Nelson 2002; Jensen and Murray 2005).

Figure 5 underscores the fact that although 43% of grants are associated with patents, "important" patents—those pertaining to advanced drug candidates, or to FDA-approved treatments—are still relatively rare. Even twenty years after approval, only 5% of NIH grants produce research cited

by a patent associated with an FDA-approved drug; this figure is only slightly higher for highly cited patents, 10%.

Finally, Figure 6 shows that a grant is just as likely to produce research relevant for patents primarily associated with other disease areas as it is for patents associated with its own disease area. Our matching process allows a patent to be associated with more than one Institute (conditional on being linked to a DST, the average patent is linked to 7 different ICs). For each patent, we define its primary disease area as the IC responsible for funding the plurality of the publications that it cites. Then we categorize each patent-to-grant linkage as being for the same disease or for a different disease, where the reference disease is simply given by the funding IC for the focal grant. Figure 6 also shows that both private- and public-sector entities take advantage of NIH-funded research.

From here on, we focus on the impact of NIH funding on private-sector patents. This designation would exclude patents to universities, governments, hospitals, and other non-profit institutions. Appendix Table I5 reports our main results with public-sector patents instead.

4.2 DST-level Patent Match

Recall that our analysis it as the DST level: each observation is an institute-study section pairing at a point in time, and we are interested in how funding for this DST relates to later patenting. Table 3 describes the characteristics of the DSTs in our sample. The average DST supports 11 grants totaling $47 million in funding (weighted by DST size). Table 3 also indicates that 13,027 or over 80% of DSTs produce research that is potentially relevant for patenting. Before describing the number of patents we associate to each DST, it is worth describing how we attribute credit when a patent is associated with more than one DST.

In general, the correct attribution of patents to DSTs depends on the innovation production function and the degree to which any particular piece of knowledge is instrumental in generating the patent. If DSTs are pure substitutes in the production of patents and if a patent is linked to N DSTs, then each DST should receive credit for $1/N^{\text{th}}$ of that patent. Table 3 shows that the average DST in our sample produces research that is directly cited by 12.8 private-sector patents and is intellectually related to a total of 24.8 patents, using this "fractional" patent count. If, instead, the contributions of various DSTs are complements, then a patent should count for more than $\frac{1}{N}$; in

the extreme, support from each DST is critical such that production is Leontief. In this case, DSTs should receive full credit for each patent it is linked to, which we designate as a "unit" patent count. Applying this assumption to our data, we find that the average DST is directly cited by 102 unit patents. The distribution of patent counts at the DST level exhibits skewness, as can be observed in the histograms displayed in Figure 7.

5 Main Results

Tables 4 and 5 present the fixed effects estimates of the impact of NIH funding on our two measures of patent outcomes. The top panel of Table 4 describes the impact of NIH funding on the number of patents that cite NIH-funded work, using fractional patent counts. Without any controls, we find that a $10 million increase in funding for a research area (DST) is associated with 2.6 more patents. Adding fixed effects for research areas (disease/science groupings) reduces this coefficient to 2.3. We add increasingly detailed fixed effects in each successive column; interestingly, our estimates remain relatively stable. One explanation for this is consistency is that, at the time it makes funding decisions, the NIH may not be able to anticipate which DSTs have greater future innovative potential. In this case, the amount of funding that a DST receives may be relatively uncorrelated with its future patent output. With our full set of controls, we estimate that a $10 million increase in funding leads to 2.5 additional patents. With an average grant size of $1.6 million, this is equivalent to about one patent for every 2 to 3 NIH grants.

The bottom panel presents our results under the assumption that every publication a patent cites is necessary for that patent's creation and cannot be substituted with a non-NIH-funded publication. With unit patent counts, we estimate that $10 million leads to 18.4 more patents, or about 2 to 3 patents for every additional NIH grant.

The estimates in Table 4 would not reflect the true value of NIH funding if public support for science either crowds out private investment or if it spurs patenting in ways that cannot be captured by a direct grant-publication-patent link. The top panel of Table 5 reports the impact of NIH expenditures on the total amount of private-sector patenting in areas related to a DST, whether or not these patents directly cite NIH-funded research. This specification is designed to assess the net impact of NIH funding on private-sector innovation in an area, accounting for both

the possibility of crowd-out and the possibility that not all patents spurred by NIH funding can be linked via direct citations. Column 5 of Table 5 finds that a $10 million increase in DST funding results in a 3.2 net increase in the number of related private-sector patents, or about one patent for every two NIH grants.

If NIH funding fully crowded out industry investments, we would expect the coefficients reported in Table 5 to be zero. In fact, the magnitude of the impact of NIH funding on total patenting is slightly larger than its effect on patenting that can be directly linked to NIH funds (cf. Table 4). This is consistent with the absence of crowd out. Alternatively, even if NIH funding crowds out some private investment, it is offset by increases in the number of patents related to NIH funding through indirect citation channels, or by increases in the productivity of private R&D investments.[18]

The bottom panel of Table 5 reports these results with fractional patent counts, yielding effect sizes that are an order of magnitude larger. These results, however, are unlikely to reflect the true effect of NIH funding. Recall that this final outcome measure is designed to capture the influence that NIH funding may have on patenting that does not require a direct citation linkage between funding and patents. In this measure, patents are linked to study sections through shared intellectual foci, reflecting the notion that public funding in a particular area produces knowledge that enhances productivity of others working in that area. Each DST is associated with many more patents in this way, thus driving a large wedge between fractional and unit impacts. Unlike the direct method which connect patents to a small number of study sections, our indirect method often yields connections to hundreds of study sections in related intellectual realms. While all linkages may be important, it is harder to imagine that each unit of knowledge is instrumental, and thus we favor the more conservative fractional approach in this case. Going forward, we will discuss estimates of the effect of funding on overall patent production using only the more conservative fractional counts (we continue to report the results corresponding to unit counts in the tables).

Table 6 displays 2SLS estimates using our instrumental variable for funding. Column 1 reports the first stage estimate of the relationship between total DST funding and windfall DST funding, controlling flexibly for raw scores and science ranks, as well as the number of applications that

[18]This may occur, *inter alia*, because researchers trained with NIH funds find jobs in the private sector where they go on to patent in the same area, or because NIH investments clarify the scientific potential of different research areas, allowing biopharmaceutical firms to target their investments more efficiently. In both cases, total private patenting in an area may still increase even if overall private investment decreases.

a disease/science paring has in a 25-grant window surrounding that disease's (e.g., IC's) funding threshold for that year. Table 6 also reports tests of the strength of our windfall funding instrument. We obtain a Cragg-Donald Wald F-statistic of 478 and a Kleibergen-Paap Wald F-statistic of 37.5; both reject the null hypothesis that our instrument is weak. Because our IV strategy requires that we control for these additional variables, which we do not use in Tables 4 and 5, we report both our IV estimates as well as OLS estimates using the same set of first stage controls. Using our instrument, we find similar effects of NIH funding on the number of directly cited patents (2.5 vs. 2.0) and a slightly smaller effect for the total number of patents related to an NIH research area (3.6 vs. 2.3). We take the 2.3 figure in Column 5 as our preferred estimate of the impact of NIH funding on private-sector patenting. Appendix Table H1 reports reduced-form estimates using windfall funding as the explanatory variable; we find similar, if not slightly larger results.

5.1 Robustness Checks

We probe the robustness of our results using a variety of approaches, described in more detail in Appendices E, H, I, and J.

Appendix E discusses the idea of "missing" DSTs, *i.e.*, those DST observations that are absent in our sample of 14,085 DSTs. Appendix Table E1 repeats our analysis on a balanced panel of 7,966 contiguous DSTs—those DS combinations that receive funding in all years between the first and last year in which the DS is observed. Our estimates are almost numerically identical.

Appendix H investigates the robustness of our identifying assumptions. For example, the NIH occasionally funds grant applications out of the order in which they are scored. If DSTs that receive more out-of-order funding also have unobservably higher innovative potential, then this may bias our estimates. We discuss a variety of specification checks that together demonstrate that this threat to identification is not a concern empirically. Appendix H also provides evidence for the plausibility of the exclusion restriction for the instrument. We show that $WindfallFunding_{dst}$ is not correlated with windfall funding in previous or future years; we also show that it is not correlated with the non-windfall funding that a DST receives. Finally, we also show that $WindfallFunding_{dst}$ is not correlated with the quality of previous applicants to a DS (same area, different time), or to past patent output in a DS.

Appendix I considers alternative specifications and samples. We show that our results are robust to not using weights in our regressions, so that each DST contributes the same to our estimation, regardless of how many grants it supports. We estimate non-linear specifications using logs of funding and patenting, as well as a Poisson parametrization. Our main results also hold when restricting our sample to NIH Institutes that are the most directly identified with disease and body system areas.

Finally, Appendix J shows that our results are robust to alternative linking strategies. In particular, a potential concern with our approach is that our definition of a DST's "intellectual area" can vary over time. If funding allows a disease/science area to expand the set of topics that it supports, then we may associate increased funding with more patents simply because higher levels of grant expenditures leads us to credit DSTs with patents over a wider slice of technological space. To ensure that our results are not driven by this phenomenon, we repeat the matching exercise using a definition of "intellectual area" that is fixed for a given disease/science (DS) combination over time. Various implementations of this alternative linking strategy produce a battery of estimates that are similar or slightly larger to those presented in Section 5.

5.2 Heterogeneity

In addition to quantifying the impact of NIH funding on overall patenting, we also examine which type of patents are most responsive to NIH expenditures. The impact of NIH funding on the development of high-value patents need not be similar to its impact on overall patenting; if firms direct their resources to the most promising projects, then the marginal patent that is created because of NIH funding may be relatively low quality. Conversely, if it is unprofitable for firms to invest in risky or early-stage research, then the marginal patent supported by the NIH may be of high quality. Column 1 of Table 7 reproduces the estimates of the impact of funding on total private-sector patenting from Table 6. Column 2 focuses on "important" patents, those that either pertain to advanced drug candidates or to FDA-approved biopharmaceuticals (traditional "small molecule" drugs as well as vaccines and biologics).

The OLS and IV estimates reported in Column 2 of Table 7 show that a $10 million increase in DST funding leads to a net increase of 0.05 to 0.08 patents associated with advanced drug

candidates (those that have entered clinical trials) and FDA-approved drugs. While this figure is small in magnitude, it translates into an elasticity of patenting with respect to funding of between 0.4 to 0.6, comparable to the elasticity we estimate for private-sector patents in general. We will discuss alternative measures of patent value in the next section, when we discuss the economic magnitude of our results.

Many studies document cases in which existing medical treatments have been successfully used to treat new conditions (Gelijns et al. 1998; Wurtman and Bettiker 1994). Similarly, drug development efforts often build on research originally intended for other diseases, reflecting the importance of knowledge spillovers across diseases (Henderson and Cockburn 1996). Our results provide evidence on the magnitude of these cross-disease knowledge spillovers. To measure spillovers, we assign a primary disease affiliation to each patent in our data by finding the NIH Institute that is responsible for funding the plurality of publications cited by that patent. We find that NIH funding directed toward one disease area is as likely—if not more likely—to translate into patents that are primarily affiliated with other disease areas as it is to translate into patents affiliated with its own. The IV estimate in Column 3 of Table 7 indicates that a $10 million increase in funding for a DST generates 1.20 additional patents with the same primary disease affiliation. This is likely the effect that Congress is interested in when allocating funds for particular diseases. Column 4, however, shows that this same funding also generates 1.89 additional patents with a different primary disease affiliation. Part of the reason for such large cross-disease funding spillovers may be due to the fact that much of the research that the NIH supports centers on scientific questions that are relevant to many disease areas. The National Cancer Institute may, for instance, fund a study of cell division in frog embryos; this research may also be relevant for the study of tissue regeneration and aging-related disorders. These findings highlight the importance of using a patent-linking strategy that does not assume that funding only impacts innovation in its intended area. Had we made this assumption, we would have failed to account for over half of the relevant innovative outputs.

Finally, Table 7 also shows that NIH investments increase patenting for both large and small assignees. While larger assignees produce a larger number of patents in response to increases in NIH funding, the response of small assignees is equally elastic. This finding is consistent with our summary statistics in Table 2, which show that a greater proportion of patents assigned to small firms cite NIH-funded research.

5.3 Valuing the Impacts of NIH Investments

Our results suggest that a $10 million increase in NIH funding leads to a net increase of 2.3 weighted private-sector patents. Putting a dollar value on these patents is difficult, for several reasons. It is well known that patent value distributions are highly skewed (Harhoff, Scherer, and Vopel 2003). Moreover, typically only the private value of patents is calculated, and the social value can be much larger.

One approach to valuing the returns to NIH funding in dollars, rather than patents, is to rely on estimates for the market value of patents taken from the literature. Bessen (2009) quantifies the effect of patent stocks on Tobin's q, and uses these estimates to derive the market value of a patent across sectors of the economy. In the biopharmaceutical sector, his estimates imply that an additional patent is valued by the stock market at about $11.2 million (2010 dollars). Combined with our estimate in Table 6, Column 5, a back-of-the-envelope calculation indicate that a $10 million dollar in NIH funding would yield $34.7 million in firm market value. As Bessen (2009) notes, a problem with this approach is that patents may be picking up the effects of other factors correlated with market value; accordingly this figure probably represents an upper bound.

A different approach is to focus on patents associated with marketed drugs. Very few of the patents in our sample are for drugs, let alone marketed drugs. However, for this set we have another measure of private value, drug sales. DiMasi, Grabowski, and Vernon (2004) report that the mean present discounted value (PDV) of lifetime sales for new drugs approved by the FDA between 1990 and 1994 was approximately $3.47 billion (2010 dollars). More recent research (Berndt et al. 2015) shows similar orders of magnitude, although the returns appear to have been declining over time.

Table 8 presents implied drug valuation estimates of our results based on the DiMasi et al. figure reported above. Column 1 reproduces our findings from Table 7 with respect to all advanced drug candidates. Another variation is to restrict the outcome to patents associated with FDA-approved drugs. Column 2 reports OLS and IV estimates using only these patents to construct the outcome variables at the DST level and finds that a $10 million dollar increase in funding results in approximately 0.034 more such patents. In this definition, we include all patents we can link to a drug (including those listed in the Orange Book, as well as additional patents from IMS Patent Focus); there are approximately eight patents associated with every FDA-approved drug on average

(cf. Appendix B). If the inventions associated which each of these eight patents are essential to the development of the corresponding drug, then we should fully credit each with the value of that drug. In this case, we would expect $10 million dollar increase in funding to generate an expected PDV of $0.034 \times \$3.47$ billion = $149.2 million dollars in sales.

If we instead assumed that the invention underlying each patent contributes equally to the drug, we would expect this funding amount to translate into $0.034/8 = 0.004$ drugs, with an expected PDV of $0.004 \times \$3.47$ billion = $14.7 million.

However, even within drug, there may be heterogeneity in patent importance.[19] Many "secondary" Orange Book patents are not even filed until well after the product is launched (Kapcynski et al. 2012; Hemphill and Sampat 2013); IMS patents may be even more peripheral.[20] Attributing the same share of product sales to these patents as to the "main patent" associated with that drug may lead to overstating the effect of NIH funding. To explore this heterogeneity, we ran several additional models. The first looks only at "pre-approval" patents (from the Orange Book and/or IMS), those filed *before* drug approval (on average, there are five such patents per drug). In Column 4, we are more conservative, limiting the outcome variable to the first patent associated with a marketed drug, on the assumption that this is the main patent. (No scaling is required in this case since we are only looking at one patent per drug.) Finally, Column 5 examines drug level outcomes: in this case, we match the number of discrete drugs associated with a DST, rather than the number of patents. In all three of these columns, the OLS estimates are statically significant and similar in magnitude to those reported for FDA approved drugs, from Column 2, but the IV estimates are smaller and statistically insignificant.[21]

Assigning value to individual patents is notoriously difficult, and the different approaches above yield different magnitudes for the effects of NIH funding. Accordingly, beyond presenting a range

[19] The active ingredient patent is typically thought to be more important than other Orange Book-listed patents (on average there is a single active ingredient patent per drug, and three total Orange Book patents). As an illustration of this, generics typically are able to enter after the expiration of the active ingredient patent: later Orange Book patents are often found to be irrelevant or invalid (Hemphill and Sampat 2012).

[20] On average, 5 of the 8 patents for each drug were in IMS only. These were patents that did not meet the FDA's standards for being relevant to the marketed drugs. Nevertheless, as discussed in Appendix B, we include IMS patents since the Orange Book has very limited coverage for biologic drugs, even though it does introduce many peripheral patents for traditional, "small molecule" drugs.

[21] In our data, there are only 332 drugs and 270 "main" patents that can be matched to NIH grants over the course of our 25 year sample. Because the IV estimates rely on limited variation around an IC's funding payline, there may not be enough data to obtain reliable IV estimates when these extremely rare patents are used to construct outcome variables at the DST level.

of implied drug valuations, we are not in a position to report a specific rate of return. Any such estimate would only capture the private value of the patented technologies; for biopharmaceuticals, the social value of an innovation can exceed its private value by a factor ranging from 4 to 20 (Lakdawalla et al. 2010; Philipson and Jena 2006, Goldman et al. 2010). Finally, as we will emphasize in the conclusion, there are many effects of NIH funding that do not result in patentable research at all.

6 Assessing Firm Reallocation of R&D Expenditures

So far, our results have examined the impact of NIH funding on firm patenting in related research areas. Yet in the cases of both crowd-in and crowd-out, the additional resources that a firm devotes to—or diverts from—a DST must come from somewhere else in its budget. One possibility is that these resources come from either an expansion in the firm's total R&D budget (in the case of crowd-in) or a contraction in the firm's R&D budget (in the case of crowd-out). In this case, the impact of NIH expenditures estimated in Tables 5 through 8 is the same as its impact on overall firm R&D. Another possibility, however, is that firms respond to public investments by reallocating resources to and from other parts of their R&D portfolio. In this case, one needs to know the consequences of NIH investments on firm investments in other areas in order to assess its full impact on private innovation.

If firms respond to increased NIH funding for a DST by adjusting their portfolio of investments, then the effect of NIH funding for a DST would be two-fold: the direct effect on private innovation in the area of that same DST, and the countervailing reallocation effect on private innovation in the other research areas that a firm reallocates to or from. If firms divert funds from other areas in order to invest in the DST with increased NIH funding, we think of this as "reallocated crowd-in." Conversely, firms may divert resources away from a DST with increased NIH funding toward other research areas; we refer to this as "reallocated crowd-out."

We attempt to directly measure the extent of firm reallocation in response to NIH funding. First, we note that our second outcome measure—the total number of patents that draw on research related to a DST—is already likely to take into account some of the impact of reallocation. This is because our patent linking approach defines the area of a DST quite broadly. If the NIH increases

spending on, for instance, cancer (D) cell signaling (S) research in 1990 (T), we measure net impact of this change on total innovation in *all* parts of the firm's R&D portfolio that are related to cancer/cell signaling research from 1990. This may include patents related to cell signaling in other disease areas, cancer patents unrelated to cell signaling, or any other set of projects similar to research that is supported by the DST. Reallocation within this set would already be captured in the results displayed in Table 5.

Firms, however, may also choose to reallocate funds to or from projects that are completely unrelated to a DST's research. If NIH funding in one DST leads firms to reallocate funds away from that DST, then we should observe an increase in non-DST patenting within that firm. If, instead, NIH investments in a DST lead firms to reallocate funding away from other projects toward the area of NIH investment, then we should observe a decrease in non-DST patenting within that firm.

To measure the extent of reallocation, we would ideally like to focus on the set of firms that actually faced a decision about whether to invest more or less in a DST as a result of NIH funding. In the absence of these data, we focus on firms that actively patent in a DST area and construct a measure of the number of non-D, non-S patents that they produce in the same year. We have two final variables of interest. $TotalPatents_{-d,-s,t}$ measures the total number of non-D, non-S patents that are produced by firms that also produce a DST-linked patent in the same year. $AveragePatents_{-d,-s,t}$ measures the average number of non-D, non-S patents a firm produces for every DST-linked patent it produces, averaged over all firms in that DST.

The advantage of this approach is that we restrict our analysis to firms that are indeed affected by changes in funding for a particular DST. If these firms spend more resources in another area, it is likely that these funds could have also been spent on DST research. The downside of this approach, however, is that it limits the kinds of reallocation we can study. If DST funding leads a firm to reallocate toward other areas entirely, then we would no longer be able to associate it to the original DST. Our results, then, document the impact of DST funding on the reallocation of firm investments on the intensive margin, conditional on firms not switching away entirely.

Table 9 shows that, in general, an increase in NIH funding for one area of a firm's R&D portfolio does not decrease the number of patents that those firms develop in other areas. Our estimates in Columns 1 and 2 indicate that a $10 million increase in DST funding leads to an additional four

to five patents, although these estimates are noisy. NIH funding does not appear to increase the average number of non-DST patents assigned to firms.

These findings, when combined with our previous results, indicate that overall firm patenting appears to increase in response to NIH funding. This finding suggests that NIH investments lead firms to weakly increase their overall patenting. Another interpretation for this finding is that there is a larger direct impact of NIH funding for a DST than we capture through our main outcome measures. If, for instance, firms respond to increased NIH funding by expanding their scientific labor force, and these scientists work on a variety of projects, then an increase in NIH funding for one DST can impact other patenting areas in ways our main outcome measures cannot capture; some of those effects may be reflected in Table 9.

The elasticities we estimate under all of these specifications are smaller than the ones we estimate for the direct effect of DST funding on patenting in the same area. These smaller magnitudes are to be expected. In the case of reallocated crowd-in, the patents that are lost in the area from which the firm diverts funds should be fewer than the number that are gained, as long as the firm is reallocating optimally. Similarly, in the case of reallocated crowd-out, the patents that are gained in the area to which firms divert funds should be fewer than the number that are lost in the original area, as long as firms had initially allocated their investments optimally.

7 Conclusion

Public investments in science are motivated by the belief that these investments carry high social returns. This rationale is most famously expressed Vannevar Bush's 1945 report on postwar science policy, which characterizes basic research as "the pacemaker of technological progress" and the source of new economically valuable technologies. Yet despite this high-level policy consensus, there is little credible evidence on the returns to science funding (Garber and Romer 1996; Cockburn and Henderson 1996; Murphy and Topel 2003). And there has been periodic questioning of the benefits from science by policy makers as well, especially when discretionary budgets have been tight (Brooks 1995).

In this paper, we examine the effects of public science on private sector innovation in the life sciences. Our results show that NIH investments in an area increase subsequent private-sector patenting in that area; a $10 million increase in funding for an area leads to 2.3 additional patents or, equivalently, we expect one private-sector patent generated for every two NIH-funded grants. This result holds across a variety of OLS and IV specifications. This positive impact, moreover, does not appear to be associated with lower private investments in other research areas. We cannot perform a formal rate of return calculation since our analysis focuses on only one aspect of the effect of NIH funding, that of sales associated with patented drugs. One rough calculation (based on all patents associated with marketed drugs) suggests that $1 dollar in NIH funding generates around $1.40 in drug sales.

We find that over half of the patents that result from NIH funding flow across disease areas. This has implications for measurement: had we looked only at patents in the same disease area, we would have missed half the output. This finding speaks to a long-standing question in postwar medical research policy: the feasibility and desirability of targeting research to diseases. Claims that scientific research often flows across disease areas have been common from NIH Directors since the agency's founding, especially during Congressional debates about whether particular diseases are over/underfunded or in response to advocates lobbying for a new Institute for "their" disease (Sampat 2012). Our results support the view that there are strong cross-disease spillovers. The organization of the agency around disease-specific Institutes, though useful for mobilizing funding, may not reflect the importance of the interplay of ideas from different disease areas and fields in shaping biomedical research progress.

Throughout the text, we emphasized numerous caveats. We highlight several here. First, we are examining only one type of return to NIH funding, those that flow through patented innovations. This neglects a number of other socially important benefits of publicly-funded medical research, including applied epidemiological and clinical research that changes medical practice or health behaviors. Previous research (Cutler and Kadiyala 2003; Heidenreich and McClellan 2003) suggests this research has high value. Ignoring these outcomes could lead to large underestimates of the value of NIH funding.

Second, we rely on patent-to-publication citations, and assume these citations capture knowledge flows from researchers to inventors. This may not always be the case: for example, articles may be cited for strategic legal reasons, or as background knowledge, even if the results contained therein were not crucial for the development of the citing patent. This would lead to overestimates of the effects of NIH funding.

Third, our implied drug valuations were based on publicly available estimates on the distribution of drug sales, and assumptions about how to divide a drug's value across its many patents. There is likely considerable heterogeneity in the private and social value of drugs (Garthwaite and Duggan 2012), and individual patents (Hemphill and Sampat 2011), which our back-of-the-envelope calculations could not fully incorporate.

Finally, our analysis implicitly assumes a "linear" flow from science to technology, and does not account for the complementary investments made by other actors (e.g., the NSF, or venture capital firms) in the path from laboratory to marketplace, or the feedbacks from technology to the progress of science. This "linear model" of research is well known to be an oversimplification, but even its detractors acknowledge that it is more reasonable in the life sciences than in other fields, and that alternative models would be far less empirically tractable (Balconi et al. 2010).

Despite these limitations, our analysis provides new estimates on a question of longstanding importance to economists and policy makers, using novel data and a new source of identification. In future work, we plan to extend the analyses and framework to examine a range of other science policy questions, including heterogeneity in types of research (whether more or less targeted research has higher impact) and how the presence or absence of intellectual property rights affects returns to public research investments.

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Figure 1
Overview of Data and Construction of Patent Outcome Measures

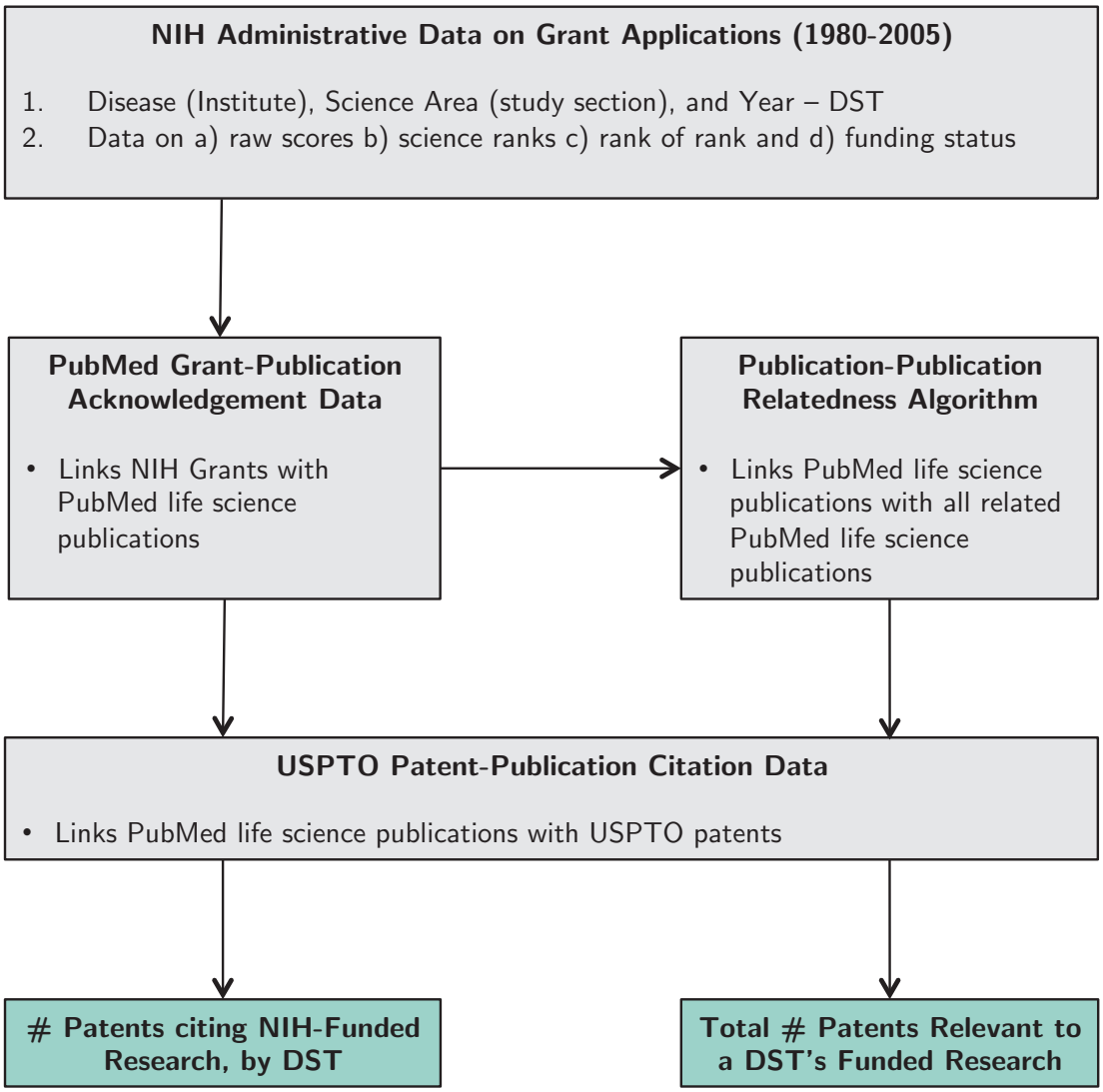


Figure 2
Example of Variation in Funding Unrelated to Quality

Cell Signaling Study Section

Grant ID	*Science Rank*	*Disease*	*Raw Score*
G1	1	Cancer	10
G2	2	Diabetes	9.8
G3	3	Cancer	9.2
G4	4	Cancer	9.1
G5	5	Cancer	8.2
G6	6	Diabetes	7.6
G7	7	Cancer	7.6
G8	8	Diabetes	7.4

Tumor Physiology Study Section

Grant ID	*Science Rank*	*Disease*	*Raw Score*
G9	1	Cancer	8.2
G10	2	Cancer	8.1
G11	3	Cancer	7.6
G12	4	Cancer	6.4
G13	5	Cancer	5.4
G14	6	Diabetes	5.2
G15	7	Diabetes	4.8
G16	8	Diabetes	4.4

Cancer Institute (NCI)

Grant ID	*Rank of Ranks*	*Science Rank*	*Study Section*	*Raw Score*
G1	1	1	Cell	10
G9	2	1	Tumor	8.2
G10	3	2	Tumor	8.1
G3	4	3	Cell	9.2
G11	**5**	**3**	**Tumor**	**7.6**
G4	6	4	Cell	9.1
G12	7	4	Tumor	6.4
G5	8	5	Cell	8.2
G13	9	5	Tumor	5.4
G7	**10**	**7**	**Cell**	**7.6**

Diabetes Institute (NIDDK)

Grant ID	*Rank of Ranks*	*Science Rank*	*Study Section*	*Raw Score*
G2	1	2	Cell	9.8
G6	2	6	Cell	7.6
G14	3	6	Tumor	5.2
G15	4	7	Tumor	4.8
G8	5	8	Cell	7.4
G16	6	8	Tumor	4.4

Note: This is an example of how raw scores and science ranks can result in idiosyncracies in funding. There are two disease areas, cancer and diabetes, and two science areas, cell signaling and tumor physiology. Each row represents a grant application. The darkened cells are grants that are not funded and the dark line represents the funding threshold in each disease area. Cell signaling receives, on average, applications with higher quality, as reflected by their raw scores. NIH funding, however, requires that Institutes (disease areas) fund applications in order of their science rank. In this example, we assume that cancer can fund five applications and diabetes can fund four. The top two panels list the science rankings of each study section/science area, along with the disease area of each application and its raw score. The bottom two panels show the funding decision at the cancer and diabetes institutes, which is based on the "Rank of Rank." We see that, within a science area in the same year, applications from two different disease areas with the same score may have different funding outcomes. In particular, the fact that cancer applications in tumor physiology have high science rankings means that cancer applications in cell signaling are less likely to be funded. Similarly, it is also possible for two applications with the same raw score within the same disease area to have different funding outcomes. In this case, tumor-physiology applications are less competitive than cell-signaling applications.

Figure 3
Grant-Patent Lags by Disease Area — Top 10 ICs

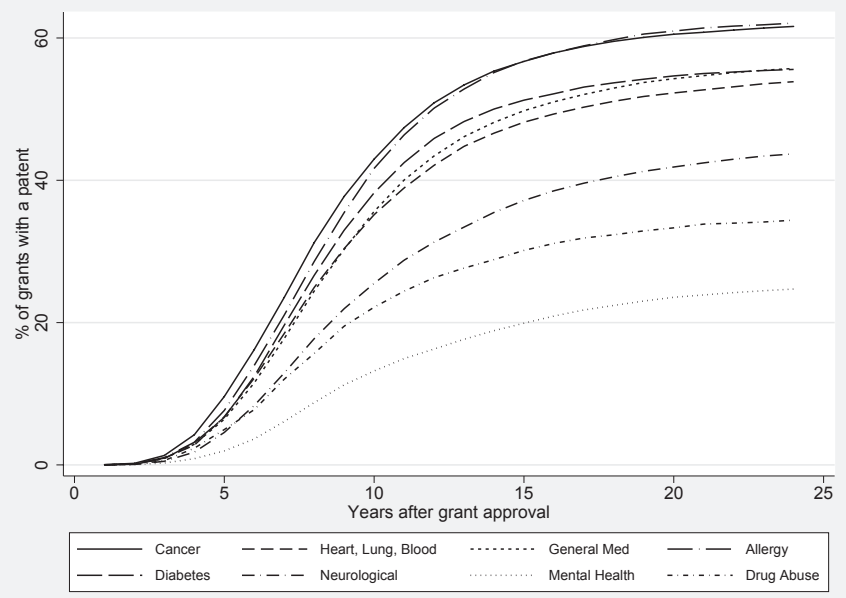


Figure 4
Grant-Patent Lags by Grant Cohort

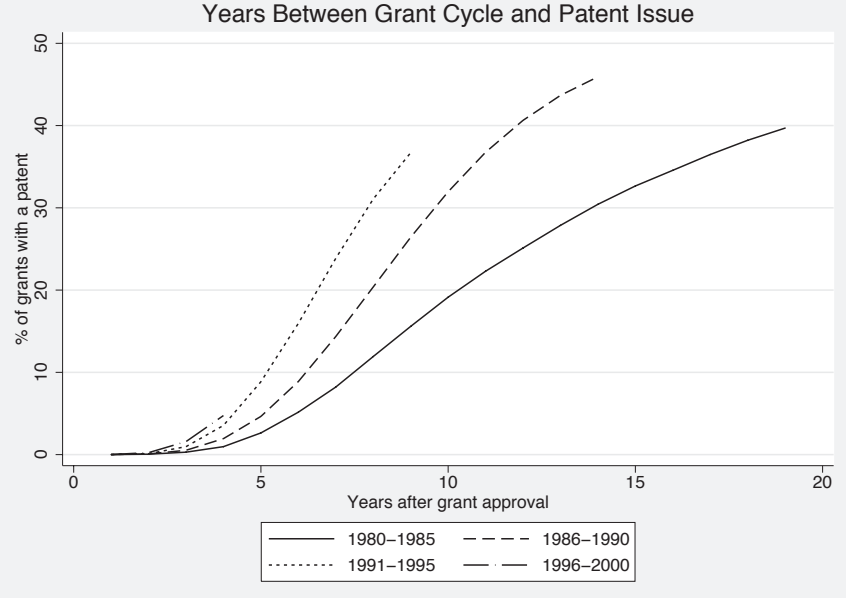


Figure 5
Grant-Patent Lags by Patent Quality

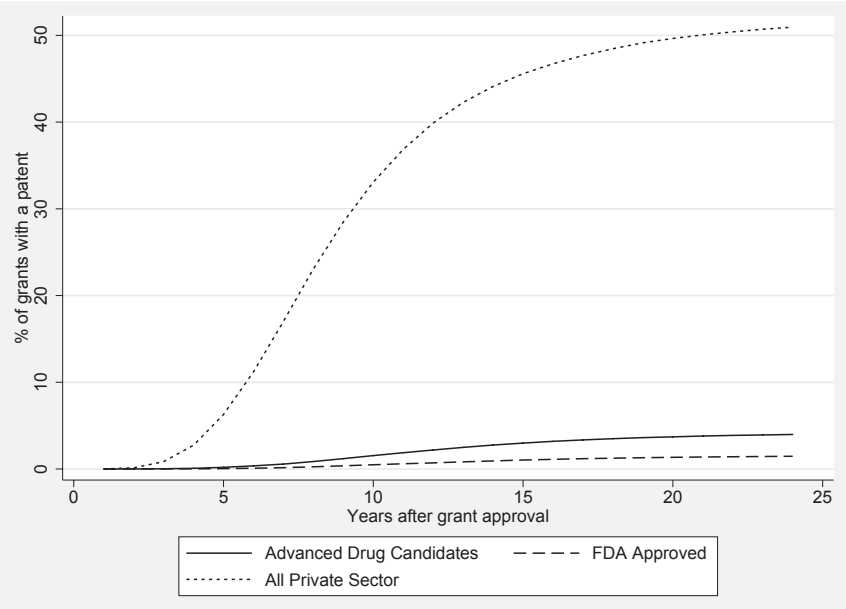


Figure 6
Grant-Patent Lags by Patent Type

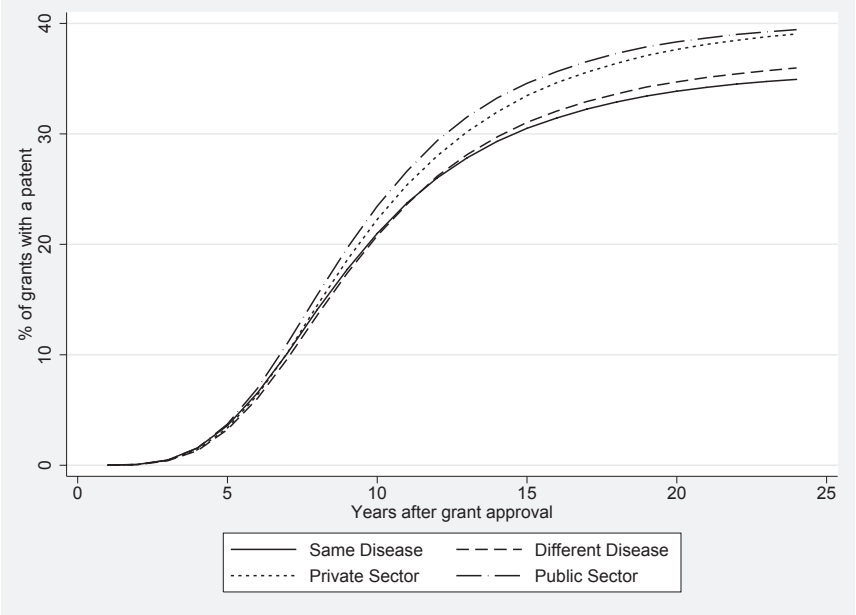


Figure 7
Outcome Measures by DST

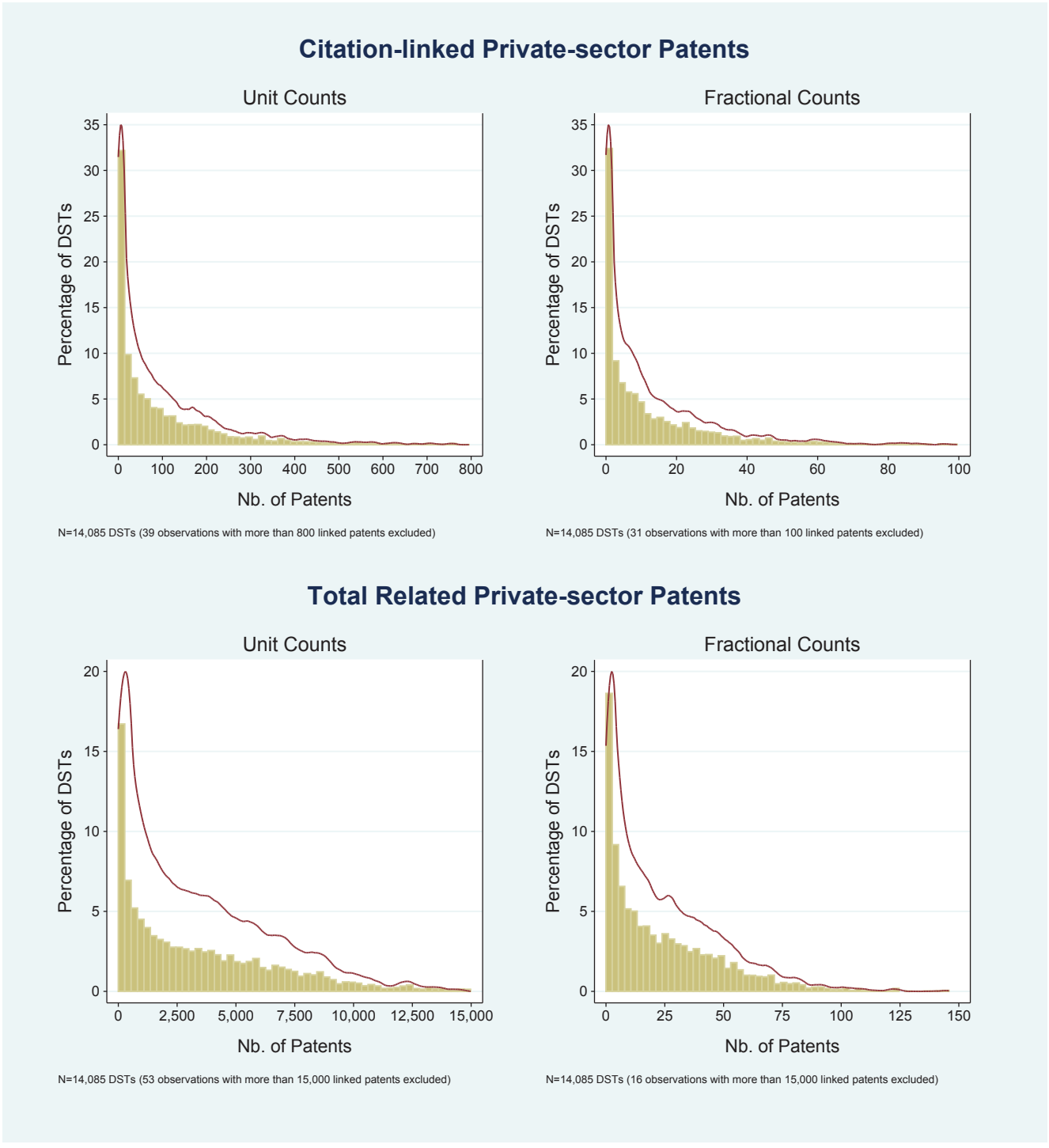


Table 1: Grant Characteristics, 1980-2005

		Grants Linked to Private-sector Patents	
	Full Sample	**Cited by Patents**	**Related to Patents**
Sample Coverage			
# Grants	153,076	66,085	123,872
# Disease Areas (Institutes)	17	17	17
# Science Areas (Study Sections)	624	548	598
# DSTs	14,085	8,886	13,037
Grant Characteristics			
% R01 equivalent Grants	73.72	77.46	74.30
% Center Grants	3.26	4.79	3.20
% Teaching or Fellowship Grants	11.43	10.12	11.27
% New	59.50	51.08	58.55
Funding Amount (total project allocation, 2010 dollars; mean & s.d.)	$1,556,572 *($2,197,603)*	$1,875,779 *($2,783,272)*	$1,568,894 *($2,215,366)*

Note: Sample is the set of all NIH-funded grants from 1980-2005, excluding NINR, NLM, and NIMHD grants (see Appendix A for a full list of ICs in the sample) and evaluated by chartered study sections. The sample is restricted to new and competitive renewal grants so that there is one observation per successful grant application cycle. A grant is defined as cited by patents if there exists a patent that cites a publication that acknowledges funding from that grant. A grant is matched with a publication if it acknowledges the project number of the grant and is published within 5 years of the grant's funding year. A patent is citation-linked to a grant if it cites a publication that is linked to a grant. A grant is considered related to a patent if that grant produces a publication that is similar (as defined by the PubMed Relatedness Matching Algorithm) to a publication that is cited by a patent. In this paper, we require that similar publications be published within 5 years of each other. A grant is an R01 equivalent (e.g. a large project-based grant) if its NIH funding mechanism is either an R01, R23, R29, or R37. Center grants are those grants whose mechanism starts with a "P" (e.g., a P01 grant containing multiple projects). A teaching or fellowship grant is one whose grant mechanism designation begins with a "T" or an "F." New grants are projects that have not previously received NIH funding.

Table 2: Patent Characteristics, 1980-2012

	Full Sample	Patents Linked to NIH Funding	
		% Citing NIH Funded Research	% Related to NIH Funded Research
Sample Coverage			
# Patents	315,982	44.00	84.10
Patent Characteristics: General			
Private Sector	232,276	39.38	82.33
Public Sector	83,394	56.91	89.07
Patent Characteristics: Private Sector Only			
Advanced Drug Candidates	4,718	49.92	88.22
FDA Approved Drugs	1,999	42.47	86.79
Large Asssignee	164,431	36.23	80.37
Small Asssignee	29,183	51.37	87.89

Note: Sample is the set of all USPTO granted patents from 1980-2012 that meet the following criteria: (i) they are either in NBER Patent Categories 1 ("Chemicals") or 3 ("Drugs and Medical") and (ii) they cite at least one publication in the PubMed database. A patent is defined as citing NIH-funded research if it cites a publication that acknowledges the project number of an NIH grant and is published within 5 years of that grant's funding year. A patent is considered related to NIH funding if it cites a publication that is similar (as defined by the PubMed Relatedness Matching Algorithm) to a publication that acknowledges NIH funding. We require that similar publications be published within 5 years of each other. A patent is labelled "Private Sector" if it is assigned to a domestic US or foreign corporation (NBER assignee categories 1 and 2 minus foundations, universities, and hospitals). A patent is labelled "Public Sector" if it is assigned to a US or foreign goverment (NBER categories 5 and 6) or if it is assigned to a foundation, university, or hospital. A patent is labeled an advanced drug candidate if it is associated with a drug or biologic in Phase III clinical trials or beyond (these are listed in Orange Book and/or IMS Patent Focus); A patent is associated with an FDA approved drug if that patent is associated with a marketed treatment accoding to IMS Health. A patent is associated with a large assignee if its assignee employs over 500 employees; it is considered small otherwise.

Table 3: NIH Research Area (DST) Characteristics, 1980-2005

		DSTs Linked to Patents	
	Full Sample	**Cited by Patents**	**Related to Patents**
Average # of Grants	10.85 *(16.58)*	15.60 *(19.05)*	11.62 *(17.01)*
Output Characteristics			
Funding Amount (DST)	$40,631,460 *(43,611,800)*	$45,556,350 *(44,448,260)*	$41,397,230 *43,683,690*
# of Patents Citing NIH-Funded Research (Fractional counts)	12.82 *(19.17)*	14.71 *(19.85)*	13.07 *(19.28)*
# of Patents Citing NIH-Funded Research (Unit counts)	101.7 *(153.6)*	116.8 *(159.1)*	103.7 *(154.4)*
# of Patents Related to NIH-Funded Research (Fractional counts)	24.84 *(27.95)*	28.33 *(28.31)*	25.30 *(28.00)*
# of Patents Related to NIH-Funded Research (Unit counts)	3,520 *(3,742)*	4,023 *(3,755)*	3,589 *(3,745)*
N	14,085	8,886	13,027

Note: Sample is the same as that in Table 1, except aggregated to the NIH Disease/Science/Time level. See the notes to Table 1 for additional definitions. The funding and patent variables are weighted by average DST size, i.e., the average yearly number of grants in a Disease/Science research area. In fractional patent counts, a patent matched to N distinct DSTs counts as $1/N^{th}$ of a patent for each DST. In unit patent counts, a single patent matched to N distinct DSTs counts as one patent for each DST. Funding amounts are expressed in 2010 dollars (deflated by the Biomedical R&D Producer Price Index).

Table 4: Effect of NIH Investments on Follow-On Patenting by Private-Sector Firms

	# of Patents Citing NIH-Funded Research				
	(1)	(2)	(3)	(4)	(5)
Fractional Patent Counts: Mean=12.82; SD=19.17					
DST Funding (×$10 mln.)	2.595***	2.281***	2.242***	2.550***	2.450***
Mean=4.06; SD=4.36	*(0.171)*	*(0.267)*	*(0.254)*	*(0.294)*	*(0.288)*
Elasticity	0.822	0.723	0.71	0.808	0.777
R^2	0.417	0.600	0.641	0.918	0.933
Unit Patent Counts: Mean=101.7; SD=153.6					
DST Funding (×$10 mln.)	21.830***	17.830***	17.841***	18.626***	18.412***
Mean=4.06; SD=4.36	*(1.343)*	*(2.103)*	*(2.053)*	*(2.177)*	*(1.980)*
Elasticity	0.872	0.712	0.713	0.744	0.735
R^2	0.447	0.674	0.710	0.944	0.956
Observations	14,085	14,085	14,085	14,085	14,085
Year FEs	Incl.	Incl.	Incl.	Incl.	Incl.
Disease × Science FEs		Incl.	Incl.	Incl.	Incl.
Disease × Year FEs			Incl.	Incl.	Incl.
Science × Year FEs				Incl.	Incl.
Application Count FEs					Incl.

Note: Each observation is Disease/Science/Time (DST) combination. A patent is citation-linked to a DST if it cites research that acknowledges funding from that DST. For more details on this sample, see the notes to Tables 1 and 3. Funding is defined by the sum of project-cycle allocations for all new and competing renewal grants that are associated with that DST. The patent sample is restricted to those with private sector assignees, and weighted by average DST size, i.e., the average yearly number of grants in a Disease/Science research area. See Table 2 for more details. Year FEs are fixed effects for the fiscal year associated with a DST. NIH Institutes are taken to represent diseases and NIH study sections (review committees) are taken to represent science areas. Elasticities are evaluated at sample means. Application count FEs are indicator variables for the number of applications that a DST receives.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table 5:
Effect of NIH Investments on Total Related Private-Sector Patenting

	# of Patents Related to NIH-Funded Research				
	(1)	(2)	(3)	(4)	(5)
Fractional Patent Counts: Mean=24.8; SD=28.0					
DST Funding (×$10 mln.) Mean=4.06; SD=4.36	4.516*** *(0.278)*	3.593*** *(0.434)*	3.590*** *(0.420)*	3.712*** *(0.445)*	3.239*** *(0.284)*
Elasticity	0.738	0.588	0.587	0.607	0.530
R^2	0.536	0.759	0.783	0.965	0.974
Unit Patent Counts: Mean=3,969; SD=3,918					
DST Funding (×$10 mln.) Mean=4.06; SD=4.36	603.063*** *(34.936)*	456.657*** *(55.780)*	453.108*** *(54.616)*	504.727*** *(54.459)*	445.981*** *(32.671)*
Elasticity	0.696	0.527	0.523	0.583	0.515
R^2	0.561	0.843	0.861	0.978	0.983
Observations	14,085	14,085	14,085	14,085	14,085
Year FEs	Incl.	Incl.	Incl.	Incl.	Incl.
Disease × Science FEs		Incl.	Incl.	Incl.	Incl.
Disease × Year FEs			Incl.	Incl.	Incl.
Science × Year FEs				Incl.	Incl.
Application Count FEs					Incl.

Note: Each observation is Disease/Science/Time (DST) combination. A patent is considered to be in the same area as an NIH grant if it cites a publication that is similar (as defined by the PubMed Relatedness Matching Algorithm) to a publication that is linked to a patent. For more details on this sample, See the notes to Tables 1 and 2. Funding is defined by the sum of project-cycle allocations for all new and competing renewal grants that are associated with that DST. The patent sample is restricted to those with private sector assignees, and weighted by average DST size, i.e., the average yearly number of grants in a Disease/Science research area. See Table 2 for more details. Year FEs are fixed effects for the fiscal year associated with a DST. NIH Institutes are taken to represent diseases and NIH study sections (review committees) are taken to represent science areas. Elasticities are evaluated at sample means. Application count FEs are indicator variables for the number of applications that a DST receives.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table 6: Effect of NIH Investments on Private-Sector Patenting
Windfall Funding IV

	First Stage		Citation Linked		Total Related	
	DST Funding (× $10 mln.)		Mean=12.82; SD=19.17		Mean=24.8; SD=28.0	
			OLS	IV	OLS	IV
	(1)		(2)	(3)	(4)	(5)
Windfall Funding (×$10 mln.)	1.251***	DST Funding (×$10 mln.) Mean=4.06; SD=4.36	2.478***	2.002**	3.614***	2.329***
	(0.232)		*(0.496)*	*(0.853)*	*(0.671)*	*(0.834)*
		Elasticity	0.785	0.634	0.592	0.381
Cragg-Donald Wald *F*-stat	478					
Kleibergen-Paap Wald *F*-stat	37.51					
R^2	0.921		0.738	0.515	0.863	0.623
Observations	14,085		14,085	14,085	14,085	14,085
Year FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Disease × Science FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Disease × Year FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Science × Year Linear Trends	Incl.		Incl.	Incl.	Incl.	Incl.
Application Controls	Incl.		Incl.	Incl.	Incl.	Incl.

Note: See notes to Tables 4 and 5 for details about the sample. The outcome variables are fractional patent counts. The instrument is the total amount of funding (2010 dollars) for the subset of grants funded by a DST whose rank of rank scores were marginal, i.e., were within 25 applications of the award cutoff for their specific disease area (Institute). Application controls include (i) FEs for the number of applications that a DST receives; (ii) FEs for the number of applications associated with a DST that are also in a 25-grant radius around the relevant IC payline, as well as (iii) cubics in the average raw and rank scores of applications associated with a DST that are also in a 25-grant radius around the payline. Elasticities are evaluated at the sample means.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table 7: Effect of NIH Investments on Private-Sector Patenting Heterogeneity by Patent Type

	All Private Sector	Advanced Drug Candidates	Same Area	Different Area	Large Assignee	Small Assignee
	Mean=24.8; SD=28.0	*Mean=0.546; SD=0.864*	*Mean=18.9; SD=23.8*	*Mean=15.9; SD=19.0*	*Mean=17.5; SD=20.7*	*Mean=3.47; SD=4.18*
	(1)	(2)	(3)	(4)	(5)	(6)
OLS						
DST Funding (×$10 mln.)	3.614***	0.081***	2.698***	2.297***	2.561***	0.506***
Mean=4.06; SD=4.36	*(0.671)*	*(0.015)*	*(0.419)*	*(0.547)*	*(0.487)*	*(0.101)*
Elasticity	0.592	0.602	0.580	0.587	0.594	0.592
IV						
DST Funding (×$10 mln.)	2.329***	0.053**	1.202**	1.894***	1.658***	0.362**
Mean=4.06; SD=4.36	*(0.834)*	*(0.026)*	*(0.561)*	*(0.685)*	*(0.574)*	*(0.162)*
Elasticity	0.381	0.394	0.258	0.484	0.385	0.424
Observations	14,085	14,085	14,085	14,085	14,085	14,085

Note: See notes to Tables 5 and 6 for sample details. The outcome variables are fractional patent counts. All specifications include disease-science FEs, disease-year FEs, science by year linear time trends, FEs for the number of applications to the DST, cubics in the average raw score and average science rank received by applications in the 25-grant radius window around the IC payline, and FEs for number of DST applicants in a 25-grant radius around an IC's funding cutoff. A patent is labelled "Private Sector" if it is assigned to a domestic US or foreign corporation (NBER assignee categories 1 and 2 minus foundations, universities, and hospitals). A patent is labeled an advanced drug candidate if it is included in IMS Patent Focus, which has information on patents on drugs in Phase III trials or further. A patent is in the same disease area as a DST if the plurality of NIH research areas that it is linked are also associated with that same "D" disease area. A patent is associated with a large assignee if its first assignee employs more than 500 employees; it is considered small otherwise.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table 8: Implied Drug Valuation of NIH Investments

	Advanced Drug Candidates	FDA Approved	Pre-approval	Main	Drug-level
	Mean=0.546; SD=0.864	*Mean=0.316; SD=0.532*	*Mean=0.212 SD=0.358*	*Mean=0.035; SD=0.084*	*Mean=0.059; SD=0.099*
	(1)	(2)	(3)	(4)	(5)
OLS					
DST Funding (×$10 mln.)	0.081***	0.046***	0.032***	0.005***	0.008***
Mean=4.06; SD=4.36	*(0.015)*	*(0.010)*	*(0.007)*	*(0.001)*	*(0.001)*
Elasticity	0.602	0.591	0.613	0.580	0.551
Implied Drug Value ($ mln.)	—	$20.0	$22.2	$17.4	$27.8
IV					
DST Funding (×$10 mln.)	0.053**	0.034**	0.017	0.001	0.004
Mean=4.06; SD=4.36	*(0.026)*	*(0.017)*	*(0.013)*	*(0.003)*	*(0.004)*
Elasticity	0.394	0.437	0.326	0.116	0.275
Implied Drug Value ($ mln.)	—	$14.7	$11.8	$3.5	$13.9
Observations	14,085	14,085	14,085	14,085	14,085

Note: See notes to Tables 5 and 6 for sample details. The outcome variables are fractional patent counts. All specifications include disease-science FEs, disease-year FEs, science by year linear time trends, FEs for the number of applications to the DST, cubics in the average raw score and average science rank received by applications in the 25-grant radius window around the IC payline, and FEs for number of DST applicants in a 25-grant window around an IC's funding cutoff. A patent is labelled "Private Sector" if it is assigned to a domestic US or foreign corporation (NBER assignee categories 1 and 2 minus foundations, universities, and hospitals). A patent is labeled an advanced drug candidate if it is included in IMS Patent Focus, which contains information on patents on biopharmaceutical candidates in Phase III trials or further. We do not generate an implied value for these patents since they are not necessarily associated with an approved drug/biologic. Within this set, patents are labeled as "FDA approved" if linked to an approved drug/biologic. A patent is labeled "pre-approval" if it is "FDA approved" and was filed prior to the time at which corresponding received marketing approval. A patent is labeled as "main" patent if it is the first patent ever filed associated with a marketed drug. Column 5 aggregates results to the drug level, reweighting by the number of unique drugs associated with a DST. Implied drug values are calculated assuming a mean lifetime discounted value of $3.47 billion, in 2010 dollars. This figure comes from DiMasi, Grabowski, and Vernon (2004). All estimates assume that there is one pivotal patent per drug; FDA approved patents are scaled by 8; pre-approval patents by 5; main patents and drug specific outcomes are not scaled. For instance, the OLS estimate in column (2) imply that an additional $10 mln. in NIH funding for a DST would result in $22.6 mln. in downstream pharmaceutical sales.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table 9: Effect of NIH Investments on Firm Reallocation of R&D Investments

	Total non-DST patents		**Average non-DST patents, per DST-linked patent**	
	Citation	Related	Citation	Related
	Mean=122.6; SD=289.1	Mean=178.1; SD=197.7	Mean=2.57 SD=3.20	Mean=21.05; SD=66.9
	(1)	(2)	(3)	(4)
DST Funding (×$10 mln.)	5.561	4.877***	0.467	0.049
	(3.964)	*(1.393)*	*(1.336)*	*(0.045)*
Elasticity	0.184	0.111	0.738	0.009
R^2	0.898	0.983	0.825	0.908
Observations	14,085	14,085	14,085	14,085

Note: Each observation is Disease-Science Area-Time (DST) combination. The outcome variables are fractional patent counts. Total non-DST patents are calculated by first identifying all assignees that produce a patent linked to a DST (either through citations or through PMRA relatedness). We then find all non-D, non-S patents issued to that restricted set of assignees in the same year. This is our "Total non-DST" patent count. "Average non-DST" patents normalizes this by the number of DST-linked patents. A patent is assigned to the disease area to which it is most often associated. All regressions include disease-science FEs, disease-year FEs, science-year FEs, and FEs for the number of applications to the DST, and cubics in the number of DST-linked patents that are matched.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Appendix A: A Primer on NIH Funding

The National Institutes of Health (NIH) is the primary organization within the United States government with responsibilities for health-related research. The NIH is the single largest funder of biomedical research, with an annual budget of approximately $30 billion. According to its own web site, NIH's mission is *"to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability."*

NIH comprises 21 different Institutes (plus an assortment of centers that our analysis will ignore), each with a distinct, though sometimes overlapping, research agenda. For example, the National Institute for Mental Health, as the name suggests, focuses on mental health related research. It shares interests with the National Institute of Aging on issues related to dementia. All Institutes receive their funding directly from Congress, and manage their own budgets. Table A1 lists each of the agency's component institutes.

Figure A1(i) provides an example of language from an appropriations bill for the National Cancer Institute; here, Congress uses the disease burden associated with pancreatic cancer to underscore the need for more research in this field. Figure A1(ii) compiles a list of the mostly commonly used words in the Congressional appropriations documents for all NIH Institutes, for a sample year. The highest-frequency word in both House and Senate appropriations is, unsurprisingly, "research." The majority of the remaining list are medicine or disease focused: "disease," "health," "child," "behavior," "patients," "syndrome," etc. This reasoning is supported by research showing that funding levels for particular Institutes are more highly correlated with disease burden than with scientific advances (Gillum et al., 2011).

Approximately 10% of the overall NIH budget is dedicated to the intramural research program, with almost all Institutes providing some support. The program directly supports about 6,000 scientists working within the federal laboratories on NIH Campuses. Unlike the intramural program, where allocation decisions are relatively opaque, the operations of the extramural program are quite transparent. More than 80% of the total budget supports extramural research through competitive grants that are awarded to universities, medical schools, and other research institutions, primarily in the United States. The largest and most established of these grant mechanisms is the R01, a project-based renewable research grant which constitutes half of all NIH grant spending and is the primary funding source for most academic biomedical labs in the United States. There are currently 27,000 outstanding awards, with 4,000 new projects approved each year. The average size of each award is 1.7 million dollars spread over 3 to 5 years and the application success rate is approximately 20 percent (Li 2014).

Requests for proposals identify priority areas, but investigators are also free to submit applications on unsolicited topics under the extramural research program. All applications are assigned to a review committee comprised of scientific peers, generally known as a study section (Table A2 lists the 173 study sections that currently exist). Reviewers are asked to ignore budgetary issues, limiting their attention to scientific and technical merit on the basis of five criteria: (1) Significance [does the project address an important issue?]; (2) Approach [is the methodology sound?]; (3) Innovation [is the research novel?]; (4) Investigator [are the skills of the research team well matched to the project?]; and (5) Environment [is the place in which the work will take place conducive to project success?]. Each reviewer assigns a two digit priority score ranging from 1.0 for the best application to 5.0 for the worst. At the study section meeting, three reviewers are typically asked to discuss an application and present their initial scores. This is followed by an open discussion by all reviewers and a brief period for everyone to revise their initial scoring based on the group deliberations before anonymously submitting their final scores. The overall priority score for the proposal is based on the average across all study section members. Those applications determined to be of the lowest quality by the study section do not receive priority scores. Scores are then normalized within review groups through the assignment of percentile scores to facilitate funding decisions.

Funding decisions are decoupled from the scientific review and determined by program areas within the Institutes. In essence, each decision making unit (e.g., Division, Program, Branch) within an Institute is

allocated a fixed annual budget. Units then fund new projects in order of their priority score until their budget, net of encumbered funds for ongoing grants awarded in previous years, is exhausted. The highest percentile score that is funded is known as the payline. A grant's score is generally the sole determinant of the funding decision,[i] irrespective of proposal costs (assuming they are deemed reasonable). Researchers who do not receive funding are given the opportunity to respond to reviewer criticisms and submit an amended application.

Institutes considered in the econometric analysis. We exclude from our analytic sample observations corresponding to the National Library of Medicine (NLM), the National Institute of Nursing Research (NINR), and the National Institute on Minority Health and Health Disparities (NIMHD), which together represent less than 3% of NIH's total budget. We drop the NLM because it seldom supports extramural researchers. We drop NINR and NIMHD because we found no instances of the grants funded by these Institutes generating publications referenced in private-sector patents.

A cursory look at the names of the list of the 18 Institutes we do include in most of our analyses reveals that some of these Institutes may not be strictly disease-focused. This is certainly the case for NIGMS (which supports mostly untargeted laboratory research), for NHGRI (the genome Institute), and NIBIB (which focuses on imaging technology). In a sensitivity test, we will explore whether our main results are robust to the exclusion of these three "science-focused" Institutes. Further, we will also investigate the effects of dropping NIA, NIDCD, NIEHS, and NICHD who traditionally support research on a broad spectrum of loosely related diseases.

Study sections. As mentioned above, the majority of grant evaluation occurs in approximately 200 standing review committees, known as "study sections." Each study section is organized around a scientific topic—for instance, "Cellular and Molecular Immunology"—and is responsible for evaluating the quality of applications in its area. Traditionally, the boundaries delineating study sections have changed only very slowly (too slowly for many NIH critics). Additions and deletions of study sections is relatively rare, and often controversial. In 2006, however, the NIH reorganized its standing study sections. This involved closing or consolidating some study sections, splitting others, and creating new study sections, for instance one on data analytics, to respond to new topics and tools. The overall review process stayed largely the same. This change happens outside of our sample frame and, throughout our analysis, we refer to the old system.

Allocation of Applications to Study Sections. Could applicants improve their odds of funding by sending their applications to study sections reputed to be "weaker"? Study section shopping of this type would be almost surely unproductive, given year-to-year fluctuations in funding and the vagaries of the reapplication process (most proposals are not funded at the first review).[ii] Formally, grant applicants do not choose the study section that will review their proposals. Rather, each application is assigned by staff within the Division of Receipt and Referral at the NIH to a study section based on the needed expertise to evaluate scientific and technical merit.[iii] While many investigators ask to be reviewed by a specific study section, the NIH grants such requests based on the scientific content of the proposal, a consideration of conflicts of interest, and the administrative viability of the request (Chacko 2014). More importantly, the typical advice received by new investigators is to petition to be reviewed in the study section that is most likely to have members on their roster whom are familiar with their narrowly-defined field, and then to stick to this initial choice. Consistent with this advice, an essential component of "grantsmanship" at NIH is to build a cordial relationship with the Scientific Review Officer, the staff person within NIH's Center for Scientific Review

[i] Institute directors have the discretion to fund applications out of order if, for example, they are especially important to the Institute's mission. Since applications can only be submitted three times, Institutes may also choose to fund applications on their last evaluation cycle instead of newly submitted applications that can be reconsidered later. These exceptions appear rare (Jacob and Lefgren 2011).

[ii] Even grant administrators are usually unable to communicate to applicants how the score they received in committee is likely to translate into a final funding decision. It is implausible that grant applicants could be better informed than these knowledgeable insiders.

[iii] `http://public.csr.nih.gov/ApplicantResources/ReceiptReferal/Pages/Submission-and-Assignment-Process.aspx`, accessed August 30, 2014

who administers the logistics of the review process. These informal practices would seem to run counter any temptation to "chase the money."

We see this in the data, where there is considerable inertia in scientist-study section pairings. In a typical five year-period, 88% of NIH grant recipients are evaluated by only one study section; eleven percent are evaluated by two study sections; and only one percent are evaluated by three study sections or more. Why would a given scientist's grant applications ever be reviewed by multiple study sections? One reason is that study sections are not immutable. Some are created; others are eliminated; yet others are merged. Intellectual breadth may also explain the anomalies: In a sample of 10,177 well-funded investigators for whom we have gathered a carefully curated list of publications (cf. Azoulay et al. 2012), intellectual breadth (as proxied by the diversity of MeSH keywords that tag the publications produced by these scientists in rolling five-year windows) is strongly correlated with the likelihood of having one's work reviewed by multiple study section (Table A3). This results holds even when controlling for the total level of funding received. This results hold even when controlling for the total level of funding received. This suggests that scientists have their work reviewed by two or more committees only to the extent that they are active in subfields that are sufficiently distant in intellectual space.

Disease/Science as a level of analysis. As highlighted in the introduction, the organization of the NIH into disease-based funding Institutes and science-based review committees will play an important role in our empirical work, since our independent and dependent variables will be computed at the level of the disease/science/year (DST, technically the IC/study section/year level). If applications evaluated by a study section were always funded by the same Institute, the distinction we emphasize between the disease/science level of analysis and disease-level variation over time would not be very meaningful. However, it is indeed the case that study sections are "promiscuous," in the sense that the grant applications they pass favorable judgement on will go on to be funded by several different Institutes. Figure A2(i) shows that the majority, 75 percent, of study sections evaluated grants funded by at least two Institutes. Conversely, Figure A2(ii) shows that the typical Institute draws on applications stemming from more than 50 study sections, on average.

Not only is the DST level of analysis policy-relevant, it is tractable by using the structure of NIH grant review and mapping Institutes into disease areas, and study sections into science areas, respectively. And because of the "intellectual promiscuity" documented above, in practice, increases in funding for one disease can impact innovation in another by supporting research on the scientific foundations these two areas share.

Figure A3 plots residual variation in funding taking out, successively, fixed effects for calendar year, disease/science, disease/year, and science/year. These kernel density estimates make clear that there remains substantial unexplained variation in funding after controlling for all these fixed effects. It is this DST-level variation that we use to estimate the effect of funding on private-sector patenting.

Table A1: NIH Institutes and Centers (ICs)

Institute	Abbrev.	Established	Avg. Budget*
National Cancer Institute	NCI	1937	$4,019,793
National Heart, Lung, and Blood Institute	NHLBI	1948	$2,489,629
National Institute of Allergy and Infectious Diseases	NIAID	1948	$2,070,634
National Institute of Dental and Craniofacial Research	NIDCR	1948	$325,861
National Institute of Mental Health	NIMH	1949	$1,378,636
National Institute of Diabetes and Digestive and Kidney Diseases	NIDDK	1950	$1,491,613
National Institute of Neurological Disorders and Stroke	NINDS	1950	$1,244,241
National Eye Institute	NEI	1968	$562,126
National Institute on Alcohol Abuse and Alcoholism	NIAAA	1970	$423,341
National Institute on Drug Abuse	NIDA	1974	$960,637
National Institute of Arthritis and Musculoskeletal and Skin Diseases	NIAMS	1986	$458,273
National Institute of Child Health and Human Development	NICHD	1962	$1,043,447
National Institute of Environmental Health Sciences	NIEHS	1969	$557,645
National Institute on Aging	NIA	1974	$702,184
National Institute on Deafness and Other Communication Disorders	NIDCD	1988	$347,646
National Institute of General Medical Sciences	NIGMS	1962	$1,629,056
National Human Genome Research Institute	NHGRI	1989	$375,451
National Institute of Biomedical Imaging and Bioengineering	NIBIB	2000	$316,430
National Library of Medicine	NLM	1956	$229,442
National Institute of Nursing Research	NINR	1986	$106,880
National Institute on Minority Health and Health Disparities	NIMHD	1993	$228,287

*Over the 1980-2005 time period, In thousands of 2010 dollars (amounts deflated by the Biomedical R&D PPI)

Table A2: NIH Study Sections

Study Section	Description	Study Section	Description	Study Section	Description
ACE	AIDS Clinical Studies and Epidemiology	CPDD	Child Psychopathology and Developmental Disabilities	MSFA	Macromolecular Structure and Function A
ACTS	Arthritis, Connective Tissue and Skin	CRFS	Clinical Research and Field Studies of Infectious Diseases	MSFB	Macromolecular Structure and Function B
ADDT	AIDS Discovery and Development of Therapeutics	CSRS	Cellular Signaling and Regulatory Systems	MSFC	Macromolecular Structure and Function C
AICS	Atherosclerosis and Inflammation of the Cardiovascular System	DBD	Developmental Brain Disorders	MSFD	Macromolecular Structure and Function D
AIP	AIDS Immunology and Pathogenesis	DDNS	Drug Discovery for the Nervous System	MSFE	Macromolecular Structure and Function E
AMCB	AIDS Molecular and Cellular Biology	DDR	Drug Discovery and Mechanisms of Antimicrobial Resistance	MTE	Musculoskeletal Tissue Engineering
ANIE	Acute Neural Injury and Epilepsy	DEV1	Development - 1	NAED	NeuroAIDS and other End-Organ Diseases
AOIC	AIDS-associated Opportunistic Infections and Cancer	DEV2	Development - 2	NAL	Neurotoxicology and Alcohol
APDA	Adult Psychopathology and Disorders of Aging	DIRH	Dissemination and Implementation Research in Health	NAME	Neurological, Aging and Musculoskeletal Epidemiology
ASG	Aging Systems and Geriatrics	DMP	Drug Discovery and Molecular Pharmacology	NANO	Nanotechnology
AUD	Auditory System	DPVS	Diseases and Pathophysiology of the Visual System	NCF	Neurogenesis and Cell Fate
BACP	Bacterial Pathogenesis	DT	Developmental Therapeutics	NCSD	Nuclear and Cytoplasmic Structure/Function and Dynamics
BBM	Biochemistry and Biophysics of Membranes	EBIT	Enabling Bioanalytical and Imaging Technologies	NDPR	Neurodifferentiation, Plasticity, Regeneration and Rhythmicity
BCHI	Biomedical Computing and Health Informatics	EPIC	Epidemiology of Cancer	NMB	Neurobiology of Motivated Behavior
BDMA	Biodata Management and Analysis	ESTA	Electrical Signaling, Ion Transport, and Arrhythmias	NNRS	Neuroendocrinology, Neuroimmunology, Rhythms and Sleep
BGES	Behavioral Genetics and Epidemiology	GCAT	Genomics, Computational Biology and Technology	NOIT	Neuroscience and Ophthalmic Imaging Technologies
BINP	Brain Injury and Neurovascular Pathologies	GDD	Gene and Drug Delivery Systems	NOMD	Neural Oxidative Metabolism and Death
BMBI	Biomaterials and Biointerfaces	GHD	Genetics of Health and Disease	NPAS	Neural Basis of Psychopathology, Addictions and Sleep Disorders
BMCT	Basic Mechanisms of Cancer Therapeutics	GMPB	Gastrointestinal Mucosal Pathobiology	NRCS	Nursing and Related Clinical Sciences
BMIO	Behavioral Medicine, Interventions and Outcomes	GVE	Genetic Variation and Evolution	NTRC	Neurotransporters, Receptors, and Calcium Signaling
BMIT-A	Biomedical Imaging Technology A	HAI	Hypersensitivity, Autoimmune, and Immune-mediated Diseases	ODCS	Oral, Dental and Craniofacial Sciences
BMIT-B	Biomedical Imaging Technology B	HBPP	Hepatobiliary Pathophysiology	PBKD	Pathobiology of Kidney Disease
BMRD	Biostatistical Methods and Research Design	HDEP	Health Disparities and Equity Promotion	PCMB	Prokaryotic Cell and Molecular Biology
BNVT	Bioengineering of Neuroscience, Vision and Low Vision Technologies	HIBP	Host Interactions with Bacterial Pathogens	PDRP	Psychosocial Development, Risk and Prevention
BPNS	Biophysics of Neural Systems	HM	Hypertension and Microcirculation	PMDA	Pathophysiological Basis of Mental Disorders and Addictions
BRLE	Biobehavioral Regulation, Learning and Ethology	HSOD	Health Services Organization and Delivery	PN	Pregnancy and Neonatology
BSCH	Behavioral and Social Consequences of HIV/AIDS	HT	Hemostasis and Thrombosis	PRDP	Psychosocial Risk and Disease Prevention
BSPH	Behavioral and Social Science Approaches to Preventing HIV/AIDS	ICER	Integrative and Clinical Endocrinology and Reproduction	PTHE	Pathogenic Eukaryotes
BTSS	Bioengineering, Technology and Surgical Sciences	ICI	Intercellular Interactions	RIBT	Respiratory Integrative Biology and Translational Research
BVS	Biology of the Visual System	ICP1	International and Cooperative Projects - 1	RPIA	Risk, Prevention and Intervention for Addictions
CADO	Cellular Aspects of Diabetes and Obesity	IHD	Immunity and Host Defense	RTB	Radiation Therapeutics and Biology
CAMP	Cancer Molecular Pathobiology	III	Innate Immunity and Inflammation	SAT	Surgery, Anesthesiology and Trauma
CASE	Cardiovascular and Sleep Epidemiology	INMP	Integrative Nutrition and Metabolic Processes	SBCA	Synthetic and Biological Chemistry A
CBSS	Cancer Biomarkers	IPOD	Integrative Physiology of Obesity and Diabetes	SBCB	Synthetic and Biological Chemistry B
CCHF	Cardiac Contractility, Hypertrophy, and Failure	IRAP	Infectious Diseases, Reproductive Health, Asthma and Pulmonary Conditions	SBDD	Skeletal Biology Development and Disease
CDD	Cardiovascular Differentiation and Development	ISD	Instrumentation and Systems Development	SBSR	Skeletal Biology Structure and Regeneration
CDIN	Chronic Dysfunction and Integrative Neurodegeneration	KMBD	Kidney Molecular Biology and Genitourinary Organ Development	SCS	Somatosensory and Chemosensory Systems
CDP	Chemo/Dietary Prevention	KNOD	Kidney, Nutrition, Obesity and Diabetes	SEIR	Societal and Ethical Issues in Research
CE	Cancer Etiology	LAM	Neurobiology of Learning and Memory	SMEP	Skeletal Muscle and Exercise Physiology
CG	Cancer Genetics	LCMI	Lung Cellular, Molecular, and Immunobiology	SMI	Sensorimotor Integration
CICS	Clinical and Integrative Cardiovascular Sciences	LCOM	Language and Communication	SPC	Mechanisms of Sensory, Perceptual, and Cognitive Processes
CIDO	Clinical and Integrative Diabetes and Obesity	LIRR	Lung Injury, Repair, and Remodeling	SPIP	Social Psychology, Personality and Interpersonal Processes
CIHB	Community Influences on Health Behavior	MABS	Modeling and Analysis of Biological Systems	SSPA	Social Sciences and Population Studies A
CII	Cancer Immunopathology and Immunotherapy	MBPP	Membrane Biology and Protein Processing	SSPB	Social Sciences and Population Studies B
CIMG	Clinical, Integrative and Molecular Gastroenterology	MCE	Molecular and Cellular Endocrinology	SYN	Synapses, Cytoskeleton and Trafficking
CLHP	Community-Level Health Promotion	MCH	Molecular and Cellular Hematology	TAG	Therapeutic Approaches to Genetic Diseases
CMAD	Cellular Mechanisms in Aging and Development	MEDI	Medical Imaging	TCB	Tumor Cell Biology
CMBG	Cellular and Molecular Biology of Glia	MESH	Biobehavioral Mechanisms of Emotion, Stress and Health	TME	Tumor Microenvironment
CMIA	Cellular and Molecular Immunology - A	MFSR	Motor Function, Speech and Rehabilitation	TPM	Tumor Progression and Metastasis
CMIB	Cellular and Molecular Immunology - B	MGA	Molecular Genetics A	TTT	Transplantation, Tolerance, and Tumor Immunology
CMIP	Clinical Molecular Imaging and Probe Development	MGB	Molecular Genetics B	UGPP	Urologic and Genitourinary Physiology and Pathology
CMIR	Cellular, Molecular and Integrative Reproduction	MIM	Myocardial Ischemia and Metabolism	VACC	HIV/AIDS Vaccines
CMND	Cellular and Molecular Biology of Neurodegeneration	MIST	Molecular and Integrative Signal Transduction	VB	Vector Biology
CNBT	Clinical Neuroimmunology and Brain Tumors	MNG	Molecular Neurogenetics	VCMB	Vascular Cell and Molecular Biology
CNN	Clinical Neuroscience and Neurodegeneration	MNPS	Molecular Neuropharmacology and Signaling	VIRA	Virology - A
CNNT	Clinical Neuroplasticity and Neurotransmitters	MONC	Molecular Oncogenesis	VIRB	Virology - B
CONC	Clinical Oncology	MRS	Musculoskeletal Rehabilitation Sciences	VMD	Vaccines Against Microbial Diseases
CP	Cognition and Perception			XNDA	Xenobiotic and Nutrient Disposition and Action

Table A3: Intellectual Breadth and Study Section Affiliations

	(1)	(2)	(3)	(4)
Two Study Sections	0.141**	0.124**	0.026**	0.011**
	(0.005)	(0.005)	(0.003)	(0.003)
Three Study Sections	0.249**	0.222**	0.042**	0.018**
	(0.011)	(0.012)	(0.006)	(0.007)
Four Study Sections	0.333**	0.297**	0.065**	0.035*
	(0.033)	(0.034)	(0.017)	(0.017)
Five Study Sections	0.354**	0.313**	0.037	0.003
	(0.084)	(0.084)	(0.055)	(0.055)
Ln(NIH Funding)		0.030**		0.031**
		(0.005)		(0.003)
Scientist Fixed Effects	Not Incl.	Not Incl.	Incl.	Incl.
Nb. of Scientists	10,177	10,177	10,177	10,177
Nb. of Observations	146,661	146,661	146,661	146,661
Adjusted R^2	0.226	0.227	0.711	0.712

The dependent variable is the log odds of intellectual diversity, computed as one minus the herfindahl of MeSH keywords in a sample of 10,177 "superstar scientists." The specifications in columns (1) and (2) include indicator variables for type of degree (MD, PhD, MD/PhD), year of highest degree, and gender. All specifications include a full suite of indicator variables for calendar year and for scientist age.

Standard errors in parentheses, clustered by scientist ($^{\dagger}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$)

Figure A1: Congressional Appropriations for NIH Institutes

(i) Example of Appropriations Language

Pancreatic cancer.—Pancreatic cancer is the country's fourth leading cause of cancer death. Most patients present with advanced disease at diagnosis and the median overall survival rate for people diagnosed with metastatic disease is only about six months. The Committee is concerned that there are too few scientists researching pancreatic cancer and compliments the NCI's past efforts for increasing the research field through its program of a 50 percent formalized extended payline for grants that were 100 percent relevant to pancreatic cancer. The Committee considers this an important method for attracting both young and experienced investigators to develop careers in pancreatic cancer. In 2004, the NCI established a new policy for awarding additional grants in pancreatic cancer research and extended this initiative to research that is 50 percent relevant to pancreatic cancer. The Committee requests NCI to report in February, 2006 on how the two changes in policy have affected the pancreatic cancer portfolio, including the percentage relevancy of each grant to pancreatic cancer, and urges NCI to continue its commitment to fertilize the pancreatic cancer field.

(ii) Word Frequency in Appropriations Documents

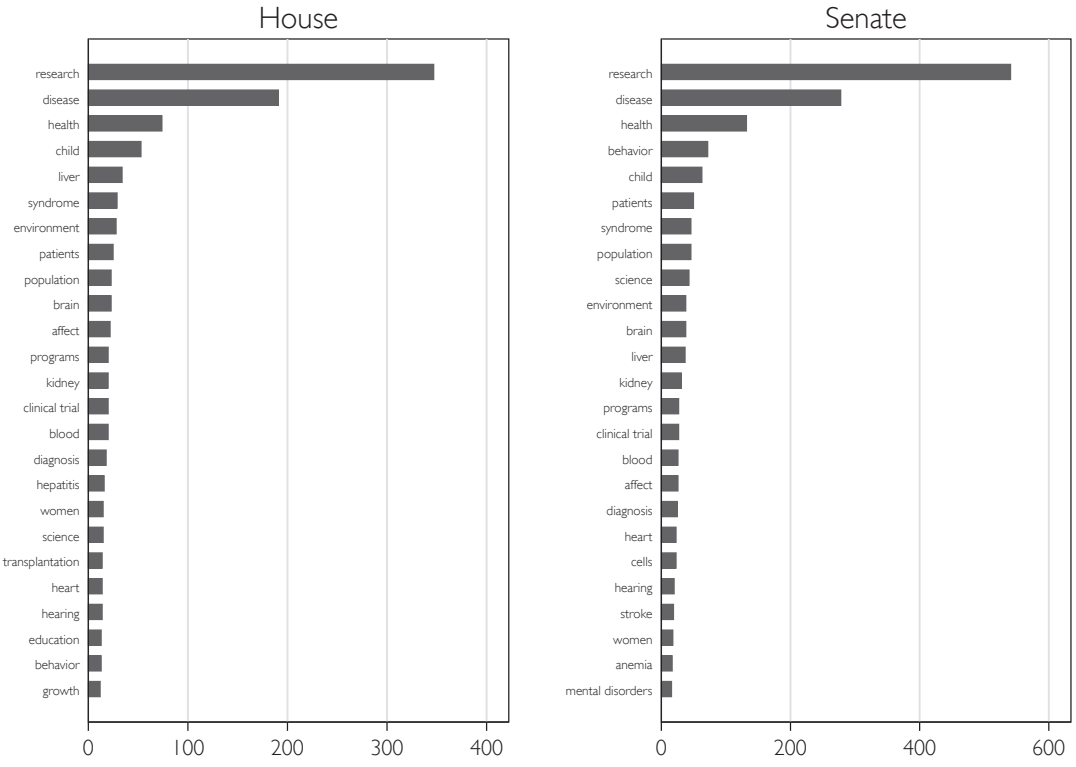
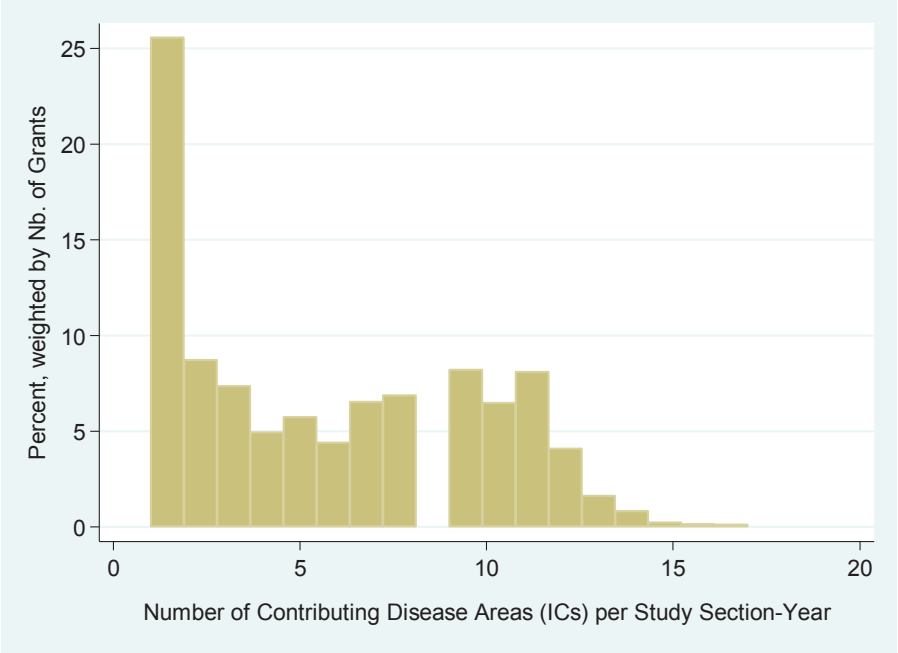


Figure A2: Institute and Study Section Overlap

(i) Number of Institutes per Study Section



(ii) Number of Study Sections per Institute

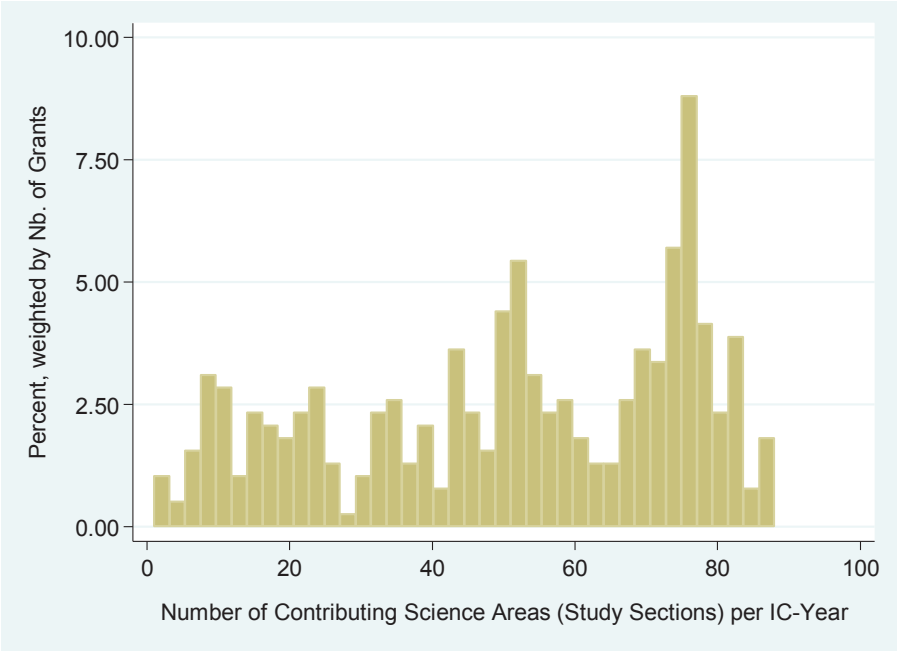
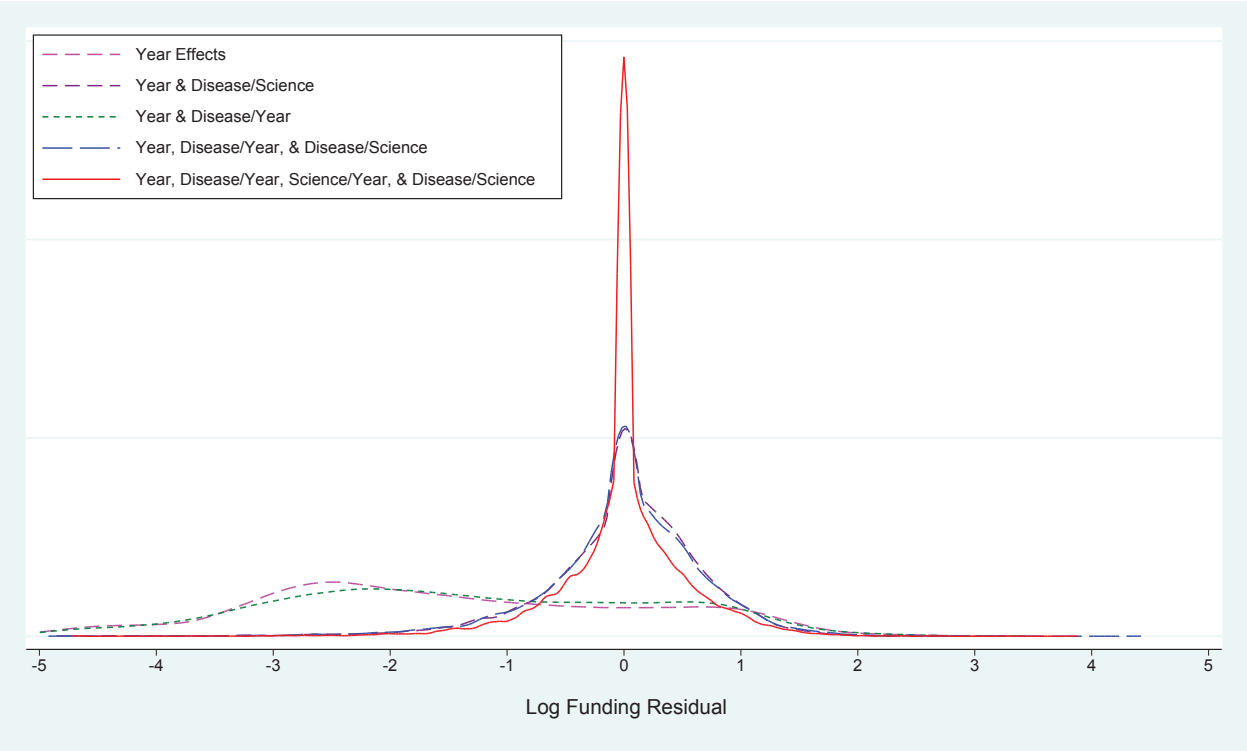


Figure A3: Residual Variation in DST Funding



Appendix B: "Life-science" Patents

To assess the impact of NIH funding, we need to define a universe of life science patents. While we do not want to impose strong restrictions on where NIH funding could have an effect (e.g., by looking in specific disease areas) focusing on a specific subset of the universe of issued patents is necessary for two reasons. From a substantive standpoint, it is important to assign most patents to one or more NIH research areas, and this would be infeasible were we to focus on all patents granted by the USPTO.[iv] From a pragmatic standpoint, linking NIH publications to patents requires probabilistic matching (see Appendix C2), and the rate of false positives is much lower if we restrict the set of potential matches.

To do so, we started with the 5,269,968 patents issued by the USPTO between 1980 and 2012. Then, using the NBER patent categorization described in Hall et al. (2001), we focused on patents in the classes belonging to NBER Categories 1 (Chemicals) and 3 (Drugs and Medical). This left 1,310,700 patents. Of these patents, 565,593 cite at least one non-patent reference. Using the algorithm described in Azoulay et al. (2012) and Sampat and Lichtenberg (2011) we determined that 312,903 patents cite an article indexed in PubMed. We refer to this set—patents in NBER Classes 1 and 3 that cite to at least one PubMed indexed article—as "life-science patents." Classes 1 and 3 cover a range of subcategories, listed in Table B1.

To provide a better sense of what this set includes, we took a random sample of 1,000 in the universe described above, and looked them up in the Thomson Reuters Innovation Database. This database includes information on the expert classification of each patent to one or more codes in the Derwent World Patents Index (DWPI 2012). Of the 1,000 patents, 656 had at least one DWPI "B" code, indicating they are in the "pharmaceuticals" category. According to DWPI 2012 (page 5) these pharmaceutical patents include:

- Compounds and proteins of pharmaceutical (or veterinary) interest;
- Compounds used as intermediates in the manufacture of pharmaceutical products;
- Compositions used for diagnosis and analysis in pharmaceuticals;
- Technologies dealing with production of tablets, pills, capsules, etc.
- Devices for dispensing pharmaceuticals.

Importantly, the "B" classes also include a range of biotechnology research tools and processes.

What about those without a "B" code, about one-third of the life science patents? The majority of these non-pharmaceutical patents are in five DWPI categories covering chemistry and medical devices: Class A (Polymers and Plastics), Class D (Food, Detergents, Water Treatment, and Associated Biotechnology), Class E (General Chemicals), Class S (Instrumentation, Measuring, and Testing), and Class P (General Human Necessities, including diagnosis/surgery).

Private sector vs. public sector patents. We are primarily interested in the effect of NIH funding on the rate of production of private-sector patents, excluding those assigned to public research entities such as universities, research institutes, academic medical centers, or government agencies (e.g., the intramural campus of NIH). This focus is justified by our desire to focus on disembodied knowledge flows. Since the Bayh-Dole act, life-science academics have considerably increased their rate of patenting (Azoulay et al. 2007; 2009). Previous scholarship has documented the growing importance of patent-paper pairs (Murray and Stern 2007) where a given piece of academic knowledge gives rise to both an article and a patent listing the authors of the article as inventors and their employer (often a public institution) as assignee. Including these patents in our analyses would make the interpretation of our results (which emphasizes indirect spillovers of knowledge) difficult. To separate private-sector from public-sector patents, we adapted

[iv] e.g., class 150, "Purses, Wallets, and Protective Covers," or Class 169, "Fire Extinguishers."

Bronwyn Hall's patent assignee name matching algorithm to isolate private-sector assignees.[v] Using this method, we restrict the sample to 232,276 patents, or 74% of the life science patents (see Table 2 in the main body of the manuscript).

Patents on drug candidates and approved drugs. Though a substantial share of the life science patents are "pharmaceuticals" not all are therapeutic molecules or proteins. Even among those that are, there is substantial heterogeneity in value, since only a small share of drugs and biologics enter trials, and of these a small share receive marketing approval.

To examine heterogeneity of the effects of NIH funding, and to assess the effects on drug development, we isolated patents associated with important drugs and biologics. We began with all patents from current and archival versions of the FDA's Orange Book (officially named Approved Drug Product with Therapeutic Equivalence Evaluations). Since the 1984 Hatch-Waxman Act, branded firms are required to list on the Orange Book patent issued before drug approval with at least one claim covering a drug's active ingredient, formulation, or methods of use for approved indications. Though there is strong incentive to list patents issued after drug approval as well (Hemphill and Sampat 2012), strictly speaking this is not required. Moreover other drug patents (methods of manufacture, formulations not covering the marketed product, methods of use covering unapproved indications) are barred.

In parts of our analysis, we look at the effects of NIH funding on "important" life science patents associated with drugs that have been approved or entered late-stage clinical trials. For doing so, the Orange Book is restrictive, for several reasons. First, it does not list all patents on a drug, as already noted. Second, it does not list patents for all biologic drugs (since these drugs were historically covered by a division of the FDA exempt from Orange Book listing rules). Third, it does not include patents on drugs and biologics in late stage trials. Accordingly, we supplemented the patent list from the Orange Book with those from IMS Patent Focus, which includes patents on drugs and biologics in Phase III trials and above, and is less restrictive about the types of patents it includes than the Orange Book.[vi]

Together 4,718 of the 232,276 life science patents were listed in the Orange Book and/or IMS. We call this set of patents "Advanced Drug Candidates."

For welfare calculations, we multiply the effects of NIH patenting with measures of the value of new drugs. In order to do so, we need to isolate the patents associated with new molecular and biological entities (NMEs and NBEs), eliminating patents on drugs that associated with other drugs (e.g., line extensions) and unapproved drugs. This is not to say that drugs beyond NMEs and NBEs are unimportant. However, doing so is necessary since our measures of private and social value of drugs are based on data on new drugs that have been approved for marketing (as opposed to line extensions or unapproved drugs).

To construct this set, we used information on all NMEs and NBEs approved by the FDA between 1984 and 2012. Specifically, we collected information on all new molecular entities and biological license applications approved by the FDA. We searched for patents on each of these in the Orange Book using application numbers, and supplemented with searches in IMS patent focus using drug names. About 30 percent of these patents were listed both in the Orange Book and IMS, 67 percent in IMS only, and 3 percent in the Orange Book only. On average, there were 7.6 patents per drug in the dataset (7.3 for NME and 9.6 for biologics). After limiting to private sector patents (see above), we were left with a set of 1,999 private sector life science patents associated with new molecules and biologics.

[v] http://eml.berkeley.edu/~bhhall/pat/namematch.html

[vi] http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Technology/Syndicated%20Analytics/Lifecycle%20and%20Portfolio%20Management/IMS_LifeCycle_Patent_Focus_Global_Brochure.pdf

Table B1: Relevant Patent Classes

Cat. Code	Category Name	Sub-Cat. Code	Sub-Category Name	Patent Classes
1	Chemical	11	Agriculture, Food, Textiles	8, 19, 71, 127, 442, 504
		12	Coating	106,118, 401, 427
		13	Gas	48, 55, 95, 96
		14	Organic Compounds	534, 536, 540, 544, 546, 548, 549, 552, 554, 556, 558, 560, 562, 564, 568, 570
		15	Resins	520, 521, 522, 523, 524, 525, 526, 527, 528, 530
		19	Miscellaneous	23, 34, 44, 102, 117, 149, 156, 159, 162, 196, 201, 202, 203, 204, 205, 208, 210, 216, 222, 252, 260, 261, 349, 366, 416, 422, 423, 430, 436, 494, 501, 502, 510, 512, 516, 518, 585, 588
3	Drugs & Medical	31	Drugs	424, 514
		32	Surgery & Medical Instruments	128, 600, 601, 602, 604, 606, 607
		33	Biotechnology	435, 800
		39	Miscellaneous	351, 433, 623

Appendix C1: Linking NIH Grants to Publications that Acknowledge NIH Support

The NIH asks of its grantees to include acknowledgements to agency support in any publications resulting from the grant, and to do so in a very specific format.[vii] Since the early 1980s, PubMed has recorded these acknowledgements in a separate field, and we use these data to link every grant in the NIH Compound Grant Applicant File (CGAF) with the publications that result. The process used to systematically map publication-to-grant linkages is relatively straightforward, but may be prone to measurement error. We discuss three potential issues below, and investigate the bias they might create for the reported results.

Dynamic linking inconsistency. In the vast majority of the cases, a grant acknowledgement provides a grant mechanism, a funding institute, and a grant serial number (as in `R01GM987654`), but typically no reference to a particular grant cycle. This limitation is potentially serious, since we need to be able to assign each publication to a particular DST, and not simply to particular DS. To fix ideas, our final dataset relies on 987,799 unique publications that acknowledge a grant funded by NIH. 100% of these acknowledgements occur in a window of ten years before the year in which the article appeared in print. 93% of these publications are linked to the same grant within seven years, 83% within five years, and 47% within two years. To find the relevant grant cycle for each publication acknowledging a grant, we adopted the following procedure: (i) look up the year of publication t_{pub} for the acknowledging publication; (ii) create a five year "catchment window" $[t_{pub}-5; t_{pub}]$; (iii) identify the most recent fiscal year t_{grant} in that window during which the grant was funded either as a new grant or as a competitive renewal; and (iv) link the publication to the funding institute identified in the grant acknowledgement, the study section that evaluated this grant according to NIH records, in the year t_{grant}.

While we cannot directly observe whether a publication was funded by a different grant cycle, we have verified that our benchmark results are robust to alternative choices for the length of the catchment window: $[t_{pub}-2; t_{pub}]$, $[t_{pub}-7; t_{pub}]$, $[t_{pub}-10; t_{pub}]$.

Overclaiming of publications. NIH grant renewal is dependent on the research and publications stemming from that stream of funding. To our knowledge, NIH does not audit the acknowledgement trail systematically—this is left to the discretion of scientific review officers (the federal employees who manage the flow of information between reviewers in a particular study section and the NIH funding apparatus). Therefore, grantees may have an incentive to "over-attribute" publications—e.g., to credit some publications to the support of a grant, even if they were in fact enabled by other streams of funding. This raises the concern that increases in DST funding, even if exogenous, can lead us to identify more related patents, but only through the spurious channel of false attributions.

We believe that our results are unlikely to be driven by this behavior for two reasons. First, the vast majority of public biomedical research funding in the US comes from NIH, meaning that most scientists do not have meaningful amounts of funding from other sources to support their research.[viii] While scientists often use grant funding to subsidize research projects that are not directly related to the topic of their grant, these projects should still be counted as a product of grant funding.

Second, if misattribution were driving our results, we would expect to see that boosts in NIH funding increase the number of patents directly linked to NIH funding (our "citation-linked" measure of patenting, see Table 4), but it would not increase the total number of patents in a DST's intellectual area (our "PMRA" measure of patenting, see Table 5). Our PMRA measure is designed to capture, through related publications, patents building on research related to a DST, regardless of whether that research is NIH-funded. If increases in

[vii] `http://grants.nih.gov/grants/acknow.htm`

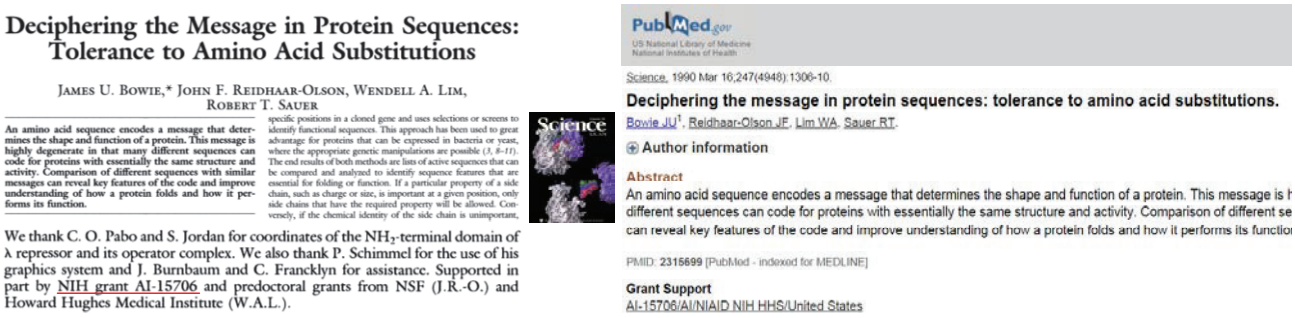
[viii] NIH accounted for 70% of the research budget of academic medical centers in 1997 (Commonwealth Fund Task Force on Academic Health Centers 1999); within Graduate Schools of Arts and Sciences, who cannot rely on clinical income to support the research mission, one would expect the NIH share to be greater still.

DST funding merely induce scientists to acknowledge these grants, we would not see the overall increase in innovation that we document in Tables 5 and 6.

Underclaiming of publications. Given the incentives created by the funding renewal decision, it seems unlikely that researchers would err by failing to credit their grant upon publication when they legitimately could. However, the number of NIH grant acknowledgements in PubMed jumps from 25,466 for articles appearing in 1980 to 56,308 for articles appearing in 1981 before stabilizing on a slow upward trend that correlates with the growth in funding thereafter. This is likely because the National Library of Medicine only gradually moved to a regime where grant acknowledgement data was systematically captured. Although the grants acknowledged in these early publications likely predate the start of our observation period (1980), this is an additional source of measurement error to which we must attend. In contrast to the second issue, however, there is no reason to suspect that erroneous capture of these data is related to the size of a DST. Year effects, included in all our specifications, should deal adequately with any secular change in NLM's propensity to accurately capture information related to grant acknowledgment.

Example. We illustrate the procedure with the case of particular publication, *Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions*, by Bowie et al., which appeared in the journal *Science* on March 16^{th}, 1990 (see the left side of Figure C1). The publication credits grant support from NIH, specifically grant `AI-15706`. Despite the fact that this acknowledgement appears at the very end of the paper as the ultimate reference in the bibliography (reference #46 on page 1310), PubMed captures this data accurately (see the right side of Figure C1). Note that the acknowledgement omits the grant mechanism, as well as the leading zero in the grant serial number. These issues, which are typical in the PubMed grant acknowledgement data, turn out to be unimportant. In particular, the National Institute of Allergy and Infectious Diseases (NIAID, code-named `AI`) has only one grant with serial number `015706`: A project R01 grant first awarded to Robert T. Sauer, an investigator in the biology department at MIT, in 1979, and competitively renewed in 1982, 1987, 1992, 1997, and 2002. The grant was evaluated by the `BBCA` (Molecular and Cellular Biophysics) study section; its title is *Sequence Determinants of Protein Structure & Stability*, with a budget of $1,211,685 for the cycle that began in 1987, three years before the date of the publication above (whose last author is also Robert Sauer). As a result, the publication is linked to the DST corresponding to the combination `AI` (Institute)/`BBCA` (study section)/`1987` (year).

Figure C1: Example of Grant Acknowledgement



Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions

James U. Bowie,* John F. Reidhaar-Olson, Wendell A. Lim, Robert T. Sauer

An amino acid sequence encodes a message that determines the shape and function of a protein. This message is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity. Comparison of different sequences with similar messages can reveal key features of the code and improve understanding of how a protein folds and how it performs its function.

specific positions in a cloned gene and uses selections or screens to identify functional sequences. This approach has been used to great advantage for proteins that can be expressed in bacteria or yeast, where the appropriate genetic manipulations are possible (*3, 8–11*). The end results of both methods are lists of active sequences that can be compared and analyzed to identify sequence features that are essential for folding or function. If a particular property of a side chain, such as charge or size, is important at a given position, only side chains that have the required property will be allowed. Conversely, if the chemical identity of the side chain is unimportant,

We thank C. O. Pabo and S. Jordan for coordinates of the NH_2-terminal domain of λ repressor and its operator complex. We also thank P. Schimmel for the use of his graphics system and J. Burnbaum and C. Francklyn for assistance. Supported in part by NIH grant AI-15706 and predoctoral grants from NSF (J.R.-O.) and Howard Hughes Medical Institute (W.A.L.).

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US National Library of Medicine
National Institutes of Health

Science. 1990 Mar 16;247(4948):1306-10.

Deciphering the message in protein sequences: tolerance to amino acid substitutions.

Bowie JU[1], Reidhaar-Olson JF, Lim WA, Sauer RT.

Author information

Abstract

An amino acid sequence encodes a message that determines the shape and function of a protein. This message is h
different sequences can code for proteins with essentially the same structure and activity. Comparison of different se
can reveal key features of the code and improve understanding of how a protein folds and how it performs its functio

PMID: 2315699 [PubMed - indexed for MEDLINE]

Grant Support

AI-15706/AI/NIAID NIH HHS/United States

Appendix C2: Linking PubMed References to USPTO Patents

We use patent-publication citation information to identify patents that build on NIH-funded research. Patent applicants are required to disclose any previous patents that are related to their research. Failure to do so can result in strong penalties for the applicant and attorney, and invalidation of the patent (Sampat 2009). There is a long history of using citation data as measures of intellectual influence or knowledge flows between public and private sector research (Jaffe and Trajtenberg 2005; Narin and Olivastro 1992). Recent work (Sampat 2010, Alcacer, Gittleman and Sampat 2009), however, shows that patent examiners rather than applicants insert many of these citations, casting doubt on their utility as measures of knowledge flows or spillovers (Alcacer and Gittleman 2006).

We will instead use information on patent citations to published scientific articles. This is appealing both because publications rather than patents are the main output of scientific researchers (Agrawal and Henderson 2002), but also because the vast majority of patent-paper citations, over 90 percent, come from applicants rather than examiners, and are thus more plausibly indicators of real knowledge flows than patent-patent citations (Lemley and Sampat 2012). Roach and Cohen (2012) provide empirical evidence on this point.

Determining whether patents cite publications is more difficult than tracing patent citations: while the cited patents are unique seven-digit numbers, cited publications are free-form text (Callaert et al. 2006). Moreover, the USPTO does not require that applicants submit references to literature in a standard format. For example, Harold Varmus's 1988 Science article "Retroviruses" is cited in 29 distinct patents, but in numerous different formats, including Varmus. "Retroviruses" Science 240:1427-1435 (1988) (in patent 6794141) and Varmus et al., 1988, Science 240:1427-1439 (in patent 6805882). As this example illustrates, there can be errors in author lists and page numbers. Even more problematic, in some cases certain fields (e.g. author name) are included, in others they are not. Journal names may be abbreviated in some patents, but not in others.

To address these difficulties, we developed a matching algorithm that compared each of several PubMed fields — first author, page numbers, volume, and the beginning of the title, publication year, or journal name — to all references in all biomedical and chemical patents issued by the USPTO since 1976. Biomedical patents are identified by technology class, using the patent class-field concordance developed by the National Bureau of Economic Research (Hall, Jaffe, and Trajtenberg 2001). We considered a dyad to be a match if four of the fields from PubMed were listed in a USPTO reference.

Overall, the algorithm returned 1,058,893 distinct PMIDs cited in distinct 322,385 patents. Azoulay, Graff Zivin and Sampat (2012) discuss the performance of this algorithm against manual searching, and tradeoffs involved in calibrating the algorithm.

Example. We illustrate the procedure with the case of particular patent, #6,687,006, issued on March 15, 2005 and assigned to the biopharmaceutical firm Human Genome Sciences, Inc. In the section of the patent entitled Other Publications, we can find a citation to "Bowie, J.U., et al., Deciphering the Message in Protein Sequences. . . ," precisely the publication we took as an example in Appendix C1. Our text-parsing algorithm identifies this reference and associates it with PubMed article identifier `2315699`. As a result, this patent will participate in the patent count corresponding to the DST `AI/BBCA/1987` (see Appendix C1).

FIGURE C2: EXAMPLE OF PATENT-TO-PUBLICATION CITATION

(12) **United States Patent**
Li et al.

(10) **Patent No.: US 6,867,006 B2**
(45) **Date of Patent: Mar. 15, 2005**

(54) **ANTIBODIES TO HUMAN CHEMOTACTIC PROTEIN**

(75) Inventors: **Haodong Li**, Gaithersburg, MD (US); **Steven M. Ruben**, Olney, MD (US); **Granger Sutton, III**, Columbia, MD (US)

(73) Assignee: **Human Genome Sciences, Inc.**, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 230 days.

(21) Appl. No.: **10/141,965**

(22) Filed: **May 10, 2002**

WO	WO 96/38559	12/1996
WO	WO 96/40762	12/1996
WO	WO 97/15594	5/1997
WO	WO-98/44118	10/1998

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Berkhout, T.A., et al., "Cloning, in Vitro Expression, and Functional Characterization of a Novel Human CC Chemokine of the Monocyte Chemotactic Protein (MCP) Family (MCP–4) That Binds and Signals through the CC Chemokine Receptor 2B," *J. Biol. Chem. 272*:16404–16413, American Society for Biochemistry and Molecular Biology, Inc. (Jun. 1997).

Bowie, J.U., et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science 247*:1306–1310, American Association for the Advancement of Science (1990).

Appendix D: PubMed Related Citations Algorithm [PMRA]

One of our outcome measures (described in more detail in Appendix F) captures all patents in the intellectual vicinity of an NIH funding area. A crucial input in the construction of this measure is the National Library of Medicine's PubMed Related Citations Algorithm (PMRA), which provides a way of determining the degree of intellectual similarity between any two publications. The following paragraphs were extracted from a brief description of PMRA:[ix]

> *The neighbors of a document are those documents in the database that are the most similar to it. The similarity between documents is measured by the words they have in common, with some adjustment for document lengths. To carry out such a program, one must first define what a word is. For us, a word is basically an unbroken string of letters and numerals with at least one letter of the alphabet in it. Words end at hyphens, spaces, new lines, and punctuation. A list of 310 common, but uninformative, words (also known as stopwords) are eliminated from processing at this stage. Next, a limited amount of stemming of words is done, but no thesaurus is used in processing. Words from the abstract of a document are classified as text words. Words from titles are also classified as text words, but words from titles are added in a second time to give them a small advantage in the local weighting scheme. MeSH terms are placed in a third category, and a MeSH term with a subheading qualifier is entered twice, once without the qualifier and once with it. If a MeSH term is starred (indicating a major concept in a document), the star is ignored. These three categories of words (or phrases in the case of MeSH) comprise the representation of a document. No other fields, such as Author or Journal, enter into the calculations.*
>
> *Having obtained the set of terms that represent each document, the next step is to recognize that not all words are of equal value. Each time a word is used, it is assigned a numerical weight. This numerical weight is based on information that the computer can obtain by automatic processing. Automatic processing is important because the number of different terms that have to be assigned weights is close to two million for this system. The weight or value of a term is dependent on three types of information: 1) the number of different documents in the database that contain the term; 2) the number of times the term occurs in a particular document; and 3) the number of term occurrences in the document. The first of these pieces of information is used to produce a number called the global weight of the term. The global weight is used in weighting the term throughout the database. The second and third pieces of information pertain only to a particular document and are used to produce a number called the local weight of the term in that specific document. When a word occurs in two documents, its weight is computed as the product of the global weight times the two local weights (one pertaining to each of the documents).*
>
> *The global weight of a term is greater for the less frequent terms. This is reasonable because the presence of a term that occurred in most of the documents would really tell one very little about a document. On the other hand, a term that occurred in only 100 documents of one million would be very helpful in limiting the set of documents of interest. A word that occurred in only 10 documents is likely to be even more informative and will receive an even higher weight.*
>
> *The local weight of a term is the measure of its importance in a particular document. Generally, the more frequent a term is within a document, the more important it is in representing the content of that document. However, this relationship is saturating, i.e., as the frequency continues to go up, the importance of the word increases less rapidly and finally comes to a finite limit. In addition, we do not want a longer document to be considered more important just because it is longer; therefore, a length correction is applied.*
>
> *The similarity between two documents is computed by adding up the weights of all of the terms the two documents have in common. Once the similarity score of a document in relation to each of the other documents in the database has been computed, that document's neighbors are identified as the most similar (highest scoring) documents found. These closely related documents are pre-computed for each document in* PubMed *so that when one selects Related Articles, the system has only to retrieve this list. This enables a fast response time for such queries.*

In Table D1, we illustrate the use of PMRA with an example taken from our sample. Brian Druker is a faculty member at the University of Oregon whose NIH grant CA-001422 (first awarded in 1990) yielded 9 publications. *"CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins"* (PubMed ID #9389713) appeared in the December 1997 issue

[ix] Available at `http://ii.nlm.nih.gov/MTI/related.shtml`

of the journal *Blood* and lists 16 MeSH terms. PubMed ID #8548747 is its fifth-most related paper according to the PMRA algorithm; it appeared in *Cancer Research* in January 1996 and has 13 MeSH terms, 6 of which overlap with the Druker article. These terms include common terms such as `Mice` and `Pyrimidines` as well as more specific keywords including `Oncogene Proteins v-abl` and `Receptors, Platelet-Derived Growth Factor`.

Table D1: PMRA and MeSH Terms Overlap — An Example

Source Article	**PMRA-Linked Article**
Carroll et al., "CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins." *Blood*, 1997.	Buchdunger et al. "Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative." *Cancer Research*, 1996.
PMID #9389713	**PMID #8548747**
MeSH Terms	**MeSH Terms**
Animals	3T3 Cells
Antineoplastic Agents	Animals
Cell Division	Cell Line, Transformed
Cell Line	Growth Substances
DNA-Binding Proteins*	Mice
Enzyme Inhibitors*	Mice, Inbred BALB C
Fusion Proteins, bcr-abl*	Oncogene Proteins v-abl*
Mice	Piperazines*
Oncogene Proteins v-abl*	Piperidines*
Piperazines*	Proto-Oncogene Proteins c-fos
Protein-Tyrosine Kinases*	Pyrimidines*
Proto-Oncogene Proteins c-ets	Receptors, Platelet-Derived Growth Factor*
Pyrimidines*	Tumor Cells, Cultured
Receptors, Platelet-Derived Growth Factor*	
Repressor Proteins*	
Transcription Factors*	
Substances	**Substances**
Antineoplastic Agents	Growth Substances
DNA-Binding Proteins	Oncogene Proteins v-abl
ETS translocation variant 6 protein	Piperazines
Enzyme Inhibitors	Piperidines
Fusion Proteins, bcr-abl	Proto-Oncogene Proteins c-fos
Oncogene Proteins v-abl	Pyrimidines
Piperazines	imatinib
Proto-Oncogene Proteins c-ets	Receptors, Platelet-Derived Growth Factor
Pyrimidines	
Repressor Proteins	
Transcription Factors	
imatinib	
Protein-Tyrosine Kinases	
Receptors, Platelet-Derived Growth Factor	

Appendix E: Structure of the Disease/Science Panel Dataset

As explained in Section 3.1, the level of analysis chosen for the econometric exercise is the disease/science/year level. With 17 NIH institutes (the "D" in DST), 624 standing study sections (the "S"), and 25 years (the "T"), one might expect our analytical sample to 265,200 DST observations (and 10,608 distinct DS research areas), but a quick perusal of the tables reveal only 14,085 DSTs, or 5.31% of the total number of potential DSTs (respectively 2,942 actual DS, or 27.73% of the total number of potential DS). Why such a seemingly high number of missing DSTs? This appendix (i) clarifies that there are different types of "missing DSTs"; (ii) explains why most of these missing DSTs are missing for benign reasons; and (iii) investigates the robustness of our results to the concern that some DSTs are missing for substantive reasons. Figure E1 provides a graphical representation of the structure of our panel dataset. For example, the purple line corresponds to the combination of the National Institute of Allergy and Infectious Diseases [NIAID] and the Molecular and Cellular Biophysics [BBCA] study section. In every year between 1980 and 2005, NIAID awarded at least three grants that were reviewed by the BBCA study sections. Therefore, in this case, all the 26 potential DSTs are accounted for.

Missing DSTs: A Taxonomy. A full 191,650 DSTs (72.27%) are missing from our data because the corresponding DS combinations are never observed. One can think of these instances as cases where the pairing of a disease with a science area would be intellectually incongruous. Consider, for instance, the pairing of the National Institute of Mental Health (NIMH) and the Tropical Medicine and Parasitology [TMP] study section. Not only are there no grants awarded by NIMH that were reviewed by the TMP study section, there is also no evidence of any *unfunded* grant application reviewed by TMP whose author designated NIMH as the funding institute. This case is represented by the orange dotted line in Figure E1.

We are left with 2,942 disease/science research areas that awarded at least one grant in at least one year during the observation period, or $2,942 \times 25 = 73,550$ potential DSTs. 55,058 of these 73,550 DSTs are missing because many study sections are not in continuous existence between 1980 and 2005: our sample is unbalanced. At regular intervals in the history of NIH, study sections have been added, dropped, split, or merged to accommodate changes in the structure of scientific disciplines as well as shifting patterns of momentum for some research areas, relative to others. DSTs that are missing because of the natural life cycle of study sections need not concern us, as long as we make the reasonable assumption that every grant application, at a given point time, has a study section that is fit to assess its scientific merits.

Figure E1 displays three examples that fall into this category. Consider first the red line, corresponding to the combination of the National Heart, Lung, and Blood Institute [NHLBI] and the Physiology [PHY] study section. The Physiology study section ceased to exist in 1998, so the NHLBI/PHY combination "misses" seven DSTs. What happened to the applications received in 2000 that would have been reviewed by the PHY study section had they been received in 1998? The answer is that newly created study sections, such as Integrative Physiology of Obesity and Diabetes [IPOD] or Skeletal Muscle Biology and Exercise Physiology [SMEP] almost certainly reviewed them. Similarly, the combination of NIDDK and the Biochemistry study section (which was born in 1991) is "missing" observations between 1980 and 1990, while the combination between NIA and the Neurology B-2 study section is missing observations between in 1980, 1981, 1982, and observations from 1998 to 2005. Notice that in all three of these cases, DSTs are not missing "in the middle," but only at the extremities.

Potentially more problematic for our analysis is the case of DS combinations that display intermediate sequences of starts and stops. Consider for example the blue line in Figure E1, which corresponds to the combination of the National Cancer Institute [NCI] and the Reproductive Biology [REB] study section. Ten of the potential 22 observations for this combination are missing between 1980 and 2001 (the REB study section ceased to exist after 2001). The story is similar for the combination of the National Eye Institute [NEI] and the Epidemiology and Disease Control 1 [EDC-1] study section. All together, out of the 2,942 DS combinations in our dataset, 2,101 (71.41%) are contiguous, and 841 are "hole-y" (for a total of 4,407 missing DSTs). We are concerned about these cases because it is possible that research was proposed in these areas,

and that at least some of it got done (maybe thanks to alternative sources of funding), leading to patents downstream which we have no way of linking back to publicly-funded research efforts. One piece of evidence that allays these concerns is that in the great majority of cases (80%), we do not observe any application in the corresponding DSTs—if no funds were awarded, it is because no research was in fact proposed to NIH for funding consideration. In light of this fact, it seems harder to imagine that patents could be linked to these areas via some alternative method which does not rely on bibliometric linkages.

Robustness check: Contiguous DSTs. In addition, we probe the robustness of our results by replicating the main specifications while restricting the sample to the set of 2,101 intact, contiguous DS areas, for a total of 7,966 DSTs (57 percent of our original dataset). In Table E1, we report the results of specifications modeled after those used to generate the estimates in Table 6, our benchmark set of results. Using this approach, we obtain coefficients that are numerically very similar to those presented in Table 6, and estimated very precisely.

In summary, the great majority of the DSTs that appear to be missing from our data are not really missing, but rather, not in existence. And the small minority of DSTs that could genuinely said to be "missing" cannot be expected to change our conclusions, since limiting the analysis to the set of intact DS areas yields identical results.

Figure E1: A Taxonomy of DSTs

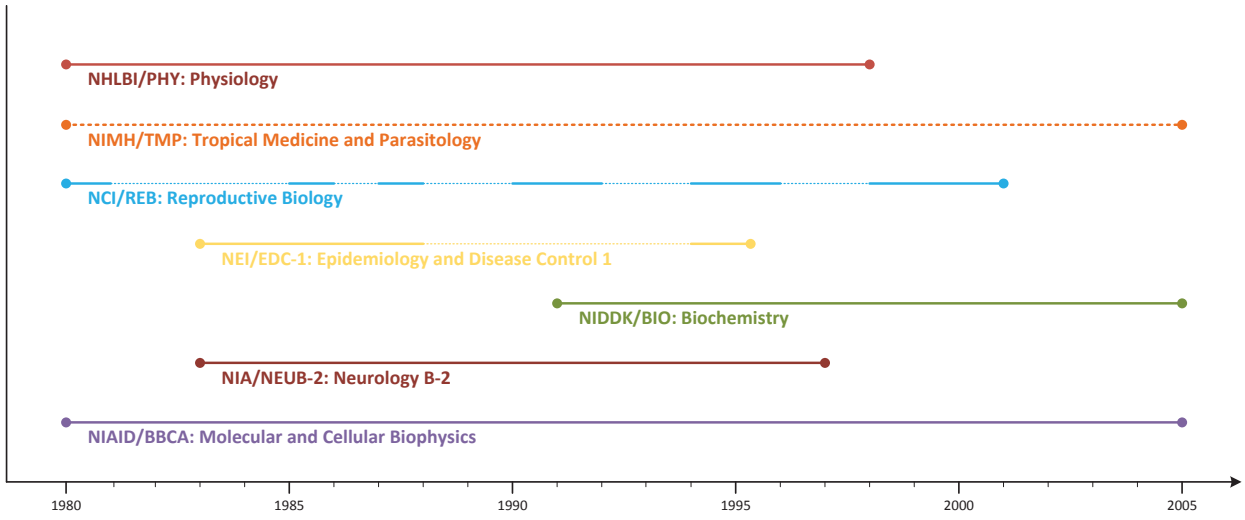


Table E1: Contiguous Disease-Science Categories Only

	First Stage		Citation Linked		Total Related	
	DST Funding (×$10 mln.)		Mean=14.2; SD=19.89		Mean=27.2; SD=28.5	
			OLS	IV	OLS	IV
	(1)		(2)	(3)	(4)	(5)
Windfall Funding (×$10 mln.)	1.170***	DST Funding ($10 mln.) Mean=4.49; SD=4.44	2.516***	2.052**	3.660***	2.114**
	(0.183)		*(0.568)*	*(0.892)*	*(0.776)*	*(0.910)*
		Elasticity	0.796	0.649	0.604	0.349
R^2	0.920		0.753	0.554	0.862	0.631
Observations	7,966		7,966	7,966	7,966	7,966
Year FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Disease × Science FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Disease × Year FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Science × Year Linear Trends	Incl.		Incl.	Incl.	Incl.	Incl.
Application Controls	Incl.		Incl.	Incl.	Incl.	Incl.

Note: See notes to Tables 4 and 5 for details about the sample. The outcome variables are fractional patent counts. The instrument is the total amount of funding (2010 dollars) for the subset of grants funded by a DST whose rank of rank scores were marginal, i.e., were within 25 applications of the award cutoff for their specific disease area (Institute). Application controls include (i) FEs for the number of applications that a DST receives; (ii) FEs for the number of applications associated with a DST that are also in a 50-grant window around the relevant IC payline, as well as (iii) cubics in the average raw and rank scores of applications associated with a DST that are also in a 50-grant window around the payline. Elasticities are evaluated at the sample means. Only contiguous disease-science areas, as defined in the text, are included.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Appendix F: Linking NIH Research Areas (DSTs) to Patents

We begin by linking the universe of funded NIH grants between 1980 and 2005 to the set of articles that it supports using grant acknowledgement data from PubMed. We then link these publications to private-sector patents using two alternative procedures; in turn, the outcome measures that build on these procedures are designed to answer slightly different questions about the impact of NIH funding. The first measure asks whether private firms build on NIH-funded research in their patented inventions. The second measure asks whether NIH funding leads to the net creation of private-sector patents that would not have otherwise been developed. We describe the two procedures below; the overall data and variable construction process is summarized in Figure 1 in the main body of the manuscript.

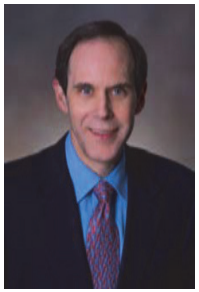
Patents building on NIH-funded research: Direct linkages. We consider how many patents explicitly build on NIH-funded research. Figure F1 illustrates the procedure with an example. In its first three years of funding, the NIH grant CA-065823 was acknowledged by four publications, among which is the article published by Thiesing et al. in the leading hematology journal Blood. We observe this link because grant acknowledgements are reported for publications indexed in the National Library of Medicine's PubMed database. Next, the Thiesing et al. article is listed as prior art in patent number 7,125,875 issued in 2006 to the pharmaceutical firm Bristol Myers Squibb.

Patents building on NIH-funded research: Indirect linkages. The second procedure links a patent to a grant if this patent refers to a publication that is "intellectually similar" to a publication that does acknowledge NIH funding. In other words, these linkages are indirect: from a grant, to a publication that acknowledges it, to the publications that are proximate in intellectual space, to the patents that in turn cite these related publications. The grant linked to patents in this way delineate the pool of research expenditures that is intellectually relevant for the creation of these patents, even in the absence of a direct linkage between the patent and the grant. Figure F2 illustrates this process. Patent number 6,894,051 was issued to Novartis in May 2005, one of the five patents listed in the FDA Orange book as associated with the drug `imatinib mesylate`, better known by its brand name, Gleevec. Patent 6,894,051 does not cite any publications which are directly supported by the NIH so it would not be linked to an NIH DST under our citation-linkage measure of innovative output. It does, however, cite PubMed publication 8548747, published in *Cancer Research* in 1996. The PubMed Related Citation Algorithm [PMRA, see Appendix D] indicates that this publication is closely related to PubMed article 9389713, which acknowledges funding from NIH grant CA-0011422. Using these second procedure, we can link the vast majority of life-science patents to an NIH disease-science area. In other words, most patents cite publications that are similar to publications that acknowledge NIH funding.

Under the indirect procedure, the same patent can be linked to many distinct grants through the inclusion of related publications. In our regressions, we adjust for this by weighting patents in the following way: regardless of what outcome measure we use, if a patent is linked to N grants, it counts as $1/N$ of a patent in each NIH research area. This means that a patent is restricted to being counted once across all NIH research areas to which it is linked.

Aggregation from the individual grant-patent linkage up to the NIH research area level [DST]. The procedures outlined above describe how to link patents to specific NIH grants. However, we do not perform the econometric analysis at the grant level. Rather, we aggregate grants up to the disease/science/time (DST) level, as explained in Section 3. Understanding the impact of NIH funding at the DST level offers conceptual advantages apart from its econometric ones. Because DSTs are defined to be intellectually coherent units in which knowledge generated by one projects is likely to benefit other projects, our estimate of the impact of NIH funding on DST-level outcomes, then, captures the benefits of potential complementarities between research in the same area. This would not be true of an analysis of grant-level funding on grant-level patenting.

Figure F1: Grant-Patent Match, Direct Linkages



Brian J. Druker, MD
Oregon Health & Science University
R01 Grant CA-065823
First award year in 1995, renewed in 2000 and 2005
Reviewed by the *Pathology B* Study Section

Acknowledges Support

blood 2000 96: 3195-3199

Efficacy of STI571, an Abl tyrosine kinase inhibitor, in conjunction with other antileukemic agents against Bcr-Abl –positive cells

J. Tyler Thiesing, Sayuri Ohno-Jones, Kathryn S. Kolibaba and Brian J. Druker

Is Cited as Prior Art by

Patent No.: US 7,125,875 B2
Date of Patent: *Oct. 24, 2006

CYCLIC PROTEIN TYROSINE KINASE INHIBITORS

Inventors: **Jagabandhu Das**, Mercerville, NJ (US); **Ramesh Padmanabha**, Hamden, CT (US); **Ping Chen**, Belle Mead, NJ (US); **Derek J. Norris**, Trenton, NJ (US); **Arthur M. P. Doweyko**, Long Valley, NJ (US); **Joel C. Barrish**, Richboro, PA (US); **John Wityak**, Robbinsville, NJ (US); **Louis J. Lombardo**, Belle Mead, NJ (US); **Francis Y. F. Lee**, Yardley, PA (US)

Assignee: **Bristol-Myers Squibb Company**, Princeton, NJ (US)

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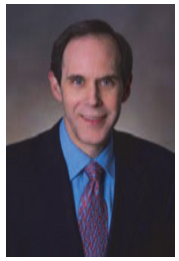
Theising et al., "Efficacy of STI571, an Abl tyrosine kinase inhibitor, in conjunction with other antileukemic agents Bcr-Abl positive cells", Blood, vol. 96, No. 9, pp. 3195-3199, 2000.

Note: The grant CA-065823 in its first cycle acknowledges 4 publications indexed in PubMed, among which is the article published by Thiesing et al. in the leading Hematology journal *Blood*. In turn, this article is listed as prior art in the 7,125,875 patent issued in 2006 to the pharmaceutical firm Bristol Myers Squibb. In this fiscal year, the Pathology B study section evaluated 66 proposals that were eventually funded, 63 of them by the National Cancer Institute (the same institute that funded Druker). Two of the remaining three proposals were funded by the National Institute of Aging (NIA), and the last was funded by the National Eye Institute. These three grants are acknowledged by 15 publications in PubMed, which are themselves cited by 11 distinct patents in the USPTO database.

Figure F2: Grant-Patent Match, Indirect Linkages



Brian J. Druker, MD
Oregon Health & Science University
K08 Grant CA-001422
Award year: 1990
Reviewed by the *Cancer Therapy* Study Section

Acknowledges Support

blood 1997 90: 4947-4952

CGP 57148, a Tyrosine Kinase Inhibitor, Inhibits the Growth of Cells Expressing BCR-ABL, TEL-ABL, and TEL-PDGFR Fusion Proteins

Martin Carroll, Sayuri Ohno-Jones, Shu Tamura, Elisabeth Buchdunger, Jürg Zimmermann, Nicholas B. Lydon, D. Gary Gilliland and Brian J. Druker

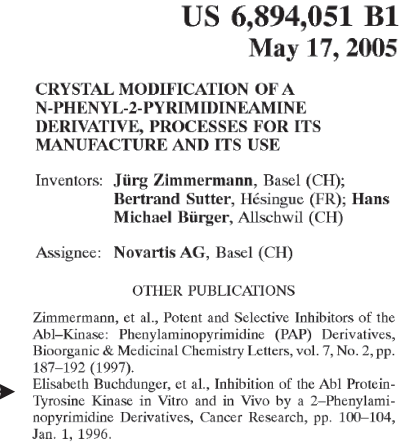
Linked by PMRA [PubMed Related Citation Algorithm]

Inhibition of the Abl Protein-Tyrosine Kinase *in Vitro* and *in Vivo* by a 2-Phenylaminopyrimidine Derivative

Elisabeth Buchdunger, Jürg Zimmermann, Helmut Mett, et al.

Cancer Res 1996;56:100-104.

Is Cited as Prior Art by



US 6,894,051 B1
May 17, 2005

CRYSTAL MODIFICATION OF A N-PHENYL-2-PYRIMIDINEAMINE DERIVATIVE, PROCESSES FOR ITS MANUFACTURE AND ITS USE

Inventors: **Jürg Zimmermann**, Basel (CH); **Bertrand Sutter**, Hésingue (FR); **Hans Michael Bürger**, Allschwil (CH)

Assignee: **Novartis AG**, Basel (CH)

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Zimmermann, et al., Potent and Selective Inhibitors of the Abl–Kinase: Phenylaminopyrimidine (PAP) Derivatives, Bioorganic & Medicinal Chemistry Letters, vol. 7, No. 2, pp. 187–192 (1997).

Elisabeth Buchdunger, et al., Inhibition of the Abl Protein-Tyrosine Kinase in Vitro and in Vivo by a 2–Phenylaminopyrimidine Derivatives, Cancer Research, pp. 100–104, Jan. 1, 1996.

Note: The grant CA-001422 is acknowledged by 10 publications, among which is the article by Carroll et al. in the journal *Blood*. In turn, this article is listed as prior art in the patent 7,232,842 issued in 2007 to Stanford University. In addition to this direct bibliometric linkage (cf. Figure 4A), we focus on indirect linkages by matching the Carroll et al. publication with its intellectual neighbors through the use of the PubMed Related Citation Algorithm [PMRA]. As can be seen above, the fifth most related publication was published in the journal *Cancer Research* in 1996. We focus on this publication because it is cited as prior art by the patent 6,894,051 issued to Novartis in May 2005. This patent is valuable indeed, since it is listed in the FDA Orange Book as one of the five patents associated with the registration of Imatinib Mesylate, better known by its brand name, *Gleevec*. These indirect bibliometric linkages are valuable to us because they enable us to link the great majority of patents in biopharmaceutical classes to a study section × institute × year strata. In other words, most patents can be traced back to one (or more) NIH grant, because most patents cite publications as prior art that are related in ideas space to another publication which acknowledges NIH funding.

Appendix G: Impact of NIH Funding, Traditional Fixed Lag Approach

Our approach differs from traditional estimates of the impact of public R&D funding in that, instead of making *ex ante* assumptions about where and when to look for its effects, the structure of the bibliometric linkages naturally reveals, *ex post*, where and with what kind of lags the effects are being felt.

Relative to the traditional approach, one might worry that our estimates reflect in part idiosyncrasies of the linking process, rather than the effect of funding. For example, if scientists over-attribute publications to their grants in order to appear productive, then DSTs with more grants will exhibit a higher number of bibliometric linkages to patents, regardless of whether the funding in these DSTs actually contributed to the development of those patents. This will artificially inflate our estimates of the impact of NIH funding on citation-linked patents in Table 4 (though it should not increase the total number of patents in a research area, as estimated in Table 5).

In this appendix, we repeat our empirical exercise using the traditional method of examining the relationship between funding in a year and patenting in subsequent years, assuming a series of fixed lags between funding and innovation. The results are broadly similar in magnitude to those obtained in the benchmark specification using our preferred "ex post" methodology, with some important caveats that we detail below. We continue to favor the *ex post* approach because bibliometric linkages offer a variety of benefits, including the ability to track innovations across disease areas.

In order to follow the traditional approach, we must find a way to identify the research area(s) that is/are likely to be responsible for a particular patented innovation. Toole (2012), for instance, assumes that funding in a given disease area impacts drug development in the same disease area, and then goes on to examine the impact of funding on new drug approvals using a distributed lag structure. Here we replicate the spirit of his work, but with two important twists: (i) our outcome variable is patents, not drug approvals, and patents are more challenging to associate *ex ante* with disease areas; (ii) we perform the exercise both using a more aggregated disease level to partition funding into research areas (the unit of analysis used in Toole (2012) and most of the literature to date), and also using a finer-grained disease/science level, which parallels the level of analysis used throughout the main body of the manuscript.

Patent mapping. We create an *ex ante* mapping of patents to research areas by exploiting the fact that NIH grants sometimes directly generate patented innovations. The 1980 Bayh-Dole Act created incentives for researchers and their institutions to patent the discoveries derived from federal funding. The Act also required that patents resulting from public funding acknowledge this fact and list specific grants in their "Government Interest" statements. We obtained this information from the NIH's *iEdison* database. In total, 1,799 NIH grants generated 1,010 distinct patents.[x] We examine the three digit main patent class in each of these 1,010 patents to create a probabilistic mapping of each patent class to research areas, where a research area is defined as a funding institute (roughly isomorphic to a broad disease area, see Appendix A). For each funding institute/patent class combination, we construct the fraction of that class' patents that are supported by funding for the institute associated with that disease:

$$F_{cd} = \frac{\#\text{ of class } c \text{ patents acknowledging funding from NIH Institute } d}{\#\text{ class } c \text{ patents}}$$

So for instance, if a patent is part of a class that includes 100 patents, 10 of which are supported by the National Cancer Institute (NCI) and 15 of which are supported by the National Heart Lung and Blood Institute (NHLBI), then it will count as 0.10 of a patent to the NCI and 0.15 to the NHLBI. Note that this mapping only relies on the empirical distribution of Bayh-Dole patents across funding institutes. Within our universe of 315,982 life science patents, 269,839 (85%) have a main patent class that is represented in the

[x] While these patents are also issued between 1980 and 2012, they do not overlap with those in our main analyses because they are overwhelmingly assigned to universities or to the NIH intramural campus, as opposed to private-sector firms.

much smaller set of Bayh-Dole patents. We use our class-to-research area mapping to allocate each of these 269,385 patents in one or more funding institute using the weights described above.

We proceed in a similar fashion to create a mapping between disease/science areas and patent classes:

$$F_{cds} = \frac{\#\text{ of class } c \text{ patents acknowledging funding from NIH Institute } d \text{ and reviewed by study section } s}{\#\text{ class } c \text{ patents}}$$

The next step is to construct the number of patents in a research area issued in a particular year t. In the case of research areas defined at the disease level:

$$Patents_{dt} = \sum_c F_{cd} \cdot \#\text{ of patents in class } c \text{ issued in year } t$$

In the case of research areas defined at the disease/science level:

$$Patents_{dst} = \sum_c F_{cds} \cdot \#\text{ of patents in class } c \text{ issued in year } t$$

i.e., the number of patents issued in a particular year t as the proportion of class c's patents that can be mapped to the NIH research area defined by disease d and science area s. Since the weights F_{cd} and F_{cds} are time-invariant, the allocation of patents to research areas is not influenced by changes in funding and other potentially endogenous factors.

Estimation. Using these outcome variables, we estimate the following regressions:

$$\text{Patents}_{d,t+k} = \alpha_0 + \alpha_{1k}\text{Funding}_{dt} + \delta_d + \gamma_t + \varepsilon_{dt} \text{ for } k = 1, \ldots, 20 \tag{1}$$

at the disease level, and

$$\text{Patents}_{ds,t+k} = \beta_0 + \beta_{1k}\text{Funding}_{dst} + \delta_{ds} + \mu_{dt} + \nu_{st} + \varepsilon_{dt} \text{ for } k = 1, \ldots, 20 \tag{2}$$

at the disease/science level. The coefficients of interests are α_{1k} and β_{1k} for $k = 1, \ldots, 20$, and we display them graphically in Panels A and B of Figures G1, together with their 95% confidence intervals. For comparison, we represent our benchmark result—from Table 6, column (5)—as an horizontal line (since this estimate does not depend on pre-specified lags).

Results. Figure G1, Panel A shows that, averaged over all the possible lags, the *ex ante* approach using the disease level of analysis yields effects whose magnitudes are quite comparable to our main *ex post* benchmark (2.33 patents for a $10 million boost in funding), and in fact surprisingly similar to it for lags of 11 to 14 years. Interestingly, however, the *ex ante* approach appears to "overshoot" in the short run, and "undershoot" in the long run. For instance, we estimate that a $10 million boost in funding to an institute would increase private-sector patenting by about 10 patents in the next year. Given the time needed both to perform the research and to complete the patent prosecution process, a near-term return to public funding of this magnitude seems highly implausible. This highlights some of the concerns with the fixed-lag approach; by assuming different lag structures, one could get very different estimates of the impact of funding, not all of which appear plausible. For this reason, we prefer the *ex post* approach.

Figure G1, Panel B, repeats the fixed lag approach using the DST as unit of analysis, paralleling our primary specifications. Here, the *ex ante* approach yields smaller estimates relative to the *ex post* benchmark (though the differences are not statistically significant for lags 11 to 14). The lack of congruence between the results in Panel A and Panel B makes sense in light of the different levels of analysis used to generate these figures. In Panel B, we do not capture in the outcome variable any patent that can be mapped *ex ante* to the same disease area unless it can also be mapped to the same science area. This is obviously very restrictive. Panel B therefore highlights another benefit of the *ex post* approach: it allows one to track innovation across research areas where *ex ante* mappings would simply assume the lack of any relation between funding and downstream innovation.

To explore the hypothesis that our disease/science level regressions yield smaller coefficients because they restrict associated patents to be ones in a narrow disease/science area, we reproduce Figure G1 using a slightly broader measure of "science area." Study sections are organized into slightly broader categories known as integrated review groups (IRGs). In our data, there are 624 study sections, and 327 IRGs. Figure G2 plots coefficients from a version of Equation (2), with patents matched to the relevant IC-IRG. Here, we find larger estimates, within range of our *ex post* results for at least some of the lags.

Figure G1: Effect of NIH Funding on Private-Sector Patenting *ex ante* Approach with Fixed Lags

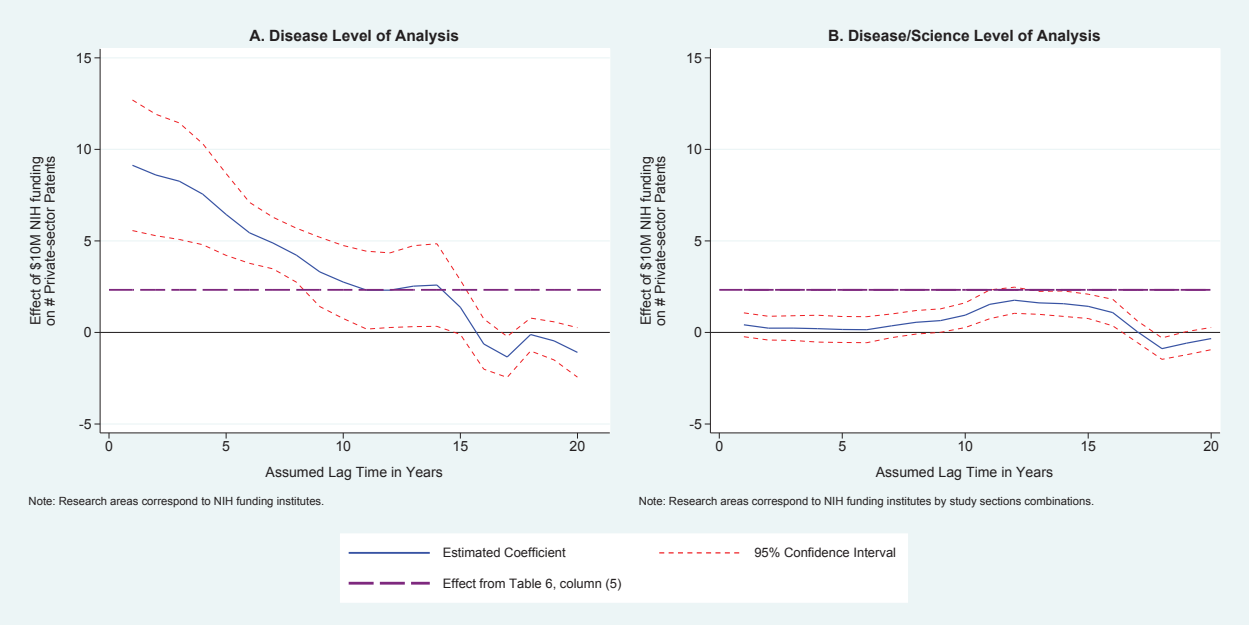
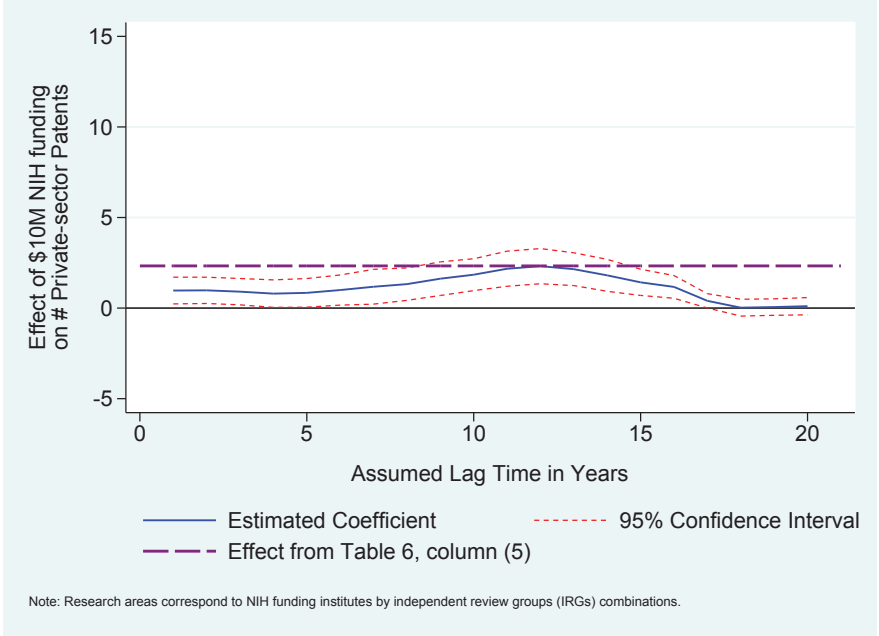


Figure G2: Reprise of Figure G1, Panel B but with broader, IRG-based level measure of science area



Appendix H: Identification Robustness Checks

The fixed effect estimation strategy outlined in Section 3 identify the causal impact of NIH funding under the assumption that NIH funding for a DST does not respond to changes in the specific innovative potential of a disease/science area combination. In this Section, we present several tests to argue that this is not the case.

Table H1 presents the IV estimates and the corresponding reduced-form estimates side-by-side. We find that the reduced-form coefficient estimates for windfall funding (Columns 1 and 3) are quite similar in magnitude with the IV coefficient estimates for actual funding in a DST, instrumented by windfall funding (Columns 2 and 4).

One potential concern is that the NIH occasionally funds grant applications out of the order in which they are scored. As discussed in Section 3.3 and Appendix B, peer review rules at the NIH make it difficult for NIH's component Institutes to direct resources to DSTs. ICs, however, do have the discretion to fund grant applications as exceptions to the standard scoring rules; approximately four to five percent of grants are funded in this way. While this usually occurs in response to the emergence of new data to strengthen the application, grants are also sometimes funded out of order if they were evaluated in an exceptionally strong committee and received a lower relative score than their absolute quality should indicate.[xi] This practice has the potential of generating a correlation between DST funding and its unobserved potential.

We show that this possibility does not appear to affect our results using two different tests. If the component Institutes do selectively fund grant applications from competitive, high-interest science areas out of order, then we would expect that the amount of funding for DSTs that share the same scientific interests should be correlated; that is, if the NCI (cancer) were allocating more money to genetics because of increased potential in that area, then we should weakly expect the NIDDK (diabetes) to do the same. Similarly, if Congress increased funding for all Institutes whose disease focus has a strong hereditary component, we would also expect cancer-genetics and heart disease-genetics funding to be positively correlated. Table H2 examines the correlation between own-disease funding for a science area, Funding_{dst}, and funding for that same science area from other diseases $\text{Funding}_{-d,st}$. Column 1, which includes only year fixed effects, shows a strong negative correlation between own and other funding. This, however, is likely due to the mechanical relationship between the size of one's own disease area in a given science area, and the size of other disease areas. Column 2 controls for this confounder by introducing disease by science fixed effects; we find no correlation between own and other disease funding. This is also true if we add disease by year fixed effects as we do in Column 3. Column 3 includes the same set of controls as we use in estimating our main results. Columns 4 through 6 repeat this exercise using the proportion of a disease area's funding devoted to a particular science area as the variable of interest. This asks: if the NCI begins spending a greater proportion of its budget on genetics, does it appear that other disease areas do the same? Again, we find that this does not appear to be the case.

Another way to address the possibility that out-of-order scoring matters is to instrument for DST funding using funding from grants that are not funded out of order. Ideally, we would add up requested funding amounts for the top ranked applications, regardless of whether they were actually funded, but we do not have data on funding requests for unfunded applications. Instead, we count funding amounts for the subset of DST grants that are funded in order. Table H3 presents our findings using this alternative strategy. Columns 1 and 2 indicate that we have a strong first stage and, using this instrument, we find that an additional $10 million in ordered funding increases net patenting by 3.7, compared with 2.8 in our main OLS specification and 2.9 in our preferred IV specification.[xii] The implied elasticities of all these estimates are similar.

Our next test checks the plausibility of the exclusion restriction for our instrument. Table H4 tests alternative first stages using past or future windfalls as an instrument. If windfall funding for a DST is correlated with

[xi] Authors' conversation with Stefano Bertuzzi, NIH Center for Scientific Review.

[xii] Note that our original lucky funding instrument already purges funding dollars to out of order grants.

time-varying observed potential in that disease/science area after conditioning on the number of applications around the payline and their raw scores and science ranks, then we might expect past or future windfalls to still be predictive of current funding; excitement about targeted cancer therapies in the wake of Gleevec might, for instance, drive funding for cancer/cell-signaling for several years. The results in Table H4 show, however, that this is not the case. While current windfalls (Column 2) are strongly predictive of total DST funding, past and future windfalls are not.

Figure H1 illustrates this point graphically. The first panel of Figure H1 plots past windfall funding on the x-axis against current windfall funding on the y-axis and finds no evidence of a relationship. The second panel does the same for current and future windfall funding. The final panel examines the relationship between windfall funding and "non-windfall" funding, i.e. $\text{Funding}_{dst} - \text{Windfall Funding}_{dst}$. If windfall funding were truly random, then it should not be correlated with the overall quality of the DST as given by the amount of non-marginal funding it receives. Again, we find no relationship.

Finally, Table H5 tests whether, after controlling for our primary set of regressors, our instrument for funding is correlated with any measures of lagged application quality or lagged patent output. Column 1 reports the F-test of the joint significance of 10 year lags in the number of patents that acknowledge NIH funding from a disease/science area, as well as the number of patents that cite publications supported by that area or which cite publications related to those funded by that area. We also examine whether windfall funding is correlated with lagged applicant scores or lagged windfall funding. Again, we fail to reject the null hypothesis in all these cases.

Figure H1: Correlation Between Windfall DST Funding and Other DST Funding

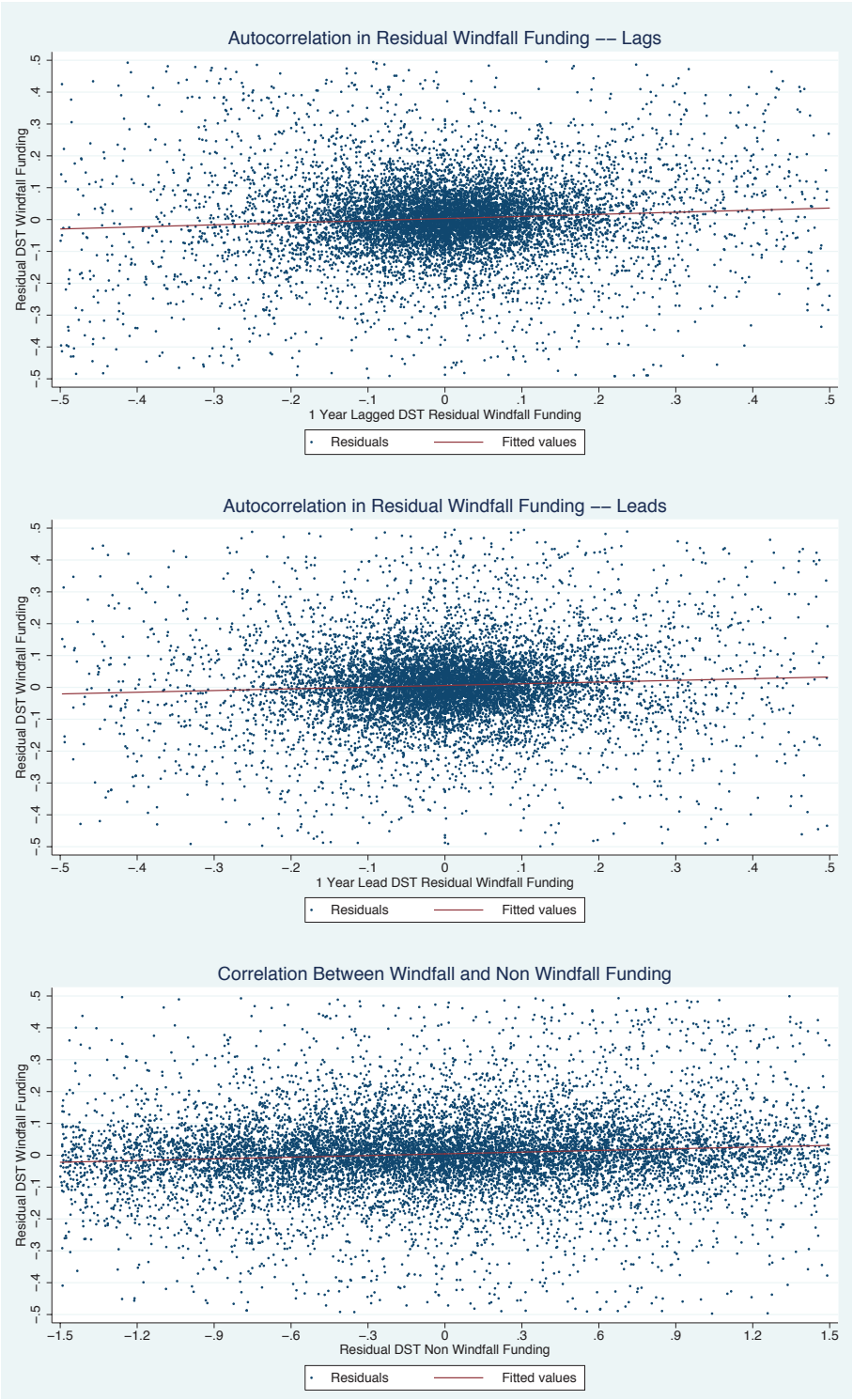


Table H1: Reduced Form and IV Estimates

	Citation Linked		Total Related	
	Mean=12.82; SD=19.17		Mean=24.8; SD=28.0	
	Reduced Form	IV	Reduced Form	IV
	(1)	(2)	(3)	(4)
Windfall Funding ($10 mln.) Mean=0.20; SD 0.52	2.504 *(1.583)*		2.914* *(1.528)*	
DST Funding ($10 mln.) Mean=4.06; SD 4.87		2.002** *(0.853)*		2.329*** *(0.834)*
R^2	0.713	0.515	0.838	0.623
Observations	14,085	14,085	14,085	14,085
Year FEs	Incl.	Incl.	Incl.	Incl.
Disease × Science FEs	Incl.	Incl.	Incl.	Incl.
Disease × Year FEs	Incl.	Incl.	Incl.	Incl.
Science × Year Linear Trends	Incl.	Incl.	Incl.	Incl.
Application Controls	Incl.	Incl.	Incl.	Incl.

Note: See notes to Table 6 for details about the sample. The outcome variables are fractional patent counts. The instrument is the total amount of funding (2010 dollars) for the subset of grants funded by a DST whose rank of rank scores were marginal, i.e., were within 25 applications of the award cutoff for their specific disease area (Institute). Application controls include (i) FEs for the number of applications that a DST receives; (ii) FEs for the number of applications associated with a DST that are also in a 50-grant window around the relevant IC payline, as well as (iii) cubics in the average raw and rank scores of applications associated with a DST that are also in a 50-grant window around the payline.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table H2: Relationship Between Own DST Funding and Funding by Other Diseases for the Same Science Area

	DST Funding ($10 mln.)		
	(1)	(2)	(3)
D'ST Funding, Other Diseases, Same Science (×$10 mln.)	-0.446***	0.009	-0.008
	(0.017)	*(0.042)*	*(0.043)*
R^2	0.134	0.732	0.771
Observations	14,085	14,085	14,085
Year FEs	Incl.	Incl.	Incl.
Disease × Science FEs		Incl.	Incl.
Disease × Year FEs			Incl.

Note: Each cell is a study section/IC/year. Funding is defined by the sum of project-cycle allocations for all Type I and II grants reviewed by that study section. See notes to Tables 1 and 2 for additional details about this sample.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table H3: Instrumenting DST Funding with Funding for Grants Funded in Order Only

	First Stage		Citation Linked		Total Related	
	DST Funding (×$10 mln.)		Mean=12.82; SD=19.17		Mean=24.8; SD=28.0	
			OLS	IV	OLS	IV
	(1)		(2)	(3)	(4)	(5)
DST Funding, Grants in Order Only (×$10 mln.)	0.629*** *(0.085)*	DST Funding ($10 mln.) Mean=4.06; SD=4.36	2.478*** *(0.496)*	2.544*** *(0.540)*	3.614*** *(0.671)*	3.733*** *(0.697)*
		Elasticity	0.785	0.806	0.592	0.611
R^2	0.949		0.738	0.519	0.863	0.634
Observations	14,085		14,085	14,085	14,085	14,085
Year FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Disease × Science FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Disease × Year FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Science × Year Linear Trends	Incl.		Incl.	Incl.	Incl.	Incl.
Application Controls	Incl.		Incl.	Incl.	Incl.	Incl.

Note: The outcome variables are fractional patent counts. The instrument is the total amount of funding for awarded DST grants that are funded in order of score (i.e., which are not exceptions). For more details on this sample, see the notes to Tables 6. Application controls include (i) FEs for the number of applications that a DST receives; (ii) FEs for the number of applications associated with a DST that are also in a 50-grant window around the relevant IC payline, as well as (iii) cubics in the average raw and rank scores of applications associated with a DST that are also in a 50-grant window around the payline.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table H4: Alternative First Stages, Past and Future Windfalls

	Dependent variable: Total DST Funding		
	Past Windfall	Current Windfall	Future Windfall
	(1)	(2)	(3)
Windfall Funding	0.067	1.251***	0.085
	(0.243)	*(0.232)*	*(0.205)*
R^2	0.927	0.921	0.927
Observations	9,326	14,085	9,326

Note: This table presents alternative first stages using past and future windfall funding. Current windfall funding is the total amount of funding for awarded DST grants within 25 grants of an Institute specific award cutoff in the same year T. Future windfall is this same amount, but defined for DS,T+1. Past windfall funding is similarly defined, for DS,T-1. Controls include disease-science and disease-year fixed effects, linear science-year time trends, as well as fixed effects for the number of applicants to a DST, the number of applicants within a 25-grant radius window around the IC payline, as well as cubics in the average raw and rank scores of applications in the funding window. The outcome variables are fractional patent counts.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table H5: Correlation Between Windfall Funding and Measures of DST Quality

RHS includes 10 Years of Lags for:	***F*-stat of Joint Significance**
# of Patents Citing Research Acknowledging NIH Funding	0.908
# of Patents Citing Research Similar to NIH-Funded Research	0.697
Raw and Rank Scores	0.156
All of the Above	0.188

Note: Each observation is a disease/science/time (DST) combination. Each column reports a regression of our windfall funding instrument on measures of DST input and output quality. We controls for the same set of variables as in our most detailed specification in Tables 4 and 5. Column 1 reports probabiities associated with an F-test for the joint significance of one to ten year lags of past DST patent production: citation-linked and PMRA-linked (20 variables).

Appendix I: Alternative Specifications and Samples

Another set of robustness checks describes alternative specifications and samples. All of the results in the body of the manuscript rely on sample weights, where each observation is weighted by the yearly average of awarded grants for a disease-by-science area. Weighting is justified by our desire to prevent small DSTs to influence too strongly the results, relative to large DSTs. Table I1 replicates the benchmark results of Table 6, with the only difference that we do not weight the sample. The difference in results between the weighted and unweighted version are minor. Though we believe that weighting by average DST size (measured by yearly number of grants in a DS) is appropriate, this choice does not affect our substantive conclusions.

Our main results rely on linear fixed effects and IV models; this may be problematic because patenting outcomes tend to be very skewed. Table I2 shows that our results hold in logs as well. Columns 1 and 2 rerun our main results for our first outcome measure, the number of patents that cite research funded by that DST; Column 1 uses the same set of controls as our main fixed effects estimates from Table 4 and Column 2 uses our IV controls. On the subsample of DSTs with nonzero patenting under this measure (63% of our main DST sample), we show that a one percent increase in DST funding increases patenting by between 0.8 and 0.9 percent. This is similar, though slightly higher, to the elasticities we find in our main results. Columns 3 and 4 repeat this exercise using our second outcome measure, the total number of related patents. Again, we find elasticities between 0.8 and 0.9, which are slightly higher than in our main results.

A shortcoming of the log-log parametrization is that it entails dropping 1,062 DST observations that are not linked to any private-sector patent. Many researchers have dealt with the problem of excess zeros through the use of *ad hoc* transformations of the dependent variable, such as $log(1+y)$. Because of Jensen's inequality, the estimates corresponding to the transformed outcome are difficult to compare numerically to the estimates when the dependent variable is left untransformed. A better approach in our view is to estimate our specifications using Quasi-Maximum Likelihood Poisson, which is consistent under very mild regularity conditions and allows us to deal with the skewness of the outcome variable as well as with its mass point at zero (Wooldridge 1997; Santos Silva and Tenreyro 2006). Table I3 estimates our benchmark specifications using the QML-Poisson approach, with one important caveat. The likelihood function fails to converge when we fully saturate the model with disease-by-science fixed effects, disease-by-year fixed effects, and science-by-year fixed effects. We are able to achieve convergence and to generate QML estimates when including disease-by-year fixed effects (columns 1 and 3), and when we combine disease-by-year and disease-by-science fixed effects (columns 2 and 4). While these specifications are not strictly analogous to the most saturated models presented in Tables 4 and 5, they remain very close to them in spirit. The magnitudes obtained with the Poisson parametrization, and the elasticities they imply, are numerically similar to the elasticities computed in Tables 4 and 5.

Next, we restrict our sample to different Institutes (ICs). In our paper, we refer to Institutes as representing diseases or body systems. In practice, however, not all ICs are organized in this way. The National Institute on Aging, for instance, does not focus on diseases in the same way as the National Cancer Institute. Other Institutes are even more difficult to think of as representing a disease or body system; the National Human Genome Research Institute (NHGRI) focuses on science areas rather than on disease areas. The fact that ICs do not always correspond to diseases does not impact the validity of our instrument, which relies only on the fact that ICs span study sections and vice versa.

It does, however, raise the concern that the IC by year fixed effects in our specifications may not, for some grants, be capturing changes in the innovative or commercial potential of their actual disease areas. For example, if the NHGRI funds research on cancer genetics, the IC by year FE associated with this grant will control for time varying potential in genetics, but not in cancer more generally. In Table I4, we restrict our sample to ICs that are more closely affiliated with disease and body system areas. Columns 1 and 2 reproduce our main results; Columns 3 and 4 exclude three science-focused ICs (general medicine, genome research, and biomedical imagine), and Columns 5 and 6 keep only ICs clearly associated with a disease or body system.

Finally, we replicate our design using public-sector patents—rather than private-sector patents—as the outcome variable. Public-sector patents are patents assigned to universities, non-profit foundations and research institutes, government entities (including the intramural research campus of the NIH), and academic medical centers. There are fewer such patents: only 47,461 can be linked "directly" through a publication they cite to a DST, compared with 91,462 private-sector patents. Our analysis focuses on the private sector because the meaning of citations to publications contained in patents is likely different for biopharmaceutical firms, and corresponds more closely to the idea of a knowledge spillover. Life-science academics sometimes patent, and yet other times found biopharmaceutical firms, typically with a license to a patent assigned to the researcher's academic employer. In other words, the same individuals might obtain NIH funding, publish results from research made possible by this funding, and choose to apply for a patent whose claims will cover these very same results. We might still be interested in assessing the magnitude of the patent-to-funding elasticity in this case. Although the question of crowd-out arises in the case of public-sector patents as well, it is probably capturing a different dynamic.

These objections notwithstanding, Table I5 replicates our benchmark results with public-sector patents as the outcome. Though the coefficient estimates differ from those displayed in Table 6, the elasticities are quite similar.

Table I1: Benchmark Results with No Weights

	First Stage		Citation Linked		Total Related	
	DST Funding (× $10 mln.)		Mean=4.72; SD=12.56		Mean=9.25; SD=18.68	
			OLS	IV	OLS	IV
	(1)		(2)	(3)	(4)	(5)
Windfall Funding (×$10 mln.)	1.184***	DST Funding (×$10 mln.) Mean=1.52; SD=2.91	2.155***	2.367***	3.404***	2.667***
	(0.218)		*(0.383)*	*(0.578)*	*(0.573)*	*(0.564)*
		Elasticity	0.894	0.762	0.559	0.438
Cragg-Donald Wald F-stat	508					
Kleibergen-Paap Wald F-stat	37.86					
R^2	0.907		0.641	0.302	0.853	0.475
Observations	14,085		14,085	14,085	14,085	14,085
Year FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Disease × Science FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Disease × Year FEs	Incl.		Incl.	Incl.	Incl.	Incl.
Science × Year Linear Trends	Incl.		Incl.	Incl.	Incl.	Incl.
Application Controls	Incl.		Incl.	Incl.	Incl.	Incl.

Note: See notes to Tables 4 and 5 for details about the sample. The outcome variables are fractional patent counts. The instrument is the total amount of funding (2010 dollars) for the subset of grants funded by a DST whose rank of rank scores were marginal, i.e., were within 25 applications of the award cutoff for their specific disease area (Institute). Application controls include (i) FEs for the number of applications that a DST receives; (ii) FEs for the number of applications associated with a DST that are also in a 50-grant window around the relevant IC payline, as well as (iii) cubics in the average raw and rank scores of applications associated with a DST that are also in a 50-grant window around the payline. Elasticities are evaluated at the sample means.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table I2: Log Patents-Log Funding Parametrization

	Log(# Citation Linked Patents)		Log(# Related Patents)	
	(1)	(2)	(3)	(4)
Log(DST Funding)	0.790***	0.874***	0.899***	0.899***
	(0.069)	*(0.059)*	*(0.031)*	*(0.030)*
R^2	0.937	0.837	0.954	0.909
Observations	8,880	8,880	13,013	13,013
Full OLS Controls	Incl.		Incl.	
Full IV Controls		Incl.		Incl.

Note: The dependent variable in Columns 1 and 2 is the log of citation-linked fractional patents, with zeros treated as missing. There are 14,085-8,880=5,205 DSTs that do not produce research ever cited by a patent. Full OLS controls are the controls used in the most saturated specification of Tables 4 and 5 (see notes to those tables). Full IV controls are those used in Table 6. Log(#Related Patents) is the log of the number of fractional patents related by our second outcome measure, using PMRA. There are 14,085-13,023=1,062 DSTs that do not produce resarch that is related to a patent in our sample.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table I3: Poisson Specification

	Log(# Citation Linked Patents)		Log(# Related Patents)	
	(1)	(2)	(3)	(4)
Log(DST Funding)	0.790***	0.874***	0.899***	0.899***
	(0.069)	*(0.059)*	*(0.031)*	*(0.030)*
R^2	0.937	0.837	0.954	0.909
Observations	8,880	8,880	13,013	13,013
Full OLS Controls	Incl.		Incl.	
Full IV Controls		Incl.		Incl.

Note: The dependent variable in Columns 1 and 2 is the log of citation-linked fractional patents, with zeros treated as missing. There are 14,085-8,880=5,205 DSTs that do not produce research ever cited by a patent. Full OLS controls are the controls used in the most saturated specification of Tables 4 and 5 (see notes to those tables). Full IV controls are those used in Table 6. Log(#Related Patents) is the log of the number of fractional patents related by our second outcome measure, using PMRA. There are 14,085-13,023=1,062 DSTs that do not produce resarch that is related to a patent in our sample.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table I4: Disease- or Body System-Specific ICs Only

	All ICs		Excluding Science-based ICs		Core Disease/Body System ICs	
	Mean=24.8; SD=28.0		Mean=24.10; SD=27.82		Mean=23.81; SD=26.80	
	OLS	IV	OLS	IV	OLS	IV
	(1)	(2)	(3)	(4)	(5)	(6)
DST Funding (×$10 mln.)	3.614***	2.329***	3.377***	2.918***	3.331***	1.944
Mean=4.06; SD=4.36	*(0.671)*	*(0.834)*	*(0.657)*	*(0.778)*	*(0.689)*	*(1.618)*
R^2	0.863	0.623	0.899	0.678	0.898	0.673
Observations	14,085	14,085	12,432	12,432	10,382	10,382

Note: Columns 1 and 2 reproduce the results from our primary sample. Columns 3 and 4 remove three IC based on methods or scientific topics. These are the National Institute of General Medical Sciences (NIGMS), the National Human Genome Research Institute (NHGRI), and the National Institute of Biomedical Imaging and Bioengineering (NIBIB). Columns 5 and 6 further restrict to a core set of ICs focused on diseases or body systems. See Appendix A for a list of these ICs. The outcome variables are fractional patent counts.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Table I5: Effect on Public-Sector Patenting

	Citation Linked		Total Related	
	Mean=6.75; SD=10.01		Mean=9.97; SD=11.05	
	OLS	IV	OLS	IV
	(1)	(2)	(3)	(4)
DST Funding ($10 mln.)	1.193***	0.910**	1.376***	0.761**
Mean=4.06; SD=4.36	*(0.259)*	*(0.461)*	*(0.275)*	*(0.351)*
Elasticity	0.771	0.588	0.560	0.310
R^2	0.790	0.558	0.896	0.678
Observations	14,085	13,043	14,085	13,043
Year FEs	Incl.	Incl.	Incl.	Incl.
Disease × Science FEs	Incl.	Incl.	Incl.	Incl.
Disease × Year FEs	Incl.	Incl.	Incl.	Incl.
Science × Year Linear Trends	Incl.	Incl.	Incl.	Incl.
Application Controls	Incl.	Incl.	Incl.	Incl.

Note: See notes to Table 6 for details about the sample. The outcome variables are fractional patent counts. The instrument is the total amount of funding (2010 dollars) for the subset of grants funded by a DST whose rank of rank scores were marginal, i.e., were within 25 applications of the award cutoff for their specific disease area (Institute). Application controls include (i) FEs for the number of applications that a DST receives; (ii) FEs for the number of applications associated with a DST that are also in a 50-grant window around the relevant IC payline, as well as (iii) cubics in the average raw and rank scores of applications associated with a DST that are also in a 50-grant window around the payline. Public sector patents are defined as those assigned to government, non-profit foundations, academic, or hospital entities.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

Appendix J: "Core PMRA" Indirect Linking Strategy

Recall that our preferred outcome measure identifies *all* patents related to an NIH funding area, whether or not these patents actually cite NIH-funded research. This allows us to account for a richer set of channels through which NIH funding may impact private-sector patenting. "Related" patents may include patents linked to NIH funding via a longer citation chain or patents by NIH-trained scientists who end up in the private sector. Crucially, these related patents may also be the result of private sector investments in related research areas; they need not be financially dependent on the NIH at all. Capturing the total number of private sector patents in an intellectual area is important because it allows us to take into account the possibility that NIH funding may crowd out private investments. If this were the case, then we would not expect NIH funds to increase the total number of patents in a given research area: it would simply change the funding source for those patents. The impact of NIH funding on total innovation in a research area captures the net effect of potential crowd-in and crowd-out.

A potential drawback with this approach is that our definition of a DST's "intellectual area" can vary over time. If funding allows a disease/science area to expand the set of topics that it supports, then we may associate increased funding with more patents simply because higher levels of grant expenditures leads us to credit DSTs with patents over a wider slice of technological space.

To ensure that our results are not driven by this phenomenon, it is important that the breadth of the space over which we attempt to link patents with grants in a DST is exogenous to the amount of funding a DST receives. One way to ensure this is true is to verify that this space is stable over time, within each disease/science (DS) area.

To do this, we categorize all MeSH keywords associated with a publication funded by a DS combination into one of two types: "stable" MeSH keywords are ones that appear in publications funded by that DS across all years in the observation window, whereas "peripheral" keywords appear only in a subset of years in the data. We then restrict our set of related publications to those that match to a DS on core keywords only. This fixes the boundaries of an intellectual area over time and therefore breaks any mechanical relationship that might exist between funding and the number of indirectly linked patents.

Concretely, for each DS, across all years in the observation window, we list all the MeSH keywords tagging the publications that *directly* acknowledge the grants in the DS. We then compute the frequency distribution of keywords within each DS. To fix ideas, in the DS corresponding to the National Institute of General Medical Sciences (NIGMS) and the Microbial Physiology II study section (MBC-2), the MeSH keyword `DNA-Binding proteins` sits above the 80^{th} percentile of the frequency distribution; `E coli` sits above the 95^{th} percentile; `Structure-Activity Relationship` sits above the 50^{th} percentile; and `Glucosephosphates` lies below the fifth percentile.

In the next step, we once again link each acknowledged article to the related articles identified by PMRA. However, we can now track whether these related articles are themselves tagged by keywords that our previous analysis has identified as "stable" within the DS—those keywords that are at the median or above of the DS-specific MeSH keyword frequency distribution.[xiii] The last step is to identify the patents that cite these indirectly linked articles, but we now restrict the citations to exist between patents and only the subset of "stable" related articles.

We experimented with several alternative ways to characterize "stable" indirectly linked articles. We report the results of specifications modeled after those used to generate the estimates in columns 4 and 5 of Table 6, our benchmark set of results. We manipulate two characteristics of keywords to generate the four variations of the strategy presented in the table below. First, for each article indexed by PubMed, some keywords are designated as main keywords, in the sense that they pertain to the article's central theme(s). We generate the keyword frequency distributions using all keywords and only main keywords, separately.

[xiii] In unreported results, we also experimented with a top quartile threshold, with little change to the results.

Second, MeSH keywords are arrayed in a hierarchical tree with 13 levels, with keywords for each article potentially sitting at any of these levels. Eighty percent of keywords that occur in PubMed belong to the third level of the hierarchy or below. For each keyword below the third level, we climb up the MeSH hierarchy to the third level to find its third-level ancestor (in the case of keywords that belong to multiple branches in the tree, we pick the ancestor at random). We recompute the keyword frequency distribution at this coarser, but more homogeneous level. Combining these two characteristics (main vs. all keywords; any levels vs. third level of the MeSH tree) provides us with four distinct keyword frequency distributions to identify the set of stable, indirectly-linked articles. Each of these in turn correspond to a column in Table J1.

Two features of the results in this table deserve mention. First, the magnitudes of the coefficients are slightly smaller than those observed in Table 6. This is to be expected, since our "stable" linking strategy shrinks the number of opportunities to associate patents with DSTs. Second, the elasticities that correspond to the estimates are comparable to those computed in Table 6. In fact, they are, if anything, a little larger.

In conclusion, the results corresponding to these alternative linking strategies bolster our claim that the indirect linking strategy presented in the main body of the manuscript allows us to identify total private-sector innovation in a DST in a way that is not mechanically related to the amount of funding this DST receives.

Table J1: Effect of NIH Investments on Total Related Private-Sector Patenting, Stable Research Area Keywords Only

	Main Keywords		All Keywords	
	Level Adjusted	Raw	Level Adjusted	Raw
	Mean=14.8; SD=17.0	*Mean=12.5; SD=14.9*	*Mean=23.1; SD=25.8*	*Mean=22.5; SD=25.2*
	(1)	(2)	(3)	(4)
OLS				
DST Funding (×$10 mln.)	2.241***	2.018***	3.371***	3.305***
Mean=4.06; SD=4.36	*(0.385)*	*(0.352)*	*(0.607)*	*(0.593)*
Elasticity	0.615	0.655	0.592	0.596
IV				
DST Funding (×$10 mln.)	2.333***	2.157***	3.543***	3.468***
Mean=4.06; SD=4.36	*(0.411)*	*(0.381)*	*(0.643)*	*(0.622)*
Elasticity	0.640	0.701	0.623	0.626
Observations	14,085	14,085	14,085	14,085

Note: The dependent variable is the number of fractional patents in the same area as a given DST, but using a more restrictive definition of relatedness than in our benchmark specification. If a patent cites a publication that directly acknowledges an NIH grant, but which does not contain any keywords that have commonly been used in that D-S, then the linked patent is not counted under this approach. See Appendix J for more details regarding this matching method. Columns 1 and 2 apply this method counting only keywords that are designated as main keywords; Columns 3 and 4 do this for all keywords. Columns 1 and 3 match two different keywords if they share the same level 3 parent keyword in the National Library of Medicine's semantic keyword tree. Columns 2 and 4 do not.

Standard errors in parentheses, clustered at the disease/science level ($^{*}p < 0.10$, $^{**}p < 0.05$, $^{***}p < 0.01$).

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