Drug Patent Citations and Value

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ABSTRACT

The number of times a patent is cited by subsequent patents is commonly used in economic research as a proxy for both the private and social value of inventions. Patent citation measures are also increasingly used by policymakers assessing the impact of innovation policies. However, there is surprisingly little direct evidence that highly cited patents are more valuable, and existing validation studies have not considered differences between private value, social value, and technological impact. The pharmaceutical sector has several features making it an attractive setting to examine these issues. In addition to being economically important, there are independent measures of different dimensions of drug value, and regulatory requirements make it possible to link drugs products to the key patents covering them.

In this paper we examine the relationship between the number of citations to a drug patent and different measures of the value of that drug. Overall, the relationship between citations and technological impact measures is strongest, and most robust across the analyses. In most of the analyses there is also a positive and significant correlation with private value, but the elasticities are small. The relationship between citations and social value is strong for some measures of social value but not others, and is not robust to alternative ways of counting patents on a drug. Finally, though one of the original rationale for using patent citations is the presence of patent examiners as quality control agents, in most of the analyses we find that citations inserted by patent examiners are less correlated with value than other citations.

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I. Introduction

Good measures of innovation are elusive, but necessary for determining the value of research and evaluating the effects of public funding, regulation, and other public policies. Patent data are the most commonly used measures of innovative output. Historically, most analyses used simple patent counts as indicators of innovation. Over the past two decades, recognition that there is considerable heterogeneity in innovation value has led to widespread use of patent citation based indicators. Specifically, the number of times a patent is cited by subsequent patents is commonly used in economics, management, legal scholarship, and by policymakers as a proxy for the value of inventions. However, there is limited direct evidence that more highly cited patents are more valuable ones. Moreover most of the existing validation studies have not considered differences between multiple dimensions of value, or across different types of citations.[2]

In this paper we leverage newly available data on drug quality, usage, characteristics, and revenue to examine how citations relate to different dimensions of drug value. There are four key characteristics of the pharmaceutical industry that make it a good context to examine relationships between patent citations and value. First, unlike all other industries, documents generated during the regulatory process make it feasible to link products to specific patents (and their citations). Second, product level sales are tracked through for drugs. Given low marginal costs of production in pharmaceuticals these sales are good measures of the private value of drug products. Third, drugs are prescribed to improve health outcomes, and their efficacy is directly measured and valued in rigorous trials. We use information from clinical studies and also expert ratings on therapeutic importance to construct estimates of the value of drugs to patients. Finally, we can measure the extent of technological innovativeness and follow-on innovation associated with specific drug products through expert drug classifications and bibliometric databases. Patent citation counts have been used as proxies for private value, social value, and technological impact (and extent of follow on innovation associated with patents) in economics. The pharmaceutical industry is a unique context where we can validate citation-based measures across all three.

There are also practical advantages reflecting the particular importance and effectiveness of patents in pharmaceuticals. There is a sixty-year empirical legacy in economics that patents are more effective at preventing imitation and appropriating returns from R&D in pharmaceuticals than in any other field (Levin et al 1987, Cohen et al 2000) and almost all

[2] For example, one of the pioneers in using citation analysis in economics concludes his recent survey of these indicators by emphasizing "Even the link between forward citations and economic value, one of the most established and used indicators, is not well understood" and emphasizes the need for validation studies (Jaffe and Rassenfosse, 2017).

new drugs are patented. Unlike many complex manufactured products that may involve hundreds or thousands of patents (e.g mobile phones or routers) drugs tend to depend on one or two key patents (Cohen et al 2000; Hemphill and Sampat 2011, 2012). As mentioned above, using information on the key patent on a drug generated by the regulatory process for patent extensions, we are able to directly link the underlying patents with products.

Overall, we find that the relationship between citations and technological impact measures is strongest, and most robust across the analyses. In most of the analyses there is also a positive and significant correlation with private value (sales), but the elasticities are small, around 0.15 in the preferred specification. The relationship between citations and clinical value is strong for some measures of social value, with an elasticity of 0.32 when using incremental QALYs as the measure. For other measures of clinical value, the relationship is not as strong and the result is not robust to alternative ways of counting patents on a drug. We also find evidence that citations are correlated with technological impact using three different measures. Finally, though one of the original rationale for using patent citations is the presence of patent examiners as quality control agents, in most of the analyses we find that citations inserted by patent examiners are less correlated with value than other citations.

The rest of the paper proceeds as follows. Section II provides background and a review of the literature. Section III describes our data. Section IV presents basic descriptive statistics and relationships between the drug value measures. Section V shows main results relating citations to value. In Section VI we discuss robustness of results to alternate measures. Section VII concludes.

II. Background

Patent Citations and the Value of Inventions

Following Jaffe (1998) we can think of three dimensions of the value of innovations, in pharmaceuticals and in other fields. First, the value to consumers. Second, the profits generated by firms. Third, the "spillover" value of an invention in helping generate subsequent inventions (and the profits and consumer value associated with those subsequent inventions).

Drawing on bibliometric work in the 1970s, Trajtenberg (1990a,b) introduced citations as a proxy for the third dimension (technological impact). Specifically Trajtenberg argued that citations reflect building of one generation of innovation on the next. However, research on patent prosecution and patent citation conducted since that has called into question some

of the assumptions about the citation generating process that motivates this idea. For example, Trajtenberg (1990a) assumed that the process of arriving at the final list of references "apparently does generate the right incentives to have all relevant patents cited, and only those" and "the U.S. patent examiner is under considerable pressure to make sure that he cites all the relevant prior art, and the quality of those patent citations is certainly more closely controlled than the overall quality of the citations within the scientific literature, which are placed there by the researcher for a myriad of reasons." More recent work by Trajtenberg and others suggests there is considerable noise in citations (Jaffe, Trajtenberg and Fogarty 2000), strategic dimensions in what to cite how to search (Lampe 2010; Sampat 2010), and heterogeneity across examiners (Lemley and Sampat 2012). Together with the fact that better data are now available for validation purposes, these new insights on how the citation-generating process actually works suggests the assumption that citations reflect follow-on research is worth a fresh look.

In addition to technological impact, Trajtenberg (1990a) also suggested that citations may reflect the economic value generated by inventions:

> *"The very existence of those later patents attests to the fact that the cited patents opened up the way to a technologically successful innovation. Moreover it presumably attests to the economic success ... since those subsequent patents are the results of costly innovational efforts undertaken mostly by profit-seeking agents ... If citations keep coming it must be that the innovation originating in the cited patent had indeed been valuable."*

In a first validation study, Trajtenberg (1990a) used discrete choice demand models to estimate social value (producer and consumer surplus) from advances in computed tomography (CT) scanner technology, and correlated temporal changes in social value with both patent counts and citation weighted patent counts in the field of CT scanner technology.[9] He found that citation-weighted patent counts perform better at predicting social value than simple patent counts (with correlation coefficients between .4 and .8 depending on assumptions about lag structure and the functional form of the relationship). He concluded his study by emphasizing limitations of this approach and difficulties in validating:

> *"All of my conclusions have been expressed in a qualified manner since they are based upon the findings from a single case study. It is important to emphasize, however, that the sort of validation of the citation-based patent index attempted here could hardly*

[9] In practice, as Trajtenberg (1990b) notes, most of the measured surplus gains were consumer rather than producer surplus.

have been done in a wider context simply because the measure of the value of innovations that would be required for that purpose are nowhere to be found" (185).

Citations have since been used as proxies for not only technological impact and follow on innovation, but also private value, social value, and as measures for patent and/or innovation "quality" in general. With the exception of Trajtenberg's logic (above) that more citations imply the economic attractiveness of a research area, the theoretical justification for using citations as measure of economic value (private or social) is not well articulated as their motivation as measures of technological impact or cumulative innovation. Rather the idea that these may be related is based mainly on empirical correlations (Jaffe and Rassenfosse 2017).

Jaffe and Rassenfosse (2017) review the validation studies citations and different aspects of economic value. Most focus on private value of the invention (or patent) to the holding firm. This includes work showing the relationship between citations and market value of firms (Hall, Jaffe, and Trajtenberg 2005), citations and litigation (Lanjouw and Schankerman 2004; Allison, Lemley, Moore and Trunkey 2003), licensing revenues (Abrams et al 2017; Sampat and Ziedonis 2005), citations and survey based measures of the private value of patents (Harhoff, Scherer, and Vopel 2003; Harhoff, Narin, Scherer, and Vopel 1999), and citations and patent renewal (Harhoff and Wagner 2009; Bessen 2008; Lanjouw et al 1998). In the paper most closely related to ours, Moser et al (2016) examine citations to 269 hybrid corn patents (including separate applicant and examiner citations) and relate to measures yield improvements for patented hybrid corn inventions from field trials of crops. (Reporting of field trial data is required for demonstrating novelty.) They find that a one percentage point increase in yield is associated with about .8 additional citations overall, but with no effects on examiner citations.[11]

The Value of Drugs

The question of how to measure the value of innovation is also a central one in pharmaceuticals. As with other technologies, at least three different dimensions are relevant: private value (to the inventing firm), consumer value (based on value to patients, or clinical value), and technological impact (the follow-on innovation enabled by the drug).

A long literature focuses on a measure of private value of pharmaceuticals (Grabowski and Vernon (1983; Berndt et al 2015.. This work uses revenues from new drugs as a measure of private value, and sometimes compares to R&D costs to measure returns on R&D investments. Consistent with the broader literature on the value of innovation (Scherer and

[11] By contrast, Hegde and Sampat (2009) found examiner citations were more highly correlated with an indicator of private value, whether the patent was renewed, than are applicant citations.

Harhoff, 2000) in pharmaceuticals most private value is skew-distributed, with profits from a small number of drugs accounting for the bulk of private value.

There is also a large literature on the clinical value of drugs. While many of these studies examine the effects of drugs on average on health and economic outcomes (Lichtenberg 1996, 2001, 2004, 2005), our analyses require data on specific drugs (which we then link to patents and their citations). For this purpose evidence from the medical literature focused on the value of individual drugs, based on clinical evidence, is more useful. Specifically, we use data from cost-effectiveness analyses that convert health outcomes from trials to a standard summary measure, Quality Adjusted Life Years (QALYs), that can be compared across drugs. Cost-effectiveness analysis is used by payers in some countries to guide coverage and reimbursement decisions. For example in the United Kingdom the National Institute for Clinical Excellence (NICE) provides advice on cost-effectiveness to the National Health Service. In France the Haute Autorité de Sante (HAS) conducts analyses of the absolute medical benefit (SMR) and the improvement of medical benefit (ASMR) of drugs being launched on the French market. The leading repository of CEA information in the U.S. Is the Tufts Cost-Effectiveness Analysis Registry (Chambers et al 2014). We use the database as our main measure of the social value of drugs, and supplement with data from the French HAS.

Interestingly, most of the literature on the value pharmaceuticals is not focused on "technology spillovers" as a central component of value. This may reflect that innovation is less cumulative in this field than others, or that patents are more effective at preventing imitation in this industry than others. There is however a large literature on incremental or me-too innovation (Globerman and Lybecker 2014), typically follow-on innovation within a drug class. Much of this literature focuses on the therapeutic value of this innovation (Cockburn, Berndt, Grepin 2006) and effects on market shares (Lichtenberg and Philipson 2002), but there is also an implicit assumption that the later drugs drew on knowledge from previous development efforts. (See however, DiMasi and Paquette 2004). The most comprehensive attempt to classify drug innovativeness in this way is Lanthier et al (2013), which we use in our analyses below, classifies innovativeness based on whether the drug was first in class, advance in class, or addition to class. Another way to capture the extent of incremental innovation (if not its value) is by looking at the number of supplemental approvals for the original drug (Cockburn, Berndt, Grepin 2006). Supplemental approvals (sNDAS) on an new drug application are used to get approvals for new dosages, combinations, formulations, and uses. According to some authors (Cockburn, Berndt, Grepin 2006) these incremental innovations are associated with significant health benefits as well. While supplemental approvals must be filed with the FDA and typically supported by formal trials, there is also significant “informal” learning about drugs by clinicians and others researchers about new molecules and their uses (Heidenreich and McClellan 2000).

Much of this is reported in the scientific literature. Following Dranove and Meltzer (1994) we can use entries in MEDLINE (the leading database of biomedical publications) relating to a specific drug as a final measure of follow on innovation related to a drug.

Under what conditions might we expect forward citations to a drug's key patent reflect these different measures of the value of the drug (technological impact, private value, and clinical)? The technological impact measure is the most plausible, and rests on the assumption that citations provide a reasonable signal of "technological antecedents" of inventions, despite the complications of this assumption (e.g. strategic citation) discussed above. In pharmaceuticals, this would mean the number of citations to a drug's compound patent would be greater for molecules that were the subject of significant incremental innovation, or for a molecule that opened up new drug classes, for example. As noted, at least in our view the theory behind the use of citations as measures of private and clinical value is less obvious. One possible channel, following Trajtenberg's logic, is that drugs with high private and clinical value attract entry or interest into technologically similar but non-infringing areas, which results in citations. High revenue patents on "blockbuster" drugs might also be well known and publicized. Since only known inventions must be disclosed under U.S. patent rules (Sampat 2010), this disclosure effect is yet another channel through which citations may reflect private value of drugs (Lanjouw and Schankerman).

However, we re-emphasize that since the theory for why we would expect a citations-economic value relationship is not always clear, ultimately these are empirical questions. In some of our analyses we also examine whether including or excluding examiner citations (those inserted by the patent examiner) and self-citations (those to a firm's own patents) matters for the direction and magnitude of the relationship in pharmaceuticals. Both examiner and self-citations have been argued to compromise citations as measures of knowledge flow and technological impact (Jaffe and Rassenhoffe 2017) and Moser (2018) suggests these citations are less correlated with measures of yield improvement from new hybrid corn strains.

IV. Data

We draw on a number of diverse datasets for this analysis, summarized in Table 1 and discussed in more detail below.

New Molecular Entities Approved Between 1987 and 2011

Our first data source is list of all 642 new molecular entities (NMEs) approved by the U.S. Food and Drug Administration between 1987 and 2011, taken from Lanthier et al (2013). As we will discuss in more detail below, beyond standard drug approval data this database also includes information on drug novelty that we use to construct one measure of technological impact. For each of these drugs, we attempted to locate the new drug application number (NDA) from the Drugs@FDA database. We were able to do so for all but 12 of the drugs (each of which appears to have been withdrawn from the market post-approval for safety or efficacy reasons) leaving a final sample of 630 drugs.

Patent Data

As we indicated above, one of the attractive features of the pharmaceutical industry is that it is possible to link patents to products. The most common source for doing so is the Food and Drug Administration's *Approved Drug Products with Therapeutic Equivalence Evaluations* also known as the Orange Book. Under the Hatch-Waxman Act, firms are required to list most pertinent patents covering the drug, and there are strong incentives to do so (Hemphill and Sampat 2011, 2012). Since the current version of the Orange Book includes only unexpired patents, and some of the drugs in our sample are quite old, we collected patent information from all Orange Books published between 1988 and 2012 using the NDA numbers to link drugs to patents.. Though the drug industry is typically viewed as a "discrete product" industry with low patent-product ratios, the growth of secondary patenting in drugs (including taking out patents on peripheral aspects of drugs) makes this an increasingly poor characterization (Hemphill and Sampat 2011, 2012). For the drugs in our sample, the mean number of patents per drug is 2.5, and the median is 2, but some drugs have as many as 19 Orange Book patents.

Previous analyses have shown that in practice there is one "main" patent per drug, the one that covers the active ingredient. (For example, most of the time generic entry occurs after this patent expires.) There is no official designation of the main patent; previous analyses have used laborious hand coding of patents to identify it (Hemphill and Sampat 2011). Here we use a different approach, relying on another institutional feature of Hatch-Waxman, patent extensions. Under the Hatch-Waxman Act, firms are given patent term extensions to compensate for patent time lost during the drug approval process. Firms are typically allowed to extend one patent per drug. This is typically the main (active ingredient) patent on the drug: nearly 80 percent of the time the main patent on a drug (based on hand coding) is also the one chosen for extension (Hemphill and Sampat 2011). The expiration of the extended patent is also highly predictive of timing of generic entry (Gilchrist 2016).

We collected this information from the USPTO list of extended patents (USPTO 2016). Since this source is not complete, we supplemented this with information from the Federal Register archives. One downside to using extended patents is that some of the drugs approved between 1987 and 2011 (190/630) do not have any patents extended since their approval time was very short or their patents were filed or issued late in the development process. While most of the analyses will focus on the 439 drugs that do, in the Appendix we also perform robustness checks using Orange Book patents instead (and unique citations to Orange Book patents on a drug).[16] For each patent we collected additional information, including assignee at issue, application date, and issue date from the USPTO Patent Database.

Patent Citations

We also collected all citations to these patents from the USPTO Patent Database and Google Full Text Patent XML files. Like nearly all previous citation analyses, our main analyses focus on so-called "front page" patent citations. We also distinguish between applications from the examiner and other sources, to see if specific kinds of citations are more related to value (Moser et al; 2017; Hegde and Sampat 2009). Information on whether the citation is an examiner citation is available beginning with citing patents issued in 2001, and we have collected this information for patents issued until the end of 2013.

Of these, 20 patents received no citations. The remaining 419 were cited by 18,629 patents, of which 14,937 are unique. About 63 percent of the citations to the patents are issued after 2001. Interestingly, only about 8 percent of citations over this period are from examiners. This is low relative to previous estimates across fields (Sampat 2010) upward of 40 percent (based on 2001-2003 citations). This may reflect that applicants are more diligent in searching in drugs than in other fields (Sampat 2010), but also reflects a general cross-field decline in the examiner share of references over time.[17] Using these citation data, we constructed forward citation counts for each of the 439 drugs (patents). When focused on examiner and other citations, we restrict some of our analyses to the 412 drugs with patents issued since 1980. This is the cutoff year after which the majority of a drug patent's citations are made by patents that were issued after examiner citation information becomes available (in 2001).

[16] In the few cases where there was more than one extended patent per drug, we focused on the first.

[17] For citations from 2001 onwards for drugs in our sample, 18 percent were examiner-inserted.
We also used assignee information for the citing and cited patents to isolate "self" citations, those from the same firm as the original assignee. About 17 percent of citations are self-citations.

Drug Value

Next, we collected information on each of the three measures of drug value, the technological impact, private value, and clinical value.

Technological Impact

The Lanthier dataset goes beyond what is available from standard FDA databases (e.g. Drugs@FDA) by coding each drug based on its "novelty compared to the existing base of pharmaceutical" (1433). Specifically, it distinguishes between first in class drugs (the first drugs approved in a pharmacologic therapy class, representing new pathways for treating a disease), advance in class (not first in class but representing advances in therapy), and addition to class drugs (those that function similarly to other drugs but do not represent major advances). We use these categories to construct measures of technological impact or innovativeness. For the drugs with patents, about half are "addition to class" representing the least innovative category, 19 percent are "advances in class" and 31 percent are "first in class" (the most innovative). To the extent the first in class drugs are necessary for development of subsequent drugs in class (e.g. by pointing to a specific mechanism of action) can be viewed as more technological impactful or generating more spillovers than other classes.

Another measure related to technological impact is the number of supplemental approvals (new dosages, formulations, indications, etc.). While Lanthier measure indicates drugs that open up new classes, this measure captures follow on innovation on a specific molecule. Following Berndt et al (2006) we collected information from the Drugs@FDA database on all supplemental approvals for each drug.

A final measure of follow on innovation used is the number of scientific publications on a molecule after FDA approval, obtained from MEDLINE, the leading database indexing biomedical publications. We searched for publications for each molecule in the Lanthier dataset by generic (active ingredient name) in the Medical Subject Heading browser (https://meshb.nlm.nih.gov/search). For 437 of the 439 drugs we were able to identify a MeSH search term, either a Descriptor (from the more curated MeSH tree) or a supplementary concept (from the MEDLINE registry file).[18] We then count the number of articles relating to each molecule.

[18] For drugs identified through Descriptors we can also look at MeSH qualifiers to examine the kinds of follow-on research identified for these molecules. The vast majority of articles relate to therapeutic uses (25%), pharmacology (22%), administration and dosage (15%), adverse effects (9%), and analogs and derivatives (6%).

Private Value

To measure private value, we also collected information on sales for each of these drugs. The Optum ClinFormatics database consists of administrative health claims (including pharmacy claims) for 2000-2014 for a large managed care company, covering 47 million users over this period. The claims table data are submitted by pharmacies for drugs dispensed on an outpatient basis. Unlike other databases, Optum also includes data on inpatient drugs. We use the Optum data to compute total expenditures associated with each drug (regardless of who paid). We also used the Optum database to examine the number of new users by year, which we will use in the clinical value analyses discussed below. Overall, we were able to locate 419 drugs in the Optum claims database. We focus, however, on the 200 drugs approved since 1999, so we do not miss pre-2000 sales data. Like patent citations, the distribution of drug value is skew. On average drugs had 12 million in annual sales in the Optum data, with a maximum of 600 million.

Clinical Value

We also collected data on the drugs from our sample that were included in the Tufts Cost-Effectiveness Registry. Of the 419 drugs in our sample with an extended patent and claims in Optum, 76 also appear in the Tufts database.[19] The median incremental QALY per drug is about .09 years, the mean is .27 years. And consistent with what Chambers et al (2014) report for the full sample of all drugs in the Tufts database (not all of which are NMEs approved between 1987 and 2011, and thus not all in our sample), about a quarter of the drugs have negative incremental QALYs. That is, they are worse than the drugs to which they were compared. The Tufts data provide incremental QALYs for each of these drugs, relative to the standard of care. We also use data from Optum to compute aggregate QALYs (across the Optum data) by multiplying each drug with QALY data with the total number of unique users.

For a second measure of the clinical value of drugs, we linked each drug to the French HAS database added medical value (ASMR) data, based on an extract of the French database for post-2000 drugs (Kyle and Williams 2017). Among the drugs from the Lanthier dataset that

[19] As described in Chambers et al (2014) the Tufts CEA Registry is a comprehensive database of 5,655 cost-utility analyses, which compiles and standardizes information from published cost-effectiveness analyses. Studies are included only if they compared the drug of study to the current standard treatment, if there was one. There is definite selection into what sorts of drugs are subject to cost-effectiveness analyses. Focusing on drugs in our sample approved since 1999 (when the Tufts data begin), overall 35 percent of the drugs appears in Tufts. While 9 percent of the first quintile of drugs (by average annual sales in Optum) appears the Tufts database, 64 percent of the top quintile does. Following Chambers et al, we exclude drugs with only industry funded studies due to concerns about bias.

were approved since 2000, slightly more than half (100 drugs) appear in the French database.

Drug ATC classes

In all of our analyses we also include controls for drug class using the ATC system, which classifies drugs according to anatomy (A), therapeutic property (T), and chemical properties (C). We obtained these data from the World Health Organization ATC/DDD Index.

V. Descriptive Statistics and Relationships Between the Drug Value Measures

Table 2 shows basic summary statistics for each of the variables in our analyses, including several measures of citations. Eliminating self-citations reduces the mean by about 6.5, or around 13 percent. The average patent in our sample has 2.7 forward citations from examiners and 13 times as many non-examiner (applicant and attorney) citations. Note that information on who added the citation is not available for 27 of our observations, because the data was not collected prior to 2001. We also find that the average patent in our sample receives 2.1 cites per year after grant. Our sample includes patents granted between 1972 and 2012 with a mean grant year of 1991. The mean drug approval year is substantially later (1999), reflecting that patents are filed (and often issued) early in the drug development process, well before FDA approval.

We use several measures of technological impact, beginning with follow-on publications. The mean number of publications related to the drugs is over 1400, with one (Rapamune) having over 15000. Another indicator of technological impact is the number of supplemental new drug applications, for which the average is 1.73. We also have a categorical measure of innovativeness, based on the Lanthier et al. expert rankings. Half of our observations fall into the "Addition to class" category from the Lanthier, et al (2013) paper rating technological impact. About 31% of the drugs are first in class (the most innovative), and 19% advance in class.

We were able to estimate revenue, our measure of private value, for 200 of the drugs in our dataset. The average is $156 million, with a great deal of variation, from approximately no revenue to over $2.8 billion. Annual revenue has a mean of $14.6 million per year, with a similar amount of variation.

Information on QALYs per user compared to the next-best alternative is only available for 76 observations, the drugs in the Tufts dataset. The mean is 0.27, but importantly the range covers both negative and substantially more positive values, from -0.43 to 4.2. This reflects the fact that some new drugs have lower average efficacy than the current standard of care. Aggregating QALYs over all users of a drug in the Optum data yields a mean of 3314 QALYs above the next-best standard of care. Finally, we report the distribution of ratings of added medical value from the French health ministry. The modal category is no incremental improvement (ASMR = 5, for 44 percent of the drugs). About 17 percent of the drugs are rated as major or important (ASMR =1 or 2), 14 percent as moderate (ASMR=3), and 25 percent as minor (ASMR=4).

Before we examine the relationship between citations and different measures of value, it is useful to determine how much internal consistency there is across our measures of value. In other words, how do the three measures of technological impact (scientific articles, supplemental applications, and the Lanthier et al ratings) vary with one another, and how do the two different clinical value measures (QALYs and the French ASMR ratings) move together?

The first three panels of Figure 1 display bivariate relationships of measures of technological impact. One observation is immediately clear from the first two panels: the Lanthier innovation categories do not have a monotonic relationship with either scientific publications or supplemental applications. In both cases, "Advance in Class" corresponds to the highest measure of the continuous variable, not "First in Class" which one might expect. The third panel is a log-log scatter plot of scientific publications and supplemental NDAs. This relationship is much closer to monotonic, although even here there is substantial variance at the high end.

The final two panels of Figure 1 show the relationship between the two clinical value measures: QALYs from the Tufts database and the French ASMR ratings. Here and in the analysis we consider two different measures based on QALYs. A first (Panel 4) is QALYs per user, i.e. what is typically reported in a cost effectiveness analysis. The second (in Panel 5) is total QALYs across all Optum users (QALYs per user times unique new users), annualized to account for the fact that older drugs have more time to generate QALYs.

In both panels 4 and 5 the QALY measure is lowest for the "none" ASMR category and highest for the "major/important" categories, as one would expect. The fourth panel indicates a monotonic relationship between QALYs and ASMR categories. This internal consistency may reflect that the French health authorities rely on the same bodies of clinical evidence as the Tufts CEA. However, the relationship between total QALYs and ASMR is more haphazard. This is not surprising, since ASMR is interested in benefits per

patient, but does highlight that the population and per patient clinical value of a drug can differ.

VI. Citations and value

Figure 2 shows the distribution of our main dependent variable, total "forward" citations to the drug patent. Since the distribution is roughly log-normal, we log-transform the dependent variable in many of the analyses below. In our preferred specifications, examining citations versus continuous measures of technological impact (supplemental approvals, publications), private value (revenues), and clinical value (total QALYs) we estimate log-log models, which provides elasticity interpretations. However, since this requires dropping observations with zero or negative values, we also estimate the relationships in levels to assess robustness.

Our first set of analyses examine the relationship between forward citations and our three measures of technological impact in turn. We begin by plotting log forward citations against the log of the number of scientific publications that cite the molecule. Figure 3 shows a binned scatterplot. The log-log plot is fairly linear indicating an exponential relationship. Table 3 shows the regression analog, including controls for patent age, patent age squared, and drug class fixed effects. Column 1 shows the elasticity is 0.289 and significantly different from zero. Column 6 reports the results of the linear regression where we find that each additional publication is associated with .0092 additional citations, which is also statistically significant. In addition to the main results in columns 1 and 6, we also investigate the impact of different types of forward citations in Columns 2-5, in logs. We next consider whether self-citations, that is citations to patents with the same original assignee, could skew the results. We find the coefficient on log publications is almost identical to that in column 1. Some previous research (Moser et al 2016; Hedge and Sampat 2012) suggests that citations inserted by examiners may have different relationships with economic value than those added by applicants. For this reason, columns 4 and 5 report only examiner and applicant cites, respectively. It is clear that the elasticity with examiner cites is substantially lower than applicant cites. Since the examiner and non-examiner citation data are available only starting in 2001, we also re-estimated the baseline model for this period alone. The overall elasticity for this period (.301) is qualitatively similar to (and statistically indistinguishable from) that from applicant citations alone (.322).

We examine the other two measures of technological impact, supplemental approvals and the Lanthier categories in Table 4 and Figures 4 and 5. A log-log regression reported in column 1 of Table 4 reveals an elasticity of almost 0.5 when NDAs are the measure of technological impact. While this elasticity is substantially higher than that for scientific

publications, a look at Figure 4 shows that the exponential fit is not particularly good, especially for drugs with higher numbers of supplemental approvals. The linear regression results (column 2) also show a strong statistically significant relationship where an additional supplemental indication is associated with almost 9 additional cites. But given the evidence in Figure 4, this is almost certainly a broad average that varies substantially over the range of supplemental approvals.

The final two columns of Table 4 show overall citations vs. the technological impact categories, and median regressions of citations vs. the impact categories. Here the conclusions depend on what specification one uses. Column 3 shows that the first and advance in class categories have a substantially larger (and statistically significant) number of citations than addition to class (the left out category). But when one accounts for the fat tail in the citation distribution by comparing the median number of citations per category (column 4) the differences go away. Figure 5 seems to differ from this finding, but this is due to the fact that just reports raw medians, without controlling for age or drug class. Taking these results together with those above, looking at correlations across different measures of technological innovation, we conclude that the two count variables (supplemental approvals and subsequent publications) have stronger relationship with forward citations.

Citations and Private Value

Next we examine the relationship between citations and revenues generated from drug sales, our measure of private value. Figure 6 shows a binned scatterplot of log citations vs. log sales, revealing a positive relationship. Table 5 shows the regression analog, here again including controls for patent age and drug class. The sample is restricted to newer drugs since the Optum sales data begins in 2000. The elasticity here is statistically significant, but substantially lower than that found for the continuous technological impact measures. Column 2 reports results from a linear regression, which indicates that an additional million dollars of sales is associated with an extra 0.0743 citations. Since sales are approximately lognormally distributed, we also perform a median regression, reported in column 3. The results are similar to the linear regression from column 2.

Citations and Clinical Value

Finally, we examined how citations relate to the two measures of clinical value, one based on QALYs and the other on the ASMR categories. The first panel of Figure 7 shows a positive relationship between log citations and log total QALYs, that is QALYs aggregated across all 2000-2014 users in Optum. The second panel of Figure 7 is a linear plot and does not aggregate across users.

Table 6 shows regression analogs. The first column shows a positive and statistically significant relationship between log cites and log total QALYs, controlling for age and drug type. Column 2 shows that in the linear specification, the coefficient is not significantly different from zero. This may be due to the fact that it includes over 50% more observations that couldn't be included in the first one because they were negative or zero. It could also indicate a complicated functional form for the relationship. Results from a median regression (column 3) are also statistically insignificant.

We next examine the relationship between mean QALY per user and citations (column 4) and find a result that is statistically insignificant (p=0.057). The median regression results in column 5 show no significant relationship between per user QALY and citations. **This suggests that perhaps the results from column 4 are driven by a handful of observations**. An examination of the upper right corner of the second panel of Figure 7 provides additional evidence in support of this notion.

Figure 8 shows median forward citations by the ASMR categories.[25] The "major/important" advance category has the most citations, but the relationship between citations and this measure of clinical value is nonmonotonic, with the "none" category having the second-most. The final two columns of Table 6 examines the relationship more formally, with log citations as the measure in column 6 and citations in column 7. After controlling for a quadratic in age and drug types, there are no significant differences in the median number of citations across ASMR categories for either specification. Taken together, there is not much evidence of a strong relationship between citations and measures of health benefits.

VII. Robustness

The analyses above show that citations are positively and significantly related to both measures of technological impact and to sales, but to only one of the two measures of clinical value. Here we report on two robustness tests.

All of our main analyses focused on the extended patent associated with the drug, under the assumption this is the main patent. We do so for simplicity and because most studies that make use of patent citations seem to implicitly begin with the assumption of a single patent per product. This may understate the number of total citations associated with a drug. In the Appendix we also perform the analysis using Orange Book patents, finding

[25] Since the top category, "major" improvement, only includes 2 drugs we combine it with the second best "important drug" category.

similar results. Specifically, using all Orange Book patents we continue to see positive and significant relationships between citations and technological impact measures and sales, with similar magnitudes as those using the extended patent alone. However, there is less evidence of a relationship between citations and clinical value.

The analyses in text used revenue data from the Optum data set. Optum is one of the most comprehensive commercially available datasets on patient claims, covering over 47 million unique patients from 2000-2014. The population is geographically diverse, spanning all 50 states. However, one should not interpret these results as a random sample from the universe of insured American patients, but as a large, diverse subset. In the Appendix we also examine robustness of our results on sales using data from the Medical Expenditure Panel Survey (MEPS), a nationally representative sample. The analyses using MEPS data also show positive and significant relationships between citations and sales (with slightly higher elasticities than with the Optum data), and that examiner citations are less responsive than other citations.

VIII. Conclusions

Measuring the value of innovation is important for evaluating a range of science and technology policies. Patent-citation based proxies for the value of innovation are commonly used in economics, but with limited direct validation. In this paper we leveraged unique administrative data from pharmaceuticals (many of which are available as an unintended result of regulations: FDA patent listing rules, Hatch-Waxman patent extension procedures, the need for CEA for reimbursement in some countries) to link patents to products and products to different measures of value.

Overall, we find positive and significant relationships between citations and technological impact measures, sales, and one of the clinical value measures. The relationship appears strongest for the technological impact measures and total QALYs, and weakest for sales and the French drug quality ratings. The basic sales results are robust to using alternative sources of sales data (MEPS). Most of the results are also robust to looking at citations to Orange Book patents, though with none of the social value measures has much of a relationship with Orange Book citations. The results provide a mixed assessment of citations, consistent with the idea that they are capturing some aspects of value but not others. The strongest result that is consistent across all analyses and robustness checks is that citations do appear to have strong relationship with technological impact.

There are a few things we can say more definitively. First, for nearly all of the value measures, the decision to include or exclude self-citations doesn't much matter. Second, in nearly all of the analyses, applicant citations have a stronger relationship with value than

examiner citations. This suggests that in most analyses removing examiner citations could improve on citation-based proxies.[26] The idea that the involvement of examiners improves the informational value of citations, a common motivation in foundational bibliometric and economic analyses, appears to be incorrect in this context.

Pharmaceutical patents are certainly not representative of all patents, and therefore it is difficult to extrapolate from the results here to patents more broadly. However, pharmaceuticals are the industry that is often pointed to as the best argument for the patent system It is the sector where patent applicants take searching for prior art most seriously. And one where patent citation based data are commonly used as indicators of value (Li et al 2017; Dranove and Meltzer 1994).

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[26] Interestingly, the overall coefficients don't change much after excluding examiner citations, even though the examiner citations coefficients are typically much smaller than those for applicant citations. This is likely because, in contrast to most other fields, the overall share of citations coming from examiners is small in pharmaceuticals.

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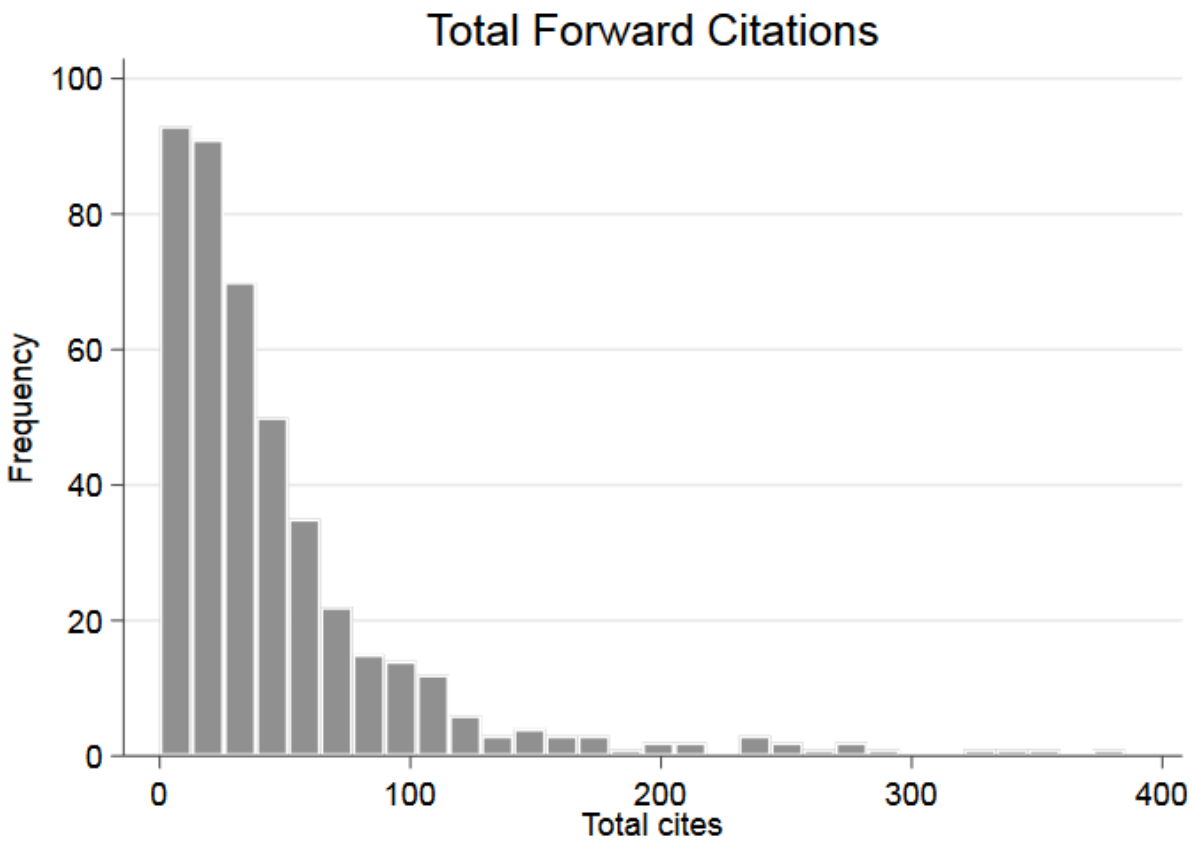
Figure 1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Frequency
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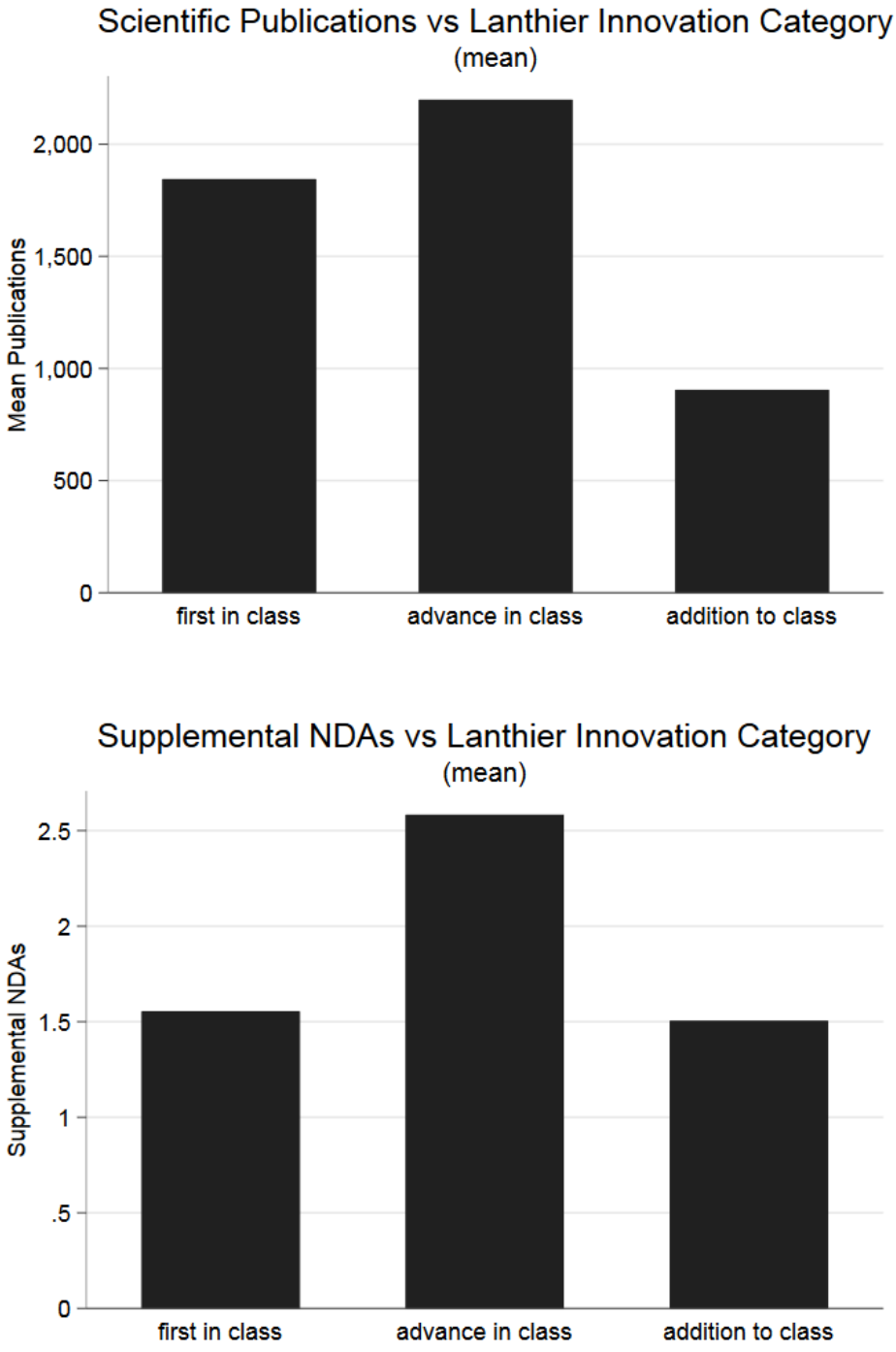
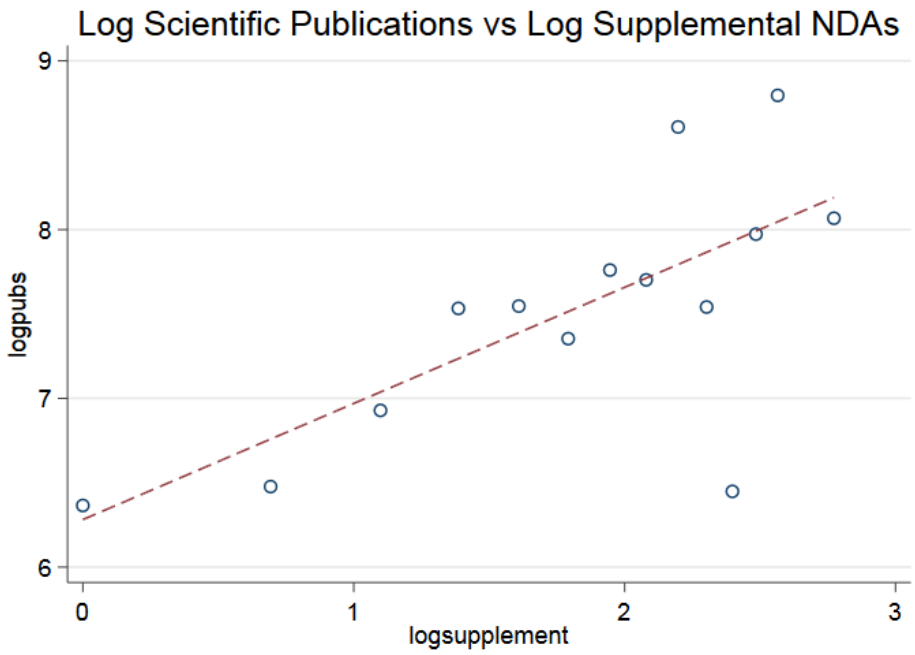
80
60
40
20
0
0
100
200
300
400
Total cites

Figure 2


Scientific Publications vs Lanthier Innovation Category
(mean)
Mean Publications
2,000
1,500
1,000
500
0
first in class
advance in class
addition to class
Supplemental NDAs vs Lanthier Innovation Category
(mean)
Supplemental NDAs
2.5
2
1.5
1
.5
0
first in class
advance in class
addition to class


Log Scientific Publications vs Log Supplemental NDAs
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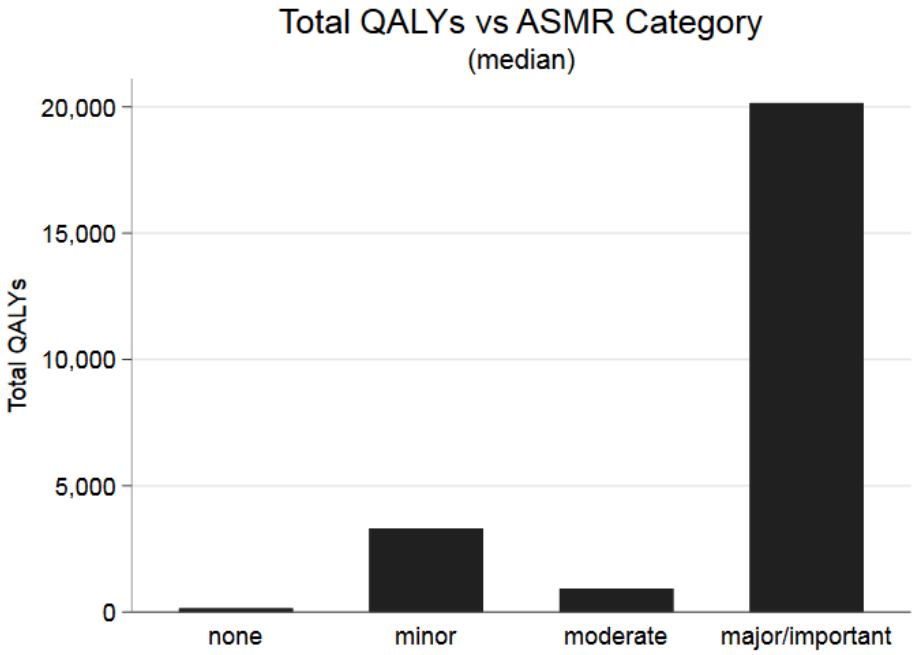
9
8
7
6
0
1
2
3
logsupplement


Total QALYs vs ASMR Category
(median)
Total QALYs
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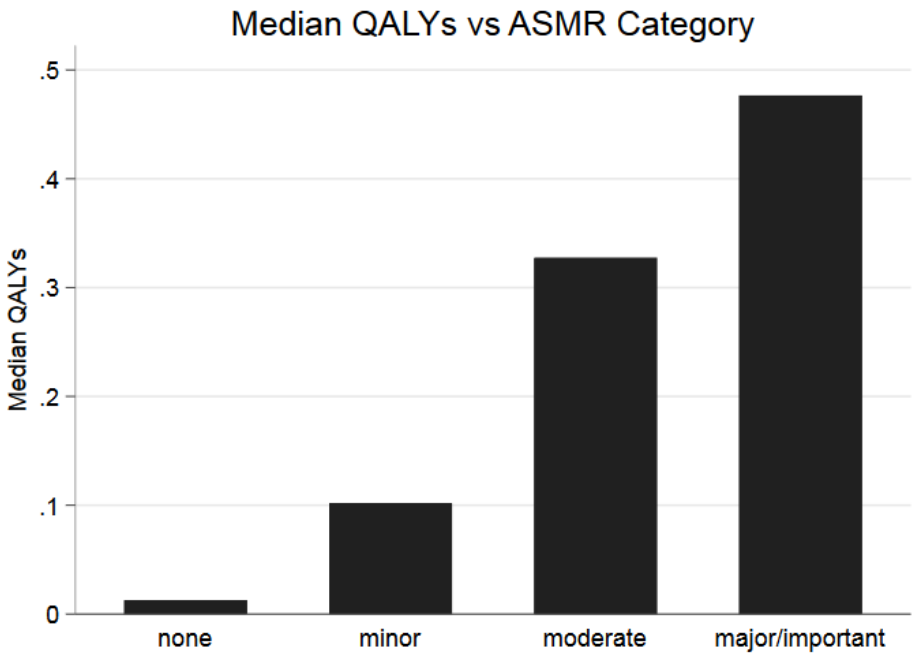
10,000
5,000
0
none
minor
moderate
major/important


Median QALYs vs ASMR Category
Median QALYs
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.3
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.1
0
none
minor
moderate
major/important

Figure 3

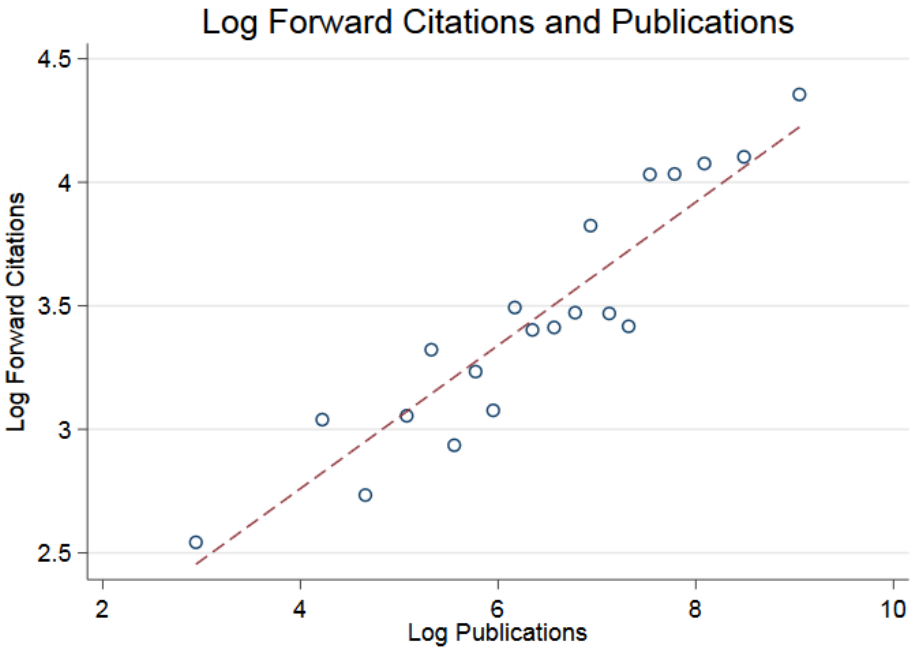


Figure 4

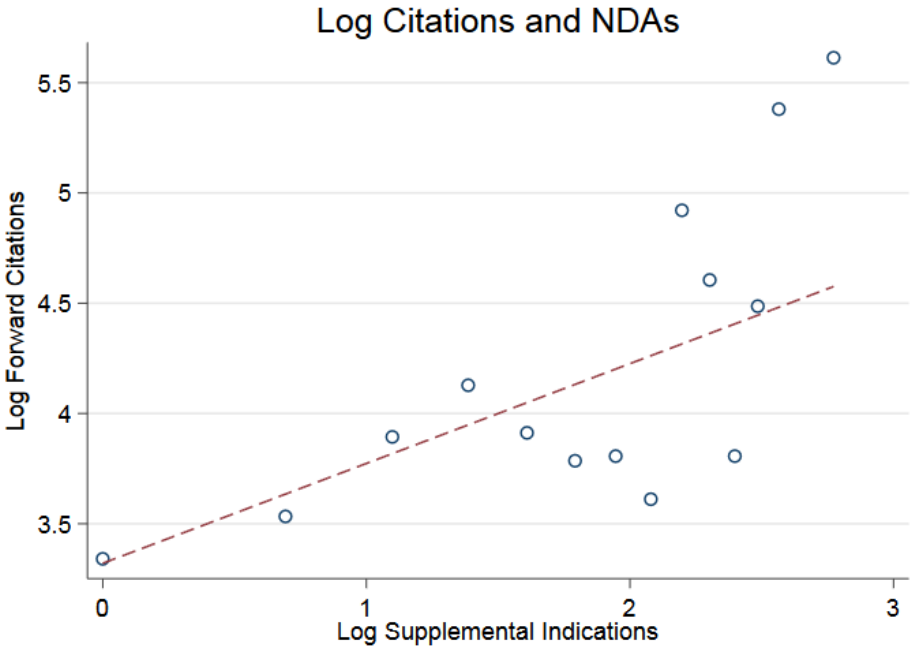


Figure 5

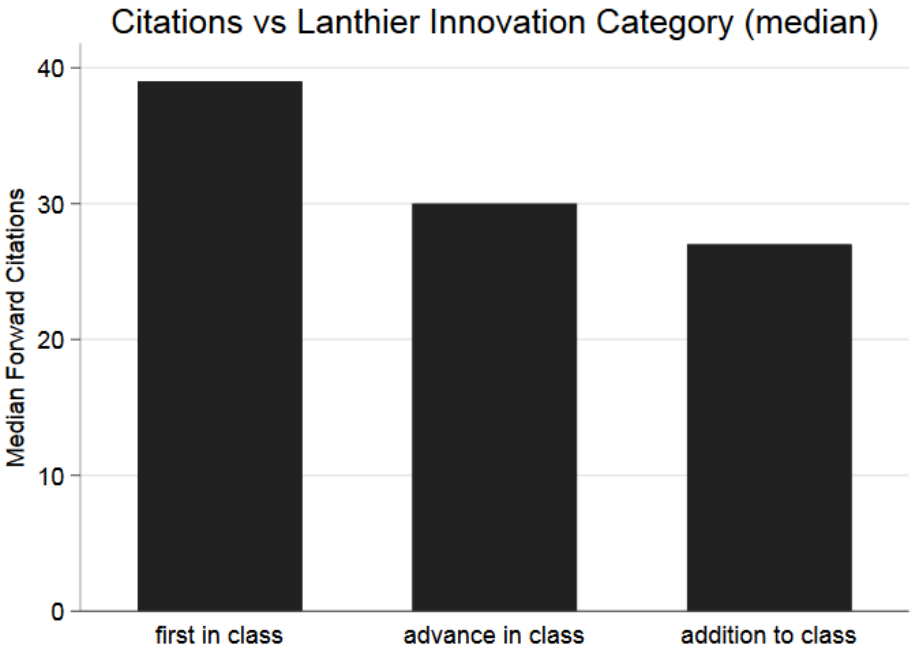


Figure 6

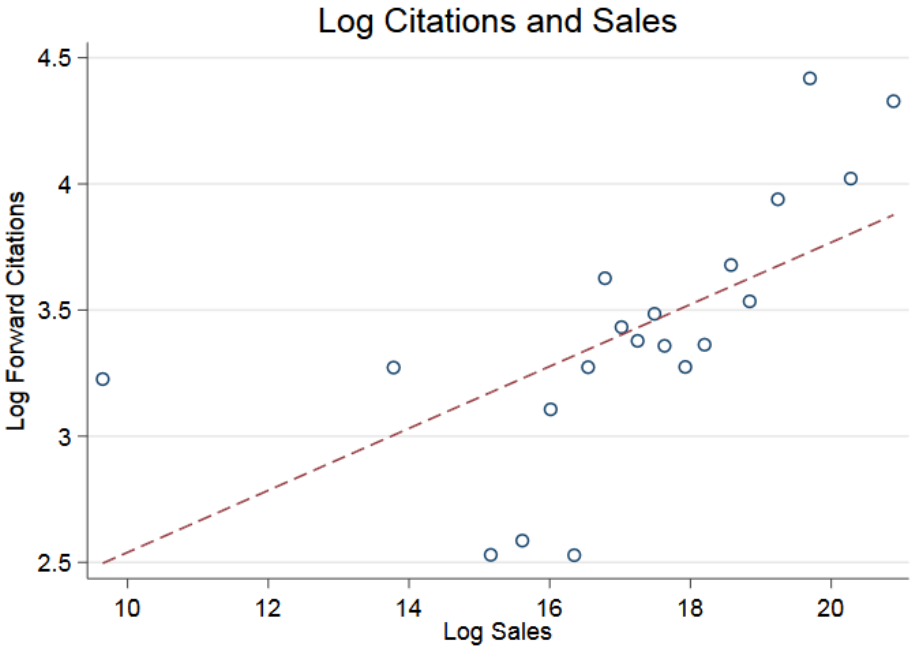


Figure 7a

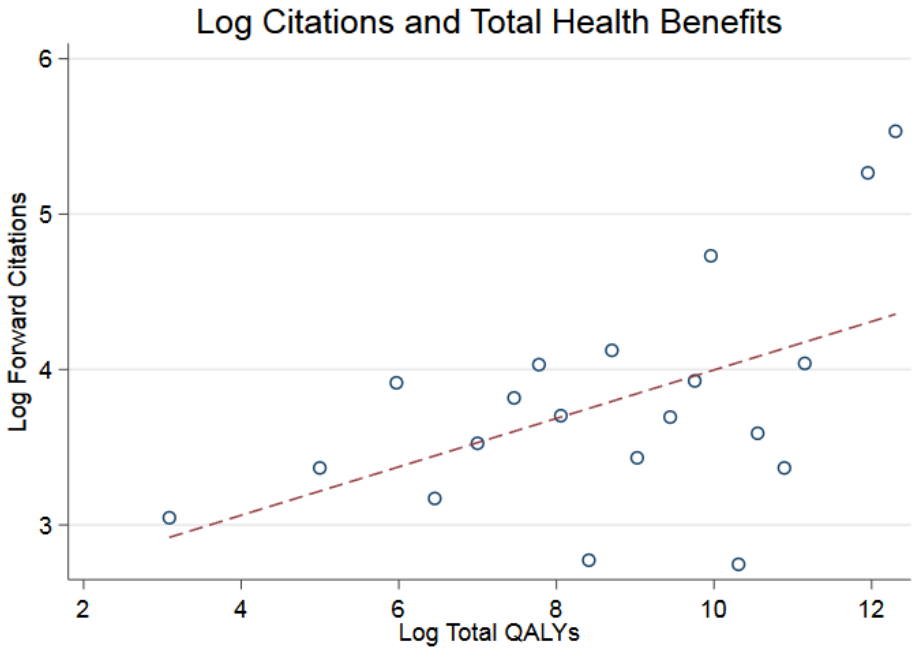


Figure 7b

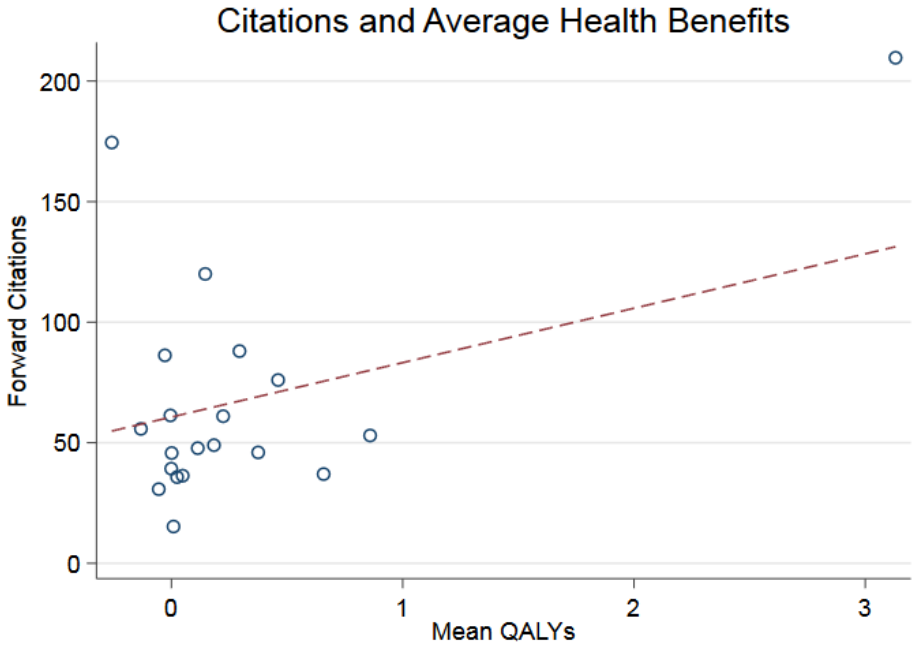


Figure 8

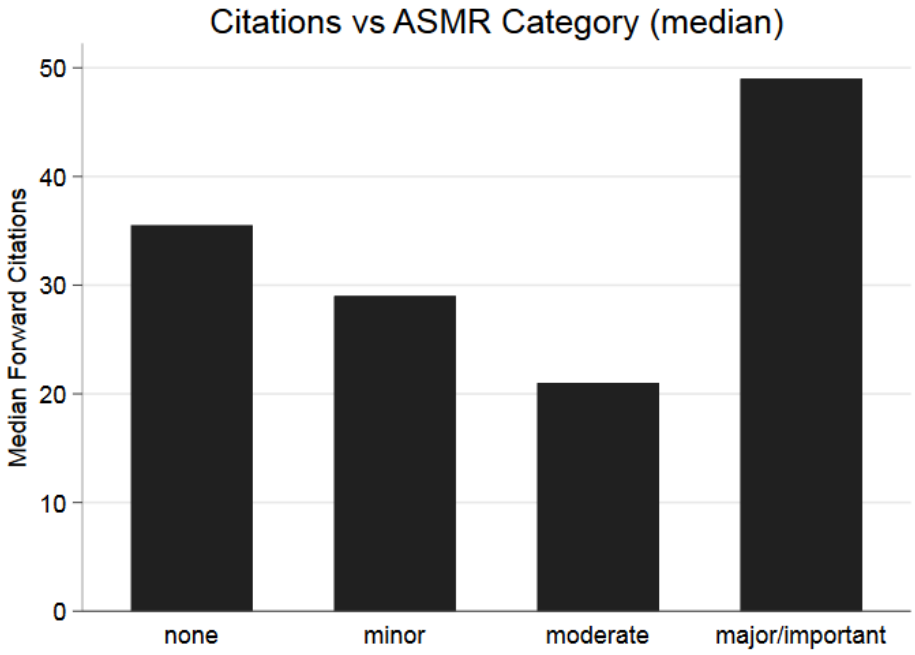

Citations vs ASMR Category (median)
Median Forward Citations
50
40
30
20
10
0
none
minor
moderate
major/important

Table 1

Name	Type of Value	Description	Key Variables	N
Optum ClinFormatics	Private Value	Administrative health claims (medical and pharmacy) for large managed care company from 2000-2014	Drug sales ($)	416
Medical Expenditure Panel Survey (MEPS)	Alternative Private Value	Nationwide survey conducted by AHRQ includes data on prescription drug use & expenditures.	Drug sales ($)	137
Tufts Cost-effectiveness Analysis (CEA) Registry	Social Value	Comprehensive database of 5,655 cost-utility analyses on wide variety of diseases & treatments	Incremental QALYs	76
Haute Autorité de Sante (HAS)	Social Value	Analyses of the absolute medical benefit (SMR) and the improvement of medical benefit (ASMR) of drugs being launched on the French market	ASMR	100
Lanthier et al. (2013) Appendix	Technological Impact	Categorization of New Molecular Entities (1987 – 2011) into innovation categories.	Innovation category: first in class, advance in class, or addition to class	642
Drugs@FDA	Technological Impact	Drug database maintained by the US Food and Drug Administration	New drug application (NDA) numbers and number of supplemental approvals	630
USPTO List of Extended Patents	Identification of key patent	Database includes patent numbers associated with patent extensions permitted by the Hatch-Waxman Act.	Extended patent number	439
Orange Book	Alternative identification of key patents	Identifies drug products approved by the FDA under the Federal Food, Drug, and Cosmetic Act and related patent and exclusivity information.	Patent number(s)	449
USPTO Patent Database	Citation and patent age data	Database from the US Patent Office (USPTO) that tracks citations between patents, including the citing/citied patent, year, self-citation and examiner-citation status. Supplemented with data from Google Full Text Patent XML files.	Patent citation counts, including total, self and examiner citation	
WHO ATC/DDD Index	Drug class controls	Database maintained and published by the World Health Organization Collaborating Centre for Drug Statistics Methodology;	Drug class as measured by ATC; DDD (defined daily dose) - a standardized measure of drug consumption	

Table 2

Summary Statistics

	Mean	Std. Dev.	Min	Max	Obs
Total Citations	49.0	57.4	0	385	439
Total Citations, excluding self	42.6	50.6	0	332	439
Total Citations, examiner only	2.7	3.6	0	30	412
Total Citations, applicant only	35.7	46.2	0	345	412
Total Citations, age-adjusted	2.1	2.7	0	22.4	439
Issue Year of Extended Patent	1991	8.1	1972	2012	439
Drug Approval Year	1999	6.8	1987	2011	439
Technological Impact					
First in class	0.31	0.46	0	1	439
Addition to class	0.50	0.50	0	1	439
Advance in class	0.19	0.39	0	1	439
N Supplemental NDAs	1.73	2.31	0	16	439
Sales, $millions	156	335	0	2822	200
Sales, $millions, age-adjusted	14.6	30.6	0.0	235.1	200
Average QALYs	0.27	0.71	-0.43	4.20	76
Annual Total Incremental QALYs	3314	16282	-18540	133292	76
Added Medical Value (ASMR)					
Major or important (ASMR = 1 or 2)	0.17	0.38	0	1	100
Moderate (ASMR = 3)	0.14	0.35	0	1	100
Minor (ASMR = 4)	0.25	0.44	0	1	100
None (ASMR = 5)	0.44	0.50	0	1	100
Value (1-5, as defined above)	3.94	1.17	1	5	100

Table 3

Citations and Scientific Publications

	Log Citations (1)	Log Citations (2001-2016) (2)	Log Citations, Excluding Self (3)	Log Citations, Examiner (4)	Log Citations, Applicant (5)	Citations (6)
Log publications	0.289**	0.301**	0.294**	0.134**	0.322**	
	(0.0334)	(0.0401)	(0.0358)	(0.0349)	(0.0436)	
Follow on publications						0.00920**
						(0.00197)
Patent Age	0.0760*	0.0452	0.0869**	0.0324	0.0543	4.236**
	(0.0315)	(0.0344)	(0.0322)	(0.0376)	(0.0459)	(1.281)
Patent Age^2	-0.00169**	-0.00176*	-0.00187**	-0.00136	-0.00195	-0.0897**
	(0.000628)	(0.000694)	(0.000637)	(0.000803)	(0.000996)	(0.0259)
ATC FE	Yes	Yes	Yes	Yes	Yes	Yes
N	417	383	415	301	379	437
R^2	0.293	0.281	0.298	0.155	0.285	0.208

Notes: Log Citations are the log of the sum of forward citations to a drug's extended patent (column 1). Column 2 is restricted to patents applied for from 2001-2016 for comparison with columns 4 and 5. Self-citations are those where the asignee of the citing patent matches that of the cited patent, which column 3 excludes. Examiner citations are those citations included by the examiner of the patent and are only observable for patents that were issued after 2000 (column 4), while applicant citations are those citations included by the patent applicant and/or attorney (column 5). Follow-on publications is a count of scientific publications on the molecule after FDA approval. The variable patent age is the number of years that have elapsed since the issue date of the extended patent and is used to control for the fact that patents have different amounts of time to accumulate citations. All specifications include Anatomical Therapeutic Chemical (ATC) category fixed effects to allow for variation by drug type. Robust standard errors are provided in parentheses.
** $p < 0.01$, * $p < 0.05$.

Table 4
Citations and Technological Impact

	Log Citations	Citations	Citations	Citations (median)
Log Supplemental NDAs	0.463**			
	(0.0790)			
Supplemental NDAs		8.969**		
		(1.268)		
Technological Impact (vs. addition to class)				
First in class			17.63*	3.229
			(7.395)	(3.437)
Advance in class			18.27*	3.582
			(7.461)	(8.014)
Patent Age	0.494***	3.275**	5.391**	3.152**
	(0.124)	(1.177)	(1.283)	(1.099)
Patent Age^2	-0.000222	-0.0574*	-0.0984**	-0.0605**
	(0.000726)	(0.0235)	(0.0253)	(0.0217)
ATC FE	Yes	Yes	Yes	Yes
N	267	439	439	439
R^2	0.235	0.223	0.123	0.060

Notes: The variable technological impact refers to the drug's degree of innovativeness and is from Lanthier et al. (2013). Robust standard errors are provided in parentheses. See main text and notes to prior tables for additional detail.
** p < 0.01, * p < 0.05

Table 5
Citations and Drug Sales

	Log Citations	Citations	Citations (median regression)
	(1)	(2)	(3)
Log sales	0.0853*		
	(0.0364)		
Sales ($MM)		0.0743**	0.0656**
		(0.0179)	(0.0247)
Patent Age	0.0631	5.887*	2.445*
	(0.0727)	(2.414)	(1.129)
Patent Age^2	-0.000942	-0.125*	-0.0411
	(0.00188)	(0.0613)	(0.0289)
ATC FE	Yes	Yes	Yes
N	188	200	200
R^2	0.224	0.356	0.152

Notes: The variable sales represents the total charges listed for prescription drug and medical claims in the Optum ClinFormatics database from 2000 through 2014. Robust standard errors are provided in parentheses. See main text and notes to prior tables for additional detail.
** $p < 0.01$, * $p < 0.05$

Table 6
Forward Citations and Health Benefits

	Log Citations	Citations	Citations (median)	Citations	Citations (median)	Log Citations	Citations
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Log Total QALY	0.177*						
	(0.0676)						
Total QALY		1.16e-05	-1.89e-05				
		(4.04e-05)	(0.000225)				
Mean QALY				35.77	-3.561		
				(18.43)	(41.92)		
ASMR Major or Important						0.0109	3.974
						(0.286)	(17.48)
ASMR Moderate						-0.164	-16.00
						(0.273)	(16.84)
ASMR Minor						-0.379	-6.006
						(0.288)	(14.08)
Patent Age	0.130	6.864	4.275	6.768	4.030	0.0974	4.886
	(0.0928)	(4.664)	(3.156)	(4.533)	(4.495)	(0.0839)	(3.318)
Patent Age^2	-0.00397	-0.149	-0.0897	-0.149	-0.0837	-0.00180	-0.0965
	(0.00242)	(0.124)	(0.106)	(0.122)	(0.130)	(0.00226)	(0.0891)
ATC FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes
N	49	76	76	76	76	97	100
R^2	0.461	0.189	0.094	0.268	0.085	0.348	0.367

Notes: The variable Total QALY aggregates per user incremental QALY estimates from Tufts data over all unique users. Mean QALY is the average incremental QALYs over the next best treatment, also from Tufts data. ASMR categories provide ratings of added medical value of a drug from French HAS database. Robust standard errors are provided in parentheses. See main text and notes to prior tables for additional detail.
** $p < 0.01$, * $p < 0.05$

Appendix 1: Robustness using MEPS sales data

In the analyses in the paper we used data from Optum to create data on sales and users for each of the drugs in the sample. The major upside of this dataset is that it includes all claims for the individuals it covers, and includes data for inpatient drugs. A drawback, however, is that it may not be nationally representative. In this appendix we examine robustness of the sales results to using another measure, national sales estimates from the Prescribed Medicines File of the Medical Expenditure Panel Survey (MEPS). Specifically we collected data on all prescriptions for each molecule using the public and restricted use MEPS files.

Since the MEPS prescription drug data are available starting in 1996, we focus on drugs from the Lanthier sample approved in 1996 or later. Overall, about 54 percent of these drugs are in MEPS. But over 85 percent of tablets and capsules are, and the vast majority of those that do not are injectable drugs, unsurprising since MEPS does not cover inpatient drugs.

Based on these drugs, we calculated the total estimated national sales for the 156 tablets and capsules in the Lanthier sample approved after 1996. Not surprisingly, for almost all drugs MEPS estimated sales are higher (since it is a nationally representative sample).

Figure A1 shows that for drugs in MEPS, total MEPS sales and total Optum sales are highly correlated:

Figure A1

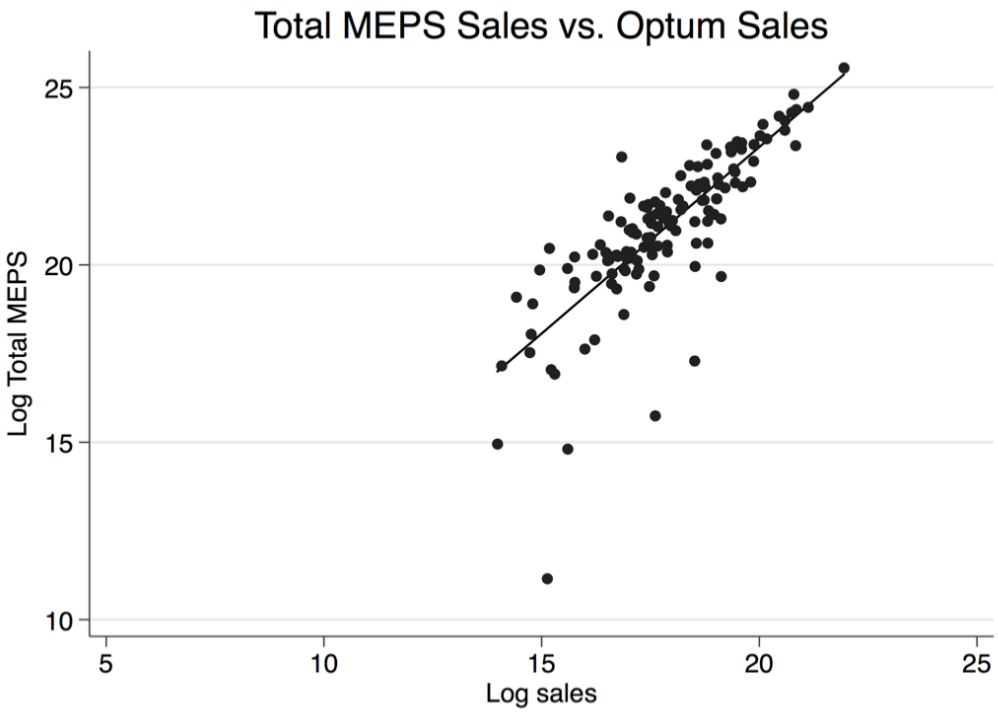
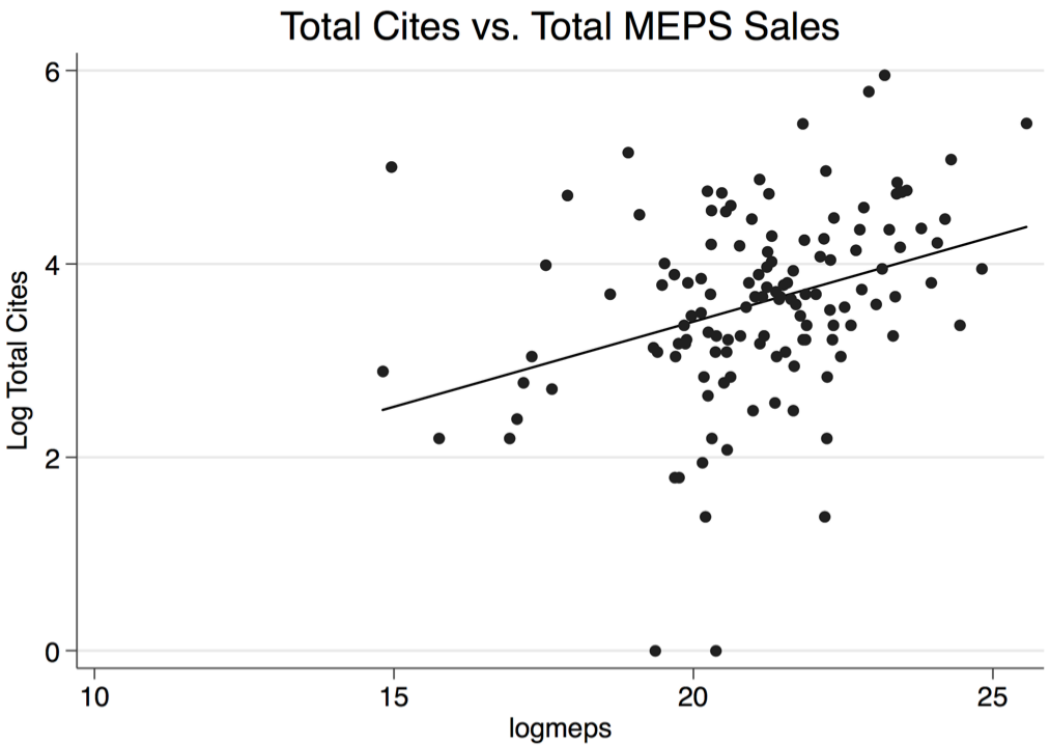

Total MEPS Sales vs. Optum Sales
Log Total MEPS
25
20
15
10
5
10
15
20
25
Log sales

Figure A2 shows the bivariate relationship between total citations to the extended patent and sales for these 156 drugs.

Figure A2



The relationship between citations and revenues is positive and significant using MEPS data, with an estimated bivariate elasticity (.18) about twice as large as what we measured using the Optum data.

We also re-ran each of the main regressions using MEPS sales, finding basic results similar to those using Optum data, though in general with larger estimated elasticities:

Table A1: **Robustness: MEPS sales**

VARIABLES	(1) Total cites	(2) Nonself cites	(3) Examiner cites	(4) Applicant cites
Log MEPS Sales	0.209***	0.192***	0.150***	0.215***
	(0.0499)	(0.0529)	(0.0518)	(0.0531)
Log patent age	0.722**	0.672***	0.0713	0.323
	(0.286)	(0.244)	(0.270)	(0.252)
Constant	-1.861	-1.467	-16.16***	-1.173
	(1.226)	(1.024)	(1.503)	(1.060)
Observations	136	136	134	134
ATC FE	YES	YES	YES	YES
Mean citations	51.99	43.82	3.284	38.83
Pseudo R2	0.333	0.317	0.113	0.293

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Appendix 2: Robustness using Orange Book citations

Throughout the paper, we focused on citations to the extended patent for each drug. Here we examine robustness of results using citations to all Orange Book patents on a drug, instead. In cases where there are multiple Orange Book patents per drug, which is typical, we focus on unique citations to all Orange Book patents on a drug.

Figure A3 shows that citations counts based on Orange Book patents and the extended patent are highly correlated:

Figure A3

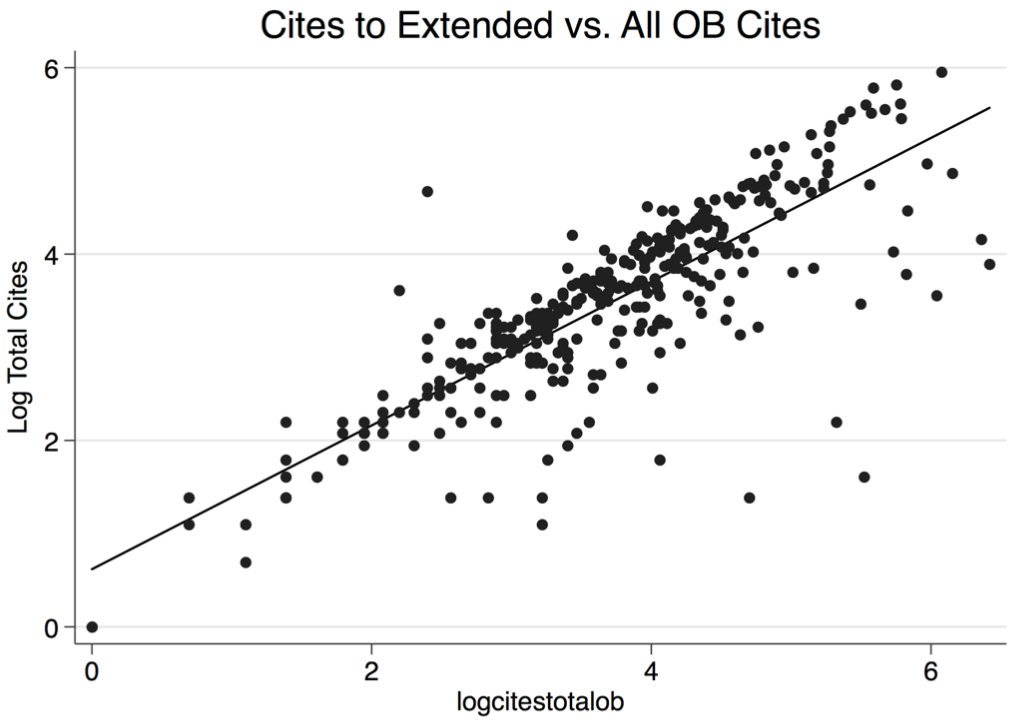
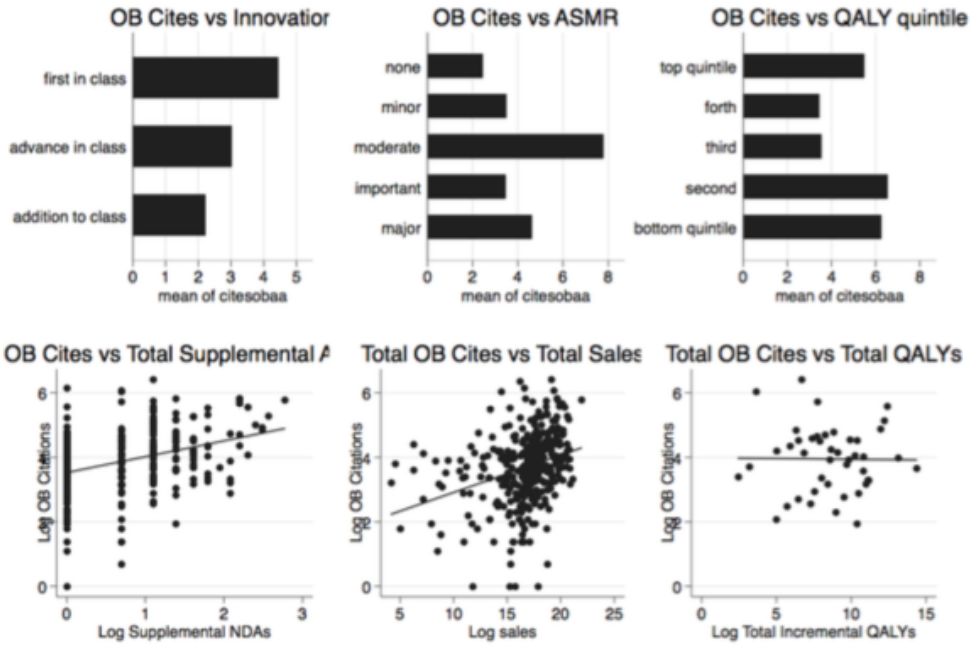


Figure A4 shows the main figures, replicated using total OB citations. Here, citations appear to be more related to private value and technological impact than the clinical value measures:

Figure A4



We also re-estimated each of the regressions where total citations was the dependent variable using total unique citations to Orange Book patents. Table A2 summarizes the results. In general we see a positive and statistically significant relationship between citations and private value, supplemental approvals, and across the innovativeness categories. But there is no obvious relationship between citations and either of the clinical value measures.