

Developing Novel Drugs*

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Abstract

We analyze firms' decisions to invest in incremental and radical innovation, focusing specifically on pharmaceutical research. We first develop a new measure of drug novelty that is based on the chemical similarity of new drug candidates to existing drugs. We show that drug candidates that we identify as ex-ante novel are riskier investments, in the sense that they are subsequently less likely to be approved by the FDA. However, conditional on approval, novel candidates are more likely to be both socially as well as privately valuable. Second, we shed light on the role of financial constraints in firms' decisions to invest in novel drug compounds. We use variation in the expansion of Medicare prescription drug coverage in the United States, which differentially benefited firms based on their drug portfolio, to isolate exogenous variation in firm cash flows. We find that firms that benefit more from the expansion of drug coverage develop more new drug candidates as a result. This increase is primarily driven by the development of more molecularly novel drug compounds.

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Innovation in health and medical care has considerable potential for improving human welfare. While investments in public health infrastructure and access to medical care were key to advancing health outcomes throughout the 20th century, pharmaceutical innovation is likely essential for future health improvements. Indeed, over the past 40 years, the greatest gains in life expectancy in developed countries have come from the development of new therapies to better treat conditions such as heart disease, cancer, and vascular disease.¹ At the same time, the expansion of new—and often incremental—drug therapies has played a large role in driving up health care costs, with critics frequently questioning the true innovativeness of expensive new treatments (Naci, Carter, and Mossialos, 2015). The success of any policy aimed at encouraging cost-effective innovation is ultimately determined by its ability to shape firm-level decisions about which drug candidates to develop; hence, understanding the economic tradeoffs involved in drug development decisions is of first-order importance.

This paper contributes to our understanding of the economic trade-offs involved in drug investment decisions along two key dimensions. First, we develop a new measure of pharmaceutical innovation based on the chemical similarity of a firm’s research pipeline to prior drug candidates. Because our metric is based on molecular properties observed at the time of a drug candidate’s initial development, it improves upon existing novelty measures by not conflating ex ante measures of novelty with ex-post measures of success (such as receiving priority FDA review) or market size (such as being the first to treat a given condition). After validating this approach, we show that novel drugs, conditional on making it to market, are more likely to be both *socially* and *privately* valuable. That said, we also find that novel drugs are substantially riskier investments in that they are less likely to receive regulatory approval; taken together, we find suggestive evidence that, from the perspective of maximizing private firm value, novel drug candidates may in fact be *less valuable* investments ex ante.

Yet, particularly in the pharmaceutical sector—where the distribution of returns for drug investments is both uncertain and highly skewed, and where private and social returns may differ—research managers within firms may base drug development decisions on additional factors other than maximizing shareholder value. In the second part of the paper, we use our measure of novelty to explore how drug development decisions respond to cashflow shocks. To do this, we use the introduction of Medicare Part D, which expanded US prescription drug coverage for the elderly, as a shock to the value of assets in place: this policy change

¹In the United States, the sharpest reductions in death rates from the period 1981 to 2001 come from heart disease. See Life Tables for the United States Social Security Area 1900-2100. https://www.ssa.gov/oact/NOTES/as120/LifeTables_Body.html See also Lichtenberg (2013), which estimates explicit mortality improvements associated with pharmaceuticals.

differentially benefited firms with more drugs targeting conditions common among the elderly, and those with sufficiently long remaining exclusivity on those drugs. Using this variation, we find that firms receiving a larger positive cash flow shock engage in more innovation; specifically, they develop not only more drugs, but also more *novel* drug candidates.

Measuring the amount of innovation in the pharmaceutical industry is challenging. Critics argue that “pharmaceutical research and development turns out mostly minor variations on existing drugs, and most new drugs are not superior on clinical measures,” making it difficult to use simple drug counts as a measure of innovation (Light and Lexchin, 2012).² To overcome this challenge, we construct a new molecular-level measure of drug novelty for small molecule drugs.³ Building upon research in modern pharmaceutical chemistry, we compute a pair-wise chemical distance (similarity) between a given drug candidate and all prior candidates in our data. This is known as a “Tanimoto score” or “Jaccard coefficient,” and it captures the extent to which two molecules share common chemical substructures. We then aggregate pairwise scores to identify the maximum similarity of a new drug candidate to all prior candidates. A novel candidate in our data is one that is molecularly distinct from previously tested candidates.

Our similarity measure has sensible properties. Pairs of drug candidates classified as more similar are more likely to perform the same function—that is, share the same indication (disease) or target-action (mechanism). Further, drugs we classify as more novel are more likely to be the first therapy of its kind. In terms of secular trends, our novelty measure indicates a decline in the innovativeness of small molecule drugs: both the number, as well as the proportion, of novel drug candidates has declined over the 1999 to 2014 period.

We next examine the tradeoffs involved with developing innovative drugs. We find that drugs we identify as more novel are *significantly less* likely to receive approval from the Food and Drug Administration (FDA). This suggests that our notion of novelty is closely related to the ex-ante riskiness of the decision to develop a ‘novel’ versus a ‘me-too’ drug. However, among approved drugs, novel drugs are *significantly more* socially and privately valuable, where social value is measured either by clinical value added or by scientific impact

²One of the more vocal critics is Marcia Angell, a former editor of the *New England Journal of Medicine*. She argues that pharmaceutical firms increasingly concentrate their research on variations of top-selling drugs already on the market, called ‘me-too’ drugs. She concludes: “There is very little innovative research in the modern pharmaceutical industry, despite its claims to the contrary.” <http://bostonreview.net/angell-big-pharma-bad-medicine>. Indeed, empirical evidence appears to be consistent with this view; Naci et al. (2015) survey a variety of studies that show a declining clinical benefit of new drugs.

³Small molecule drugs, synthesized using chemical methods, constitute over 80% of modern drug candidates (Ralf Otto, Alberto Santagostino, and Ulf Schrader, 2014). We will discuss larger drugs based on biological products in Section 3.5.

(number of citations to associated patents), and where private value is measured either by drug revenues or contribution to firm stock market value, where the latter is estimated using the methodology of [Kogan, Papanikolaou, Seru, and Stoffman \(2017\)](#). Naturally, these findings do not necessarily imply that investments in novel drug candidates have higher *ex-ante* social or private value. In fact, our point estimates suggest that this is unlikely to be the case for private value: revenue and stock market values increase more slowly with drug novelty than does riskiness, implying that more novel drugs are unlikely to have higher (private) values *ex-ante*. Naturally, this analysis is associated with several important caveats, so these conclusions should be interpreted with caution. Further, and most importantly, making a similar statement for social values is not feasible, as it is harder to attach dollar values on social returns to innovation.

Having characterized the economic tradeoffs associated with our measure of novelty, we next turn our attention to firm drug development decisions. Specifically, we examine how a firm’s research pipeline responds when faced with the capacity to develop a larger number of drugs, that is, a positive shock to cashflows. Indeed, among factors that may limit innovation in the pharmaceutical industry, financing constraints seem like a first order concern: R&D costs are high (estimated at about \$1.4 billion dollars per drug); returns are skewed and uncertain (fewer than 12% of drug candidates entering human trials ever reaching approval); and intellectual property is difficult to value or collateralize.⁴

To identify a shock to financial resources that is orthogonal to investment opportunities, we exploit the introduction of Medicare Part D (hereafter “Part D”), a program that increased drug sales to elderly Americans by expanding Medicare to include prescription drug coverage for those over 65, and led to an increase in firm profits ([Lichtenberg and Sun, 2007](#); [Friedman, 2009](#)). Part D differentially benefited firms along two pre-existing dimensions: the proportion of their drugs taken by the elderly (elderly share) and the remaining market exclusivity (patent life plus additional exclusivity granted by the FDA) on their drugs. We therefore measure firm “exposure” to Part D as the proportion of its drugs with substantial remaining exclusivity as of 2003, weighted by the proportion of its users who are elderly.

Our identification strategy allows us to disentangle the causal impact of a cashflow shock (due to increased sales of existing drugs to the elderly) from both changes in investment opportunities (firms with high elderly share may also see greater profit potential for their future

⁴Cost estimates come from [DiMasi, Grabowski, and Hansen \(2016\)](#), where we report their lower out-of-pocket estimates of drug costs rather than their higher \$2.6 billion capitalized cost figure. [Berndt, Nass, Kleinrock, and Aitken \(2015\)](#), find that post-approval volatility in new drug sales often mean that their returns are insufficient to cover their R&D costs.

products) and differences in behavior across the lifecycle of drug development (firms with greater remaining exclusivity may also have a newer vintage of drugs, and their subsequent development behavior may differ for reasons unrelated to financial constraints). Specifically, our estimation methodology compares firms with the same share of drugs sold to the elderly and the same remaining exclusivity periods across all their overall drug portfolio, and which differ only in how their remaining patent exclusivity is distributed across drugs of varying elder shares.

We find that firms receiving a larger positive cash flow shock as a result of Part D develop more new drug candidates. Importantly, this is driven by an increase in the number of chemically *novel* candidates, rather than an increase in me-too candidates. We also find some evidence that firm managers have a preference for diversification: the marginal drug candidates that firms pursue often include drugs focused on diseases and targets in which the firm has not previously worked. These new candidates are also aimed at a variety of conditions, not simply ones with a high share of elderly patients. These findings suggest that firms use marginal increases in cash to diversify their portfolios and undertake more exploratory development strategies, a fact consistent with models with financial frictions (Froot, Scharfstein, and Stein, 1993), or poorly diversified managers (Smith and Stulz, 1985). Lastly, our point estimates imply sensible returns to R&D. A one standard deviation increase in Part D exposure leads to an 11 percent increase in subsequent drug development, relative to less exposed firms. For the subset of firms for which we are able to identify cash flow, this translates into an elasticity of drug candidate development with respect of R&D expenditure of about 0.75. We obtain a higher elasticity for the most novel drugs (1.01 to 1.59) and a lower elasticity for the most similar drugs (0.02 to 0.31).⁵

The decision to invest more in novel drug candidates in response to a cash-flow shock may seem puzzling from a value-maximizing perspective, since our point estimates indicate that novel drugs are unlikely to be more valuable ex-ante than less novel drugs. Setting aside the several caveats inherent in computing ex-ante private values, it is worth emphasizing that investment decisions may be based on more variables than private valuations. For instance, project managers may value the social, scientific learning or reputational returns to developing a novel breakthrough drug, or they may simply be overconfident in their ability to bring a novel compound to market. Without additional data on managerial beliefs and preferences, disentangling between these different explanations is challenging. That said, the ability to observe the returns associated with individual projects is an important advantage of our

⁵Estimates of the elasticity of output with respect to demand, or cashflow, shocks in the literature range from 0.3 to 4. See Section 3.4 for a more detailed discussion

setting that allows us to make a distinct contribution to the literature studying the impact of financial frictions on firm investment decisions.⁶ Specifically, existing studies typically observe the response of investment (or hiring) aggregated at the level of individual firms or geographic locations. However, the fact that investments (or hiring) increase in response to cashflow shocks need not imply that firms were under-investing—from the shareholders’ perspective—while financially constrained. By contrast, our setting allows us to observe whether the *marginal* project being undertaken as a result of relaxing financial constraints is likely to be (privately) efficient. Our point estimates suggest that this is unlikely to be the case, suggesting that additional factors other than maximizing shareholder value may play a role in drug development decisions.

More broadly, our work contributes to work focusing on the measurement and determinants of innovation. Our measure of innovation is based on ex-ante information, and therefore avoids some of the pitfalls associated with patent citations (Hall, Jaffe, and Trajtenberg, 2005). Further, since our measure is based only on ex-ante data, and hence does not conflate innovation with measures of ex-post success or of market size. By contrast, existing work typically measures ‘major’ innovations using metrics based on ex-post successful outcomes, which may also be related to market size. Examples include whether a drug candidate gets FDA priority review status (Dranove, Garthwaite, and Hermosilla, 2014), or drugs with highly-cited patents (Henderson and Cockburn, 1996). A concern with these types of measures is that a firm will be credited with pursuing novel drug candidates only if these candidates succeed and not when—as is true in the vast majority of cases—they fail. Similarly outcomes such as whether a drug is first in class or is an FDA orphan drug (Dranove et al., 2014), (DiMasi and Faden, 2011; Lanthier, Miller, Nardinelli, and Woodcock, 2013; DiMasi and Paquette, 2004) may miss innovation in larger disease markets, precisely those that may benefit the greatest patient population.

Our measure of novelty can help shed light on several debates in the innovation literature. For instance, Jones (2010); Bloom, Jones, Reenen, and Webb (2017) argue for the presence of decreasing returns to innovation; our findings of declining novelty over time are consistent with this view; that said, an important caveat is that our measure cannot be computed for biologics—and biologics represent a vibrant research area. Further, our work relates to work

⁶By now, several studies have documented a causal impact of financing frictions on firm investment decisions. An incomplete list includes recent work examining the response to cashflow shocks of physical investment (Lin and Paravisini, 2013; Almeida, Campello, Laranjeira, and Weisbenner, 2011; Frydman, Hilt, and Zhou, 2015); employment decisions (Benmelech, Bergman, and Seru, 2011; Chodorow-Reich, 2014; Duygan-Bump, Levkov, and Montoriol-Garriga, 2015; Benmelech, Frydman, and Papanikolaou, 2017); and investments in R&D (see e.g. Brown, Fazzari, and Petersen, 2009; Hall and Lerner, 2010; Kerr and Nanda, 2015; Nanda and Nicholas, 2014).

which examine how regulatory policies and market conditions distort the direction of drug development efforts ([Budish, Roin, and Williams, 2015](#)); and several papers examining the impact of changes in market demand on innovation in the pharmaceutical sector ([Acemoglu and Linn, 2004](#); [Blume-Kohout and Sood, 2013](#); [Dranove et al., 2014](#)). Similar to us, [Blume-Kohout and Sood \(2013\)](#) and [Dranove et al. \(2014\)](#) exploit the impact of Medicare Part D, and find more innovation in markets that receive a greater demand shock (drugs targeted to the elderly) as a result of the passage of Part D. Even though we use the same policy shock, our work additionally exploits differences in market exclusivity (patent length) for specific drugs to isolate cash flow shocks to firms from changes in product demand due to Medicare Part D that may increase firm investment opportunities. Importantly, we find that treated firms invest in new drugs across different categories—as opposed to those that only target the elderly—strongly suggesting that our identification strategy effectively isolates cashflow shocks from improvements in investment opportunities.

1 Measuring Drug Novelty

A key contribution of our paper is to construct an ex-ante measure of drug novelty that is broadly applicable. To do so, we rely on the “Similarity Property Principle,” a key tenant of modern pharmaceutical chemistry which states that structurally similar molecules are more likely to have similar functional properties ([Johnson and Maggiora, 1990](#)). The notion of chemical similarity is widely used in the process of pharmaceutical discovery: having discovered a molecular compound with a certain desired function, drug chemists often synthesize and test chemically adjacent compounds in the hopes of finding one with improved properties (less toxic, faster acting, etc.). Our measure of drug novelty uses this same notion of chemical adjacency, but applies it historically: for a given drug candidate, we define its novelty based on how similar it is to all previously tested candidates.

We begin first describing the sources of data in [Section 1.1](#). We next describe our approach to measuring novelty in [Section 1.2](#). In [Section 1.3](#) we compare our methodology to existing approaches. [Section 1.4](#) discusses the limitations of our methodology. [Section 1.5](#) validates our novelty measure by showing that novel drugs are more likely to be the first drugs in a given disease that operate using a different mechanism (first in target class).

1.1 Data Overview

To conduct our analysis, we construct a panel dataset that tracks firm–quarter level drug development outcomes. We combine data from a number of sources. Our primary source of data is the Thomson Reuters’ Cortellis database and we use supplementary data from ChemMine Tools, the FDA, the Medical Expenditure Panel Survey (MEPS), USPTO, Compustat and [Kogan et al. \(2017\)](#).

The primary data used to construct drug output and novelty measures come from Thomson Reuters Cortellis’s Investigational Drugs database, which contains detailed development histories for over 51,623 drug candidates (as of May 2016). These data are curated by professional analysts from public records (e.g., patent filings, company press releases, financial filings, clinical trial registries, FDA submissions) and then further cleaned to assign the proper classifications (e.g., therapeutic indications and drug targets).⁷

1.2 Similarity Based on Chemical Structure

We create a measure of novelty based on the chemical structure of drug candidates. Chemical structure is one of the first things that a firm knows about a potential drug candidate and, as such, measuring novelty based on structure allows us to construct a measure of novelty defined for all candidates at the time a firm makes its investments.

The first step in constructing our measure is defining a way to compare the similarity of two molecules. To identify an appropriate approach, we look to the chemical informatics literature, where scientists have developed tools for measuring the differences between chemical structures. Many of these tools involve taking a pair of chemical structures, breaking them down into their component fragments (known as the chemical “fingerprint”) and scoring the similarity of their structural features. Chemists use these methods to help them search chemical space, build libraries for drug screening ([Wawer, Li, Gustafsdottir, Ljosa, Bodycombe, Marton, Sokolnicki, Bray, Kemp, Winchester, Taylor, Grant, Hon, Duvall, Wilson, Bittker, Dančák, Narayan, Subramanian, Winckler, Golub, Carpenter, Shamji, Schreiber, and Clemons, 2014](#)), quantify the “drug-like” properties of a compound ([Bickerton, Paolini, Besnard, Muresan, and Hopkins, 2012](#)), and expand medicinal chemistry techniques ([Maggiore, Vogt, Stumpfe, and Bajorath, 2014](#)). Most recently, ([Pye, Bertin, Lokey, Gerwick, and Lington, 2017](#)) used

⁷In our sample, we see the number of reported molecules increase sharply in the late 1990s; this increase is likely due to an improvement in the reporting of molecules. This is likely due to the Food and Drug Administration Modernization Act, passed in late 1997 and enacted in 1999, which required the reporting of clinical trials. Even though we observe some drug candidates pre-1999, we believe that our data provides fuller coverage post 1999.

chemical similarity measures to measure novelty and productivity in the discovery of natural products. The prevalence of these applications in pharmaceutical chemistry also means that tools exist to compute similarity en masse; in our calculations, we rely on ChemMine Tools, an open source program for chemical-informatics.

The most common method for creating these similarity scores is calculating the Tanimoto distance (Jaccard coefficient) between two sets of chemical fragments (Nikolova and Jaworska, 2003). The calculation returns the proportion of features shared by the two chemicals when divided by their union, yielding a score between 0 and 1. It is defined as follows:

$$T(A, B) = \frac{|A \cap B|}{|A \cup B|} = \frac{|A \cap B|}{|A| + |B| - |A \cap B|}$$

A Tanimoto distance of 0 implies that the pair of drugs have no common fragments; a score of 1 means they have the same set of atoms and bonding. However, a Tanimoto score of 1 does not necessarily mean that the two chemicals are identical because the Tanimoto score does not take into account a structure’s stereosymmetry (its orientation in space). For example, consider a classic example of a me-too drug, Nexium, and its antecedent, Prilosec. Prilosec is a “racemic mixture,” meaning that it is a mixture of two versions of the same molecule, differently oriented, whereas Nexium is comprised of only one orientation of this same molecule—despite their differing orientation, we record the pair as having a score of 1.

After calculating Tanimoto distance across all pairs of drug candidates, we define a drug’s overall similarity as its maximum similarity to prior drug candidates that have reached Phase 1 clinical trials.⁸ Figure 1 illustrates an example of how our novelty measure works, as applied to the drug class of HMG-CoA reductase inhibitors—more commonly known as “statins,” used to treat heart disease. Approved in September of 1987, Mevacor (Lovostatin) was the first statin to be approved by the FDA and it’s similarity score to prior candidates is 0.25. In October of 1991, a second statin, Pravochol (Pravastatin), was approved. Pravochol’s similarity to priority candidates is 0.61, and Mevacor was its closest prior candidates. Next, in December of 1991, a third statin was approved. As one can see from Figure 1, Zocor (Simvastatin) is quite similar to Mevacor and, indeed, its maximum similarity score is 0.82 (0.52 similarity to Pravochol and 0.82 similarity to Mevacor).

⁸We restrict the comparison set in this way to avoid mistakenly labeling a drug candidate as derivative if it was developed close to simultaneously with another candidate. See DiMasi and Faden (2011). We also define a drug’s maximum similarity to candidates in the same indication and to those developed by the same firm.

1.3 Comparison to Previous Measures

Our approach differs from previously used measures of pharmaceutical innovation, which generally fall into one of three categories: those based on the number of new candidates, their therapeutic potential, or their order of entry into a particular market. For example, [Acemoglu and Linn \(2004\)](#) examine the impact of changes in market size on the number of new molecular entities developed in particular therapeutic classes and [Blume-Kohout and Sood \(2013\)](#) examine the impact of Medicare Part D on the number of drugs entering clinical trials in therapeutic areas relevant for the elderly. [Dranove et al. \(2014\)](#) expand upon this set of outcomes and study the impact of Part D on the number of biologic drug candidates, and the number that receive FDA designations such as “Breakthrough Therapy” or “Priority Review.” Additional research in the medical literature has further focused on whether a drug is the first its in particular market or class ([DiMasi and Paquette, 2004](#); [DiMasi and Faden, 2011](#); [Lanthier et al., 2013](#)).

While these studies have expanded our understanding of how demand shapes incentives to innovate in particular markets, these measures of novelty are not ideal for use in a study that explicitly focuses on how individual firms make investment decisions. For example, the FDA Priority Review designation is assigned very late in the drug development process, just before a firm submits their final materials for ultimate drug approval. This presents two issues for our analysis: first, it cannot be applied to the early stage, pre-clinical and Phase 1 drug candidates that make up the majority of our sample; second and more importantly, because it is assigned so long after a firm decides to invest, it will label drugs as novel only if they have been successful, mis-categorizing ex ante novel projects that fail earlier in the process. Measures of novelty based on ex post outcomes need not therefore accurately measure the innovativeness of a firm’s development pipeline.

Measures of novelty based on first-in-class designations are problematic for a different reason, which is that they may conflate market size with novelty and may fail to measure novelty of candidates within a particular class. For example, it is easier to be the first candidate to treat a rare condition than a common condition because fewer firms have incentives to develop treatments for the former. As such, measures based on order of entry will tend to conflate novelty with market size. Further, they may falsely mislabel all subsequent treatments in an area as incremental, even if they are indeed novel. Because a handful of common conditions account for a great portion of disease burden, this approach will miss innovation in areas that matter to much of the population.

1.4 Caveats and Limitations

There are several important caveats to keep in mind regarding our proposed novelty measure.

First, and most importantly, there is no perfect correspondence between structural and functional similarity. Molecularly similar molecules may have divergent properties: the drug thalidomide, for instance, is comprised of two mirror image molecules, one of which is a safe sedative, the other of which causes birth defects. Conversely, chemically dissimilar compounds may have similar biological effects: Crestor and Lipitor have different structural profiles, but are often prescribed interchangeably by doctors. Despite these examples, however, chemical informatics research has shown that Tanimoto similarity measures are nonetheless useful for identifying drug qualities and novelty on average ([OHagan, Swainston, Handl, and Kell, 2015](#); [Baldi and Nasr, 2010](#); [Bickerton et al., 2012](#); [Pye et al., 2017](#)). In Section 1.5, we discuss the results of several validation exercises for our measure.

Second, we are only able to compare molecules against prior molecules in the Cortellis data. As such, our measure of maximum similarity is a lower bound for true similarity because we may be missing earlier drugs with similar properties. This is especially true for drugs with similarity scores near 0; these are disproportionately candidates for which we had few previous candidates to compare to. As such, all of our drug and firm-level analysis will be done with fixed effects for the quarter of a candidate’s earliest development date.

Lastly, our approach does not allow us to study the similarity of more complicated drug therapies whose chemical structure is more difficult to characterize. While most drugs are chemically synthesized with known structures, a growing class of new therapies, known as biologics, are based on biological products (proteins, cells, tissues, etc.) that cannot be compared with Tanimoto scores. Although biologics make up a small proportion of drug development (20%), their share of development is increasing and are often thought of to be a source of innovations in the drug industry [Ralf Otto et al. \(2014\)](#). That said, in Section 3.5 we show that increased cashflows also lead to greater development of biologics.

1.5 Validation

Before describing the characteristics of drugs we identify as novel, we first independently verify that our measure of chemical similarity captures a sense of functional similarity. Conducting this type of validation is difficult because there are no gold standard measures of functional similarity. However, we are able to conduct several intuitive checks. First, we

would expect drugs that act on the same biological target (e.g. a protein that two drugs both attempt to bind to or otherwise impact) to be more similar than drugs that do not. Similarly, though perhaps less crucially, we would expect drugs sharing the same indication (e.g. a medical condition both are designed to treat) to be more similar than those with different indications. Appendix Table A.3 reports regressions of pairwise similarity scores on indicator variables for a given pair of drugs sharing the same biological target or the same disease indication.⁹ The coefficients indicate that sharing the same target-action more than doubles pairwise molecular similarity while sharing the same indication increases this by over 25%.

Another intuitive criterion is that drugs that are labeled more novel should be more likely to be the first in their target class. The binned scatterplot presented in Figure 3 shows that this is the case: there is a strong negative relationship between a drug’s chemical similarity score and its likelihood of being the first drug candidate for a given target. Comparing two drugs treating the same indication, entering development in the same quarter, we find that a one standard deviation increase in similarity decreases a drug’s chances of being the first in its target by 42%. Appendix Table A.4 shows that these results are robust to a variety of other definitions and controls.

2 Novelty Descriptives

Having constructed our measure of drug novelty, we next explore the economic features of novelty.¹⁰ We begin in Section 2.1 by providing some basic descriptives regarding our measure, as well as some time series patterns. Next, Section 2.2 examines the relationship between novelty and project risk, using a candidate’s likelihood of FDA approval as a measure of its riskiness. In Section 2.3 we examine the correlation between drug novelty and measures of social value, as proxied by drug effectiveness and patent citations. Since firm decisions are also likely to be guided by private values, Section 2.4 explores the relationship between novelty and drug revenues and stock market valuations.

Together, this analysis will show that novel drugs are riskier investments that are less likely to be approved by the FDA, but if approved, they are more likely to be both socially as well as privately valuable. Having established this, Section 2.5 explores the ex-ante value of drug novelty.

⁹There are almost 1 billion such pairs because each drug may be act on more than one target or be used for more than one indication. We construct pairs for every possible combination.

¹⁰ Many of the results in this section are based on our full set of candidate molecules, including those associated with firms that are not in our primary cash flow analysis. All of these results, however, are robust to restricting to that subset.

2.1 Descriptive Facts

Figure 2 Panel A and Table 1 show the distribution of our similarity metric, maximum Tanimoto distance from prior candidates. Approximately 10% of our sample candidates share the same structure as a prior candidate that has also entered development. These include molecules that are stereoisomers, meaning that they differ only in orientation, as well as combination therapies that involve multiple compounds that were previously developed as separate therapies.

Figure 2 Panel B shows that the novelty of drug candidates has declined over time. This can be seen by both the increase in the average similarity of new drug candidates with existing drugs (Panel B) as well as by the increase in the fraction of new drug candidates that are very similar to prior candidates in Panel C, those with maximum Tanimoto scores of over 0.9. Going forward, we refer to such candidates as can be ‘me-too’ drugs because they represent only a small modification from existing drugs. This secular decline in drug novelty is consistent with the view that the average level of innovativeness in the pharmaceutical sector has declined over time (Light and Lexchin, 2012; Naci et al., 2015) and is also consistent with the presence of decreasing returns to scale (Jones, 2010; Bloom et al., 2017).

Table 1 provides further descriptives related to our candidate compounds, as well as for the subset of compounds that are associated with our sample firms, that is, those for which we can calculate a measure of exposure to Medicare Part D (to be discussed in Section 3.1).

2.2 Drug Novelty and Likelihood of FDA approval

Next, we find that chemically novel drugs represent a substantially riskier investment, relative to less novel drugs, as we can see in Panel A of Figure 4 and column (1) of Table 3. In particular, novel drugs are significantly less likely to be approved by the FDA: controlling again for quarter and disease (ICD-9 indication) fixed effects, a one standard deviation increase in drug novelty is associated with a 30% decrease in the likelihood that it is approved by the FDA. In the Online Appendix, Figure A.2 and Table A.5 show that this negative relationship between novelty and approval persists throughout the development pipeline, though the magnitude of the association attenuates. Conditional on reaching Phase 1 or Phase 2, a one standard deviation increase in similarity is associated with a 20% decrease in the likelihood of ultimate approval; conditional on reaching Phase 3, a one standard deviation increase in similarity increases the likelihood of approval by 8%.

2.3 Drug Novelty and Measures of Social Value

So far, we find that more novel drugs represent a riskier investment on the part of the firm, since they are less likely to be approved by the FDA. We next examine whether there is any value to a drug being ex-ante novel. We begin our analysis by focusing on measures of social value, measured either by the drug’s effectiveness, or by the number of citations the patent receives.

Drug Novelty and Effectiveness

We begin by examining how (ex-ante) drug novelty correlates with measures of drug quality or effectiveness. To do so, we use the data from the French Haute Autorité de Santé (HAS) health system, which assigns scores based on their clinical added benefits. These value-added (Amélioration du Service Medical Rendu, or ASMR) scores range from one to five (I to V), with V indicating no value added, while I indicates the highest improvement relative to existing drugs. Following [Kyle and Williams \(2017\)](#) we can separate the ASMR values into low importance (IV/V) and high importance (I/II/III).

We merge our drug-level data using both established drug naming conventions and manual matching.¹¹ The ASMR scores are assigned only to approved drugs that are available for reimbursement from the French Government health system. After limiting our attention the first approved indication for drugs covered in both data sets, and for which we can compute novelty scores, we are left with 385 drugs.¹²

Panel B of Figure 4 and column (2) of Table 3 document the correlation between our novelty measure and the drug’s ASMR score; these correlations are robust to controlling for the age of the drug, as measured by the launch year, and indication fixed effects. See Appendix Table A.6 for additional specifications. Comparing drugs of the same age, that are treating the same indication, a one-standard deviation increase in novelty is associated with a 8 percentage points increase in the likelihood that a drug is classified as adding any value ($ASMR < V$), and a 4 percentage point increase in the likelihood that it is classified as high importance ($ASMR < IV$). These magnitudes are substantial, given that the baseline

¹¹ Specifically, we first merge the Cortellis drugs to HAS drug identifiers (CIP7 codes) using the Anatomical Therapeutic Chemical (ATC) drug codes associated with the CIP7 codes in the French HAS. Next we use the HAS product names to merge to Cortellis drug names. We include exact name matches and manually reviewed the results of a “fuzzy” name matching algorithm to identify additional matches. Finally, we limited the matched set to a drug’s earliest entry in the HAS data.

¹²In total, our data from Cortellis contains roughly 1,000 small molecule drugs that achieved regulatory approval in the period of the French data coverage (2008–2013). We only match 385 to the French data due to conservative name matching (with language differences) and because not all drugs achieve regulatory approval in the European Union at the same time as they reach the market in other countries.

probability that a drug falls into these categories is 20% and 9%, respectively. These results suggest that drugs that are more novel are also more likely to have greater clinical value added, and are therefore more socially valuable.

Drug Novelty and Patent Citations

Another way to assess the value of drug novelty is to examine measures of the scientific value of the drug candidate. We do so by exploiting the link between drug candidates and patents, using a crosswalk from drugs to patents provided by Cortellis. Since a drug may be associated with multiple patents, our analysis is at the drug-indication-patent level. To focus on the main patents, we restrict our attention to patents that are filed prior to the FDA approval. The merged dataset has 3,842 observations. The Online Appendix contains additional on the match between drug candidates and patents.

Panel C of Figure 4 and column (3) of Table 3 examine the correlation between the logarithm of one plus the number of forward citations and our measure of novelty. To minimize the likelihood that this correlation is not driven by variation in unobservables, we saturate our specifications with a battery of controls and fixed effects. Specifically, we include controls for: the year the patent is granted; the indication (ICD9) treated by the drug; company and drug age (year of development) fixed effects. Appendix Table A.7 examines how the choice of controls impacts our results.

The correlation between our measure is both statistically and economically significant. Focusing on the most conservative specification, column (3) of Table 3 shows that a one-standard deviation increase in drug novelty is associated with a increase of 0.37 in the dependent variable; evaluated at the median number of citations a drug-related patent receives, this estimate implies an increase from 23 to 32 citations, given that forward citations have a standard deviation equal to 38.

2.4 Drug Novelty and Measures of Private Value

So far, we have established that novel drugs are riskier, but if approved, they are more likely to be socially valuable. Firm investment decisions are, however, likely to be guided by considerations about private rather than social values. Next, we examine the relation between chemical novelty and revenue generated by successful drug candidates. To obtain additional measures of private value, we also consider the market value of drugs as measured both by stock market reactions when the drug is approved, and stock market reactions when its component patents are issued (Kogan et al., 2017).

Drug Novelty and Revenues

We begin by examining the correlation between novelty and drug revenue conditional on FDA approval. We obtain data on drug revenue using expenditures reported in the Medicare Expenditure Panel Survey (MEPS)—see the Online Appendix B for further details.

Panel D of Figure 4 and column (4) of Table 3 show that, once approved chemically novel drugs generate more revenue for the firm than less novel drugs. This correlation is robust to controlling for drug age and indication, as well as year of measurement and company effects. The magnitudes are sizeable; a one standard deviation increase in novelty is associated with an increase in annual revenue of approximately 0.17 to 0.23 log points across the different specifications in Appendix Table A.8.

As a measure of private value, drug revenue has an obvious short-coming: it ignores the costs of production. Hence, we next turn to additional measures of private value that exploit information contained in stock market valuations.

Based on Market Reactions to FDA approvals

Here, we exploit the information contained in the stock market reaction to news about the drug’s success—that is, obtaining FDA approval. To obtain an estimate of the drug’s private value, we closely follow the methodology of Kogan et al. (2017) and refer the reader to that paper for more details. We focus on the firm’s idiosyncratic return defined as the firm’s return minus the return on the market portfolio, for up to 5 trading days following FDA approval. This window provides time for the market to incorporate this information, while also reducing the possibility that this return also incorporates unrelated events. Nevertheless, we do allow for the possibility that this return window also incorporates stock price movements that are unrelated to the value of the approved drug.¹³ We focus our attention on the first approval date for each drug. After restricting the sample to drugs with similarity scores that we can match to the CRSP dataset, we are left with 462 announcement days.

Panel E of Figure 4 and column (5) of Table 3 show that firms experience a higher stock market reaction upon the approval of more novel drugs, relative to the approval of less

¹³Specifically, we closely follow Kogan et al. (2017) and assume that the cumulative return of the firm in that 5-day window equals $R_j = v_j + \varepsilon_j$, where $v_j \sim N^+(0, \sigma_v^2)$ denotes the value of drug j – as a fraction of the firm’s market capitalization – and $\varepsilon_j \sim N(0, \sigma_\varepsilon^2)$ denotes the component of the firm’s stock return that is unrelated to the patent. To calibrate the noise-to-signal ratio $\sigma_v^2/\sigma_\varepsilon^2$ we compare the return volatility of the firm on days with drug approvals to days without drug approvals. Since the distribution of v_j is likely to depend on the drug’s novelty, we estimate the signal-to-noise ratio separately across drug novelty categories. We find that, on days in which drugs are approved, the variance of returns is approximately 11–36% larger, depending on their novelty. Our final estimate of the value of drug j is then equal to $E[v_j|r_j] M_j$, where M_j is the firm’s stock market capitalization at the end of the day prior to the FDA approval.

novel ones. This correlation is robust to controlling for year and firm fixed effects, firm size (market capitalization) and indication (ICD9). As before, we focus on our most saturated specification—which corresponds to the last column of Appendix Table A.9. In terms of magnitudes, a one standard deviation increase in novelty is associated with a 14% larger stock price increase. Panel E of Figure 4 shows the associated scatter plot (with all controls); we see that this relation appears to be monotonic across the full distribution of drug similarity.

When interpreting this magnitude, an important caveat is in order. Specifically, one interpretation of these results is that drugs that are more novel are also more likely to be (privately) valuable. Another possibility is that novel drugs are less likely to be approved by the FDA, hence the market price of the firm appreciates more upon approval. Both of these possibilities are consistent with the findings in Section 2.2. We therefore use estimates from Table A.5, regarding the relationship between novelty and FDA approval, to adjust for potential differences in approval likelihoods. Specifically, suppose that the ex-ante likelihood of FDA approval is q . Following the approval of the drug by the FDA, the value of the firm should increase by $\Delta V = (1 - q) \xi_j$, where ξ_j is the private value of the drug (in dollars). Using the point estimates from the last column in Table A.5, a one-standard deviation increase in novelty is associated with approximately a 10% increase in the likelihood of an unsuccessful FDA application, which accounts for approximately half of the associated 14% larger stock price increase. We therefore conclude that, a one-standard deviation increase in novelty is likely associated with a $14 - 10 = 4\%$ higher market value for the approved drug.

Based on market value estimates of associated patents

As further evidence that novel drugs are more privately valuable, we also examine the correlation between novelty and measures of patent values for the patents associated with each drug obtained through the methodology of Kogan et al. (2017). Since their measure is only available for publicly traded firms, we restrict attention to successful patent applications to publicly listed US companies that appear in CRSP. This leaves us with 1,812 observations, from 83 firms and 203 drugs.

Panel F of Figure 4 and column (6) of Table 3 summarize the correlation between our drug novelty score and the estimated value of related patents. As above, we focusing on the most saturated specification, which corresponds to the last column of Appendix Table A.10. The economic magnitude are substantial: a one-standard deviation increase in novelty is associated with approximately a 9% increase in the (estimated) value of associated patents, as measured by the change in the firm’s market capitalization subsequent to patent issue

days. This estimate includes controls for: the year the patent is granted; the indication (ICD9) treated by the drug; the firm’s market capitalization on the day prior to the patent grant (to ensure that we are not simply capturing differences in firm size); the year the drug is developed; the firm’s volatility (since the patent value estimate involves a nonlinear transformation of the stock return); and company fixed effects.

To the extent that patent applications associated with novel drugs are also less likely to be successful, this increase represents an upper bound on the relationship between drug novelty and the value of its underlying patents, for the same reasons discussed in the last paragraph of the previous section. Nevertheless, the fact that this estimate is comparable in magnitude to that obtained in the previous sections is suggestive that we are capturing an underlying correlation with private values, as opposed to merely variation in the likelihood of a successful patent application.

2.5 The Value of Drug Novelty

So far, we have documented that novel drugs are more likely to be both privately as well as socially valuable, conditional on FDA approval. At the same time, however, they are riskier investments less likely to receive this approval. To assess whether novel drugs have higher expected value *ex ante*, we first denote the log expected (net) payoff from investing in a novel drug by,

$$\log E[V] = \log p(\text{Approval}) + \log (E[V|\text{Approval}]) . \quad (1)$$

Here, we implicitly assume that the value of an unsuccessful (non-FDA approved) drug is zero.

Our point estimates in Section 2.2 imply that a one-standard deviation increase drug novelty is associated with a 5.2 percentage point reduction in the likelihood of approval at the time the drug enters the development phase. Focusing on drugs developed prior to 2002—given that 95% of successful drugs have had development cycles of 13 years or less—we see that the baseline probability that a drug at any stage of development obtains FDA approval is 15.2%. Hence a one-standard deviation increase in novelty lowers the first term in (1) by approximately 34%. By contrast, our estimates of the response of the average value on approval—the response of the second term in (1)—are substantially smaller; they range from 17–23% when we focus on revenues to 4–9% when we focus on stock market reactions

(Section 2.4). As a result, it is hard to make the case that the ex-ante value to shareholders is increasing in drug novelty.

Any discussion of the returns to investing in novelty is incomplete without comparing the development costs of novel versus me-too drugs. In general, assessing the costs of development is difficult because we do not have access to internal investment data and, furthermore, a large part of R&D spending is on scientific staff, who then work on multiple projects. A noisy proxy for development costs, however, are the number of patients enrolled in clinical trials and the number of trials associated with drugs: because trials are so expensive, recruiting patients and running trials constitutes a substantial proportion of a drug’s development cost. In Table A.1 and Figure A.10 in the Appendix, we consider how the number of patients and number of trials associated to a compound vary by its chemical novelty. In sum, we find no consistent relationship between these proxies of development cost and drug novelty. The left hand side panels of Figure A.10, for instance, plot bin scatters of the relationship between drug novelty and number of patients or trials for our full set of drug candidates. We find no relationship between novelty and the number of enrolled patients across all trials. We find a weakly negative relationship between similarity and the total number of trials; however, these appear to be driven by the set of drug candidates with similarity scores of exactly 1, which may include extended release formulations that should require fewer additional trials. Restricting to the set of candidates with similarity strictly less than 1, we find, if anything, that more similar drugs are more expensive, though the relation is not statistically significant.

Naturally, this analysis comes with important caveats. First, this calculation ignores standard errors. Given that some of our estimates—for instance the correlation with drug revenues—are not always very precisely estimated, we cannot rule out the possibility that the expected value to shareholders increases with novelty; that said, this possibility seems unlikely. Second, we have implicitly assumed that the relation between novelty and (log) private values is linear; given that drug revenues are highly skewed, there may be disproportionately higher returns to developing breakthrough drugs, which our analysis need not adequately capture. Third, we cannot say whether novel drugs are more *socially* efficient, since we cannot attach a dollar figure to the drug effectiveness or citation results of Section 2.3. Further, we have assumed that the value of drugs that will not be approved by the FDA is zero; this may not be a good assumption if firms (and key talent) gain expertise from failure and will lead to a downward bias in our estimate of the private return to drug novelty. Last, this calculation implicitly assumes that the likelihood that a drug candidate is successful is purely idiosyncratic. This however need not be the case; if there is some correlation in the likelihood

of success rate among candidate drugs, it is possible that novel candidates have less correlated risk than me-too drugs.

3 The Effect of Cashflow Shocks on the Development of Novel Drugs

So far, we have established a new measure of drug novelty and have documented that, among approved drugs, novelty is positively related to several measures of social and private value. However, we also show that novel drug candidates are riskier in the sense that they are less likely to be approved by the FDA; in fact, our estimates suggest that novel drugs may be ex ante less valuable to firms, although this analysis comes with numerous caveats.

In this section, we shift focus on the firms' decisions to invest in novel drug candidates. An interesting fact in our data is that more experienced firms are more likely to undertake the development and testing of novel compounds. In particular, the top panel of Appendix Figure A.9 shows that a one standard deviation increase in drug novelty is associated with approximately a 20% increase in the previous experience—as measured by number of past candidates in development—of the firm associated with the drug.¹⁴

The fact that firm size or experience is correlated with the likelihood to develop novel drugs is suggestive that financial constraints may play a role in constraining investments in novelty (regardless of whether such investments maximize shareholder value). The remainder of this section explores this idea more fully by exploiting a shock to firm cashflows to examine the novelty of a firm's marginal drug investments. In particular, Section 3.1 describes our identification strategy, in which we use the introduction of Medicare Part D—interacted with the remaining exclusivity firms had over affected drugs—as a shock to the firms' financial resources. Section 3.2 presents our main results documenting an impact of increase in cashflow (in response to Part D) on the number and novelty of new drug candidates. In Section 3.3 we further examine the types of new drugs that firms develop in response to a cashflow

¹⁴Appendix Table A.11 shows results from additional specifications. This correlation does not appear to be driven by acquisitions of novel drugs by large firms. Indeed, a popular view is that smaller firms do cutting edge research in the hopes of being acquired by larger firms, who then follow through with clinical trials and development. The data are not fully consistent with this view: as we see in the bottom panel of Appendix Figure A.9, we find the same relation between drug novelty and firm experience when we match candidates with their originating firms. However, we note that this is not necessarily conclusive: because reporting for drugs in preclinical discovery stages is not mandated, we may miss early stage acquisitions made before a drug candidate enters our data.

shock. Section 3.4 interprets and discusses the magnitudes of our findings. Section 3.5 briefly discusses robustness checks on our main results.

3.1 Empirical Strategy

Here, we describe our identification strategy, which is based on the introduction of Medicare Part D. The Medicare Modernization Act expanded insurance for elderly Americans to include coverage for prescription drugs taken at home. This Act was passed in 2003 and implemented in 2006. Previous work has shown that it lead to an increase in drug sales, for some drugs, a decrease in price, and an overall increase in the value of the firms that market these drugs (Duggan and Scott Morton, 2010; Lichtenberg and Sun, 2007; Friedman, 2009).

The extent to which a firm benefits from the introduction of Part D depends on two factors: the types of drugs that the firm sells and the amount of market exclusivity remaining on those drugs. Our empirical strategy makes use of both these sources of variation, and therefore allows us to isolate shocks to the firm’s cashflows from an improvement in their investment opportunities—an increase in demand for new drugs to the elderly. We now discuss each source of variation.

First, the extent to which a firm receives increased expected cash flows depends on the share of its customers that are in the Medicare population. A firm that with only drugs for pediatric conditions should not expect to see an increase in sales except possibly through secondary factors such as wealth effects. By contrast, a firm with drugs for osteoporosis would expect an increase in sales because Part D ensures that its potential customers will now be reimbursed for their purchase of its products. Following previous work (Blume-Kohout and Sood, 2013; Duggan and Scott Morton, 2010; Dranove et al., 2014), we use the notion of a “Medicare Market Share” (MMS) to quantify a drug’s exposure to the Part D policy shock, which is a function of the fraction of sales to elderly customers. Throughout the paper, we use the terms MMS and elderly share interchangeably. To construct drug MMS, we match approved drugs in our primary Cortellis dataset to the Medical Expenditure Panel Survey (MEPS), which contains drug-level information on sales, by patient demographics. The Online Appendix describes the matching process. For most matched drugs, we define its drug-specific MMS as of 2003 as the share of revenues generated by patients over 65 in that year. We then define a firm-level Medicare exposure by aggregating these drug-specific MMS values. This is used to construct a key variable, Firm $\text{MMS}_{f,2003}$, which is the firm-average of drug level MMS, as of 2003, just prior to the introduction of Part D.

Second, the extent to which a firm receives increased expected cash flows as a result of Part D also depends on the amount of market exclusivity remaining on its current drug portfolio. Firms whose drugs have longer remaining exclusivity at the time of Part D would expect greater increased future cash flow because of their longer horizon for charging monopoly prices. To determine remaining exclusivity for each firm’s drugs, we match drugs approved prior to 2004 to their associated patents and, where possible, link the drugs to their key patent expiration dates and FDA exclusivity extensions, relative to the base year 2003.¹⁵¹⁶ We then aggregate these drug-level measures to the firm level by defining a firm’s overall drug life, Overall Drug Life_{*f*,2003}, as the proportion of its approved drugs with long remaining exclusivity as of 2003. In our baseline results we choose $X = 5$ years as a cutoff because it is close to the median remaining life in our sample; however, our results are robust to alternative cutoffs, as discussed in Appendix Table A.21.¹⁷

Relying on either source of variation alone does not identify the impact of expected cash flow. Firms with high MMS may change their investment behavior following Part D for two reasons: first, because they may expect greater cashflow due to increased demand for their existing drugs (this is the effect we would like to identify), and second, because they may also experience an increase in their investment opportunities—that is, an increased demand for new drugs in the areas in which they have more R&D experience. Indeed, previous work has employed a similar strategy—constructing an MMS aggregated to the level of a therapeutic market—in order to study the role of demand in stimulating drug development (Blume-Kohout and Sood, 2013; Dranove et al., 2014). To isolate the impact of cashflows from an increase in the demand for new drugs (improvement in investment opportunities), we need a measure of Medicare exposure that compares firms within the *same* therapeutic market.

Similarly, firms with high overall drug life may change their investment behavior both because they expect increased cash flows and because these firms have a younger portfolio of drugs in general. For example, firms with more recent drugs may focus more on early stage experimentation while firms with older drugs may focus more on pushing new candidates

¹⁵The FDA will grant extensions on a drug’s market exclusivity period, beyond the relevant patent expiration date, in a number of scenarios. For example, the Orphan Drug Act of 1983 incentivizes the development of drugs for rare (“orphan”) diseases through different provision, including a guarantee of seven years of market exclusivity. Other legislation also sets aside additional market exclusivity for other special drug designations (e.g., five years for New Chemical Entities, and six months for Pediatric Exclusivity).

¹⁶For more information on our drug-to-patent data and patent expiration dates see the Online Appendix, Section B.3

¹⁷We use a cutoff rule rather than the measured number of years of remaining exclusivity because of measurement error in assigning exclusivity periods.

through clinical trials. If this were the case, we may observe a difference in their innovative investments post Part D simply because these firms differ where they are at different points in the same product development cycle.

To isolate the impact of changing expected cash flows, our firm-specific measures of exposure to Part D, defined below, takes into account both drug MMS and market exclusivity:

$$\text{Medicare Drug Life}_{f,2003} = \sum_{i \in A} \left[\frac{\text{Drug MMS}_{i,2003}}{\sum_{j \in A} \text{Drug MMS}_{j,2003}} \mathbb{I}(\text{on patent in } X \text{ yrs})_{i,2003} \right] \quad (2)$$

Here, firm f 's Medicare Drug Life in 2003 is defined as the proportion of its approved drugs ($i \in A$) with long remaining exclusivity as of 2003, weighted by their drug-level MMS. Firms with higher Medicare Drug Life are those with longer exclusivity on their high MMS drugs. In our baseline results we choose $X = 5$ years as a cutoff because it is close to the median remaining life in our sample; however, our results are robust to alternative cutoffs, as discussed in Appendix Table A.21.¹⁸

Our definition of treatment (2) helps us isolate the cashflow effect from an increase in future investment opportunities and from differences in product life cycle. To see this, consider two firms, A and B , both with two approved drugs, one with a high MMS of 0.75 (drug H) and another with a low MMS of 0.50 (drug L). We also suppose that both firms have one drug that will expire soon and another that will not. As such, both firms have the same Firm MMS and the same overall drug life: hence, they are predicted to experience similar demand-induced increases in their incentive to develop drugs for the elderly and they are at the same part of their drug development cycle, as proxied by remaining exclusivity on their approved drugs.

However, suppose now that at Firm A , drug H_A will remain on patent, while drug L_A will expire. Meanwhile, suppose that at Firm B the opposite is true: the high MMS drug, H_B , will expire while L_B will remain on patent. Despite their other similarities, we would intuitively expect Firm A to receive a higher cashflow shock as a result of Part D, because its high MMS drug will remain on patent. This is what our measure delivers: Firm A 's Medicare Drug Life is $\frac{75}{75+50} \times 1 + \frac{50}{75+50} \times 0 = 0.6$, while Firm B 's is $\frac{75}{75+50} \times 0 + \frac{50}{75+50} \times 1 = 0.4$.

Table 2 describes our main treatment variable. The median firm has a Medicare Drug Life of 0.54 but most firms have a value of either zero or one. This is because many firms have

¹⁸We use a cutoff rule rather than the measured number of years of remaining exclusivity because of measurement error in assigning exclusivity periods. In the robustness Section 3.5 below, we show that our results are not very sensitive to the exact cutoff choice.

only one approved drug on the market as of 2003, so that their treatment values can only be 0 or 1. Appendix Figure A.8 shows a smoother distribution of Medicare Drug Life for firms with non extremal values and we show in Appendix Tables A.24 and A.20 that our results are robust to restricting to this subsample—or to using a binary measure of treatment.

Having defined our input measures, we next discuss how we use these measures in our estimation. We estimate the causal impact of a financial shock to drug development using the following linear specification:

$$\begin{aligned} \text{Drug Development}_{ft} = & a_0 + a_1 \text{Post} \times \text{Medicare Drug Life}_{f,2003} \\ & + a_2 \text{Post} \times \text{Overall Drug Life}_{f,2003} \\ & + a_3 \text{Post} \times \text{Firm MMS}_{f,2003} + \delta_f + \delta_t + e_{ft} \end{aligned} \quad (3)$$

Our main coefficient of interest is a_1 , which captures the *cash flow* impact of our main treatment variable defined in Equation (2). We control for an interaction between Overall Drug Life and the post Part D period. This helps alleviate concerns that our estimates of the impact of Part D are not picking up differences in firm development cycles, since firms with longer patent life remaining may choose to pursue different development strategies. We also control for the overall firm’s Medicare market share (captured by a_3). Doing so ensures that we are not picking up a product demand effect. In our baseline specification we also include firm- and quarter-dummies, which account for unobservable firm differences and aggregate trends in drug development. In addition, we also estimate a specification with company-specific linear time trends (see Table A.18 in the Appendix), to ensure that our results are not driven by pre-existing trends. To account for possible serial correlation in unobservables, we cluster standard errors at the firm level.

3.2 The Effect of Cashflow on Drug Development

First, Table 2 contains summary statistics of our dataset that is aggregated to the company–quarter level. We see that the average firm in our sample has 0.55 new drug candidates per quarter, but the data are highly skewed; most firms do not have a new drug candidate under development every quarter. This implies that the outcome variables for our analysis will be zero in most company–quarters. As such, our primary outcome measures will be the logarithm of one plus the number of new or the number of novel drugs. In the Appendix, we show that our findings are robust to using alternative specifications, including count models.

Number of New Candidates

Table 4 examines the causal impact of a financial shock, as described in Equation (3), on the total number new drug candidates put forth by our sample firms. Columns 1-3 focus on the count of new candidates while Columns (4) to (6) focus on the logarithm of one plus the number of new candidates. Because drug output is highly skewed, we focus on this latter measure. Column (4) presents our estimates with only the main treatment variable and the company and time fixed effects. The estimated coefficient a_1 is equal to 0.06 and statistically significant. Looking at Columns (5) and (6), we find that controlling for overall drug life and firm MMS increases the overall magnitude of our estimate (0.268 and 0.263, respectively). In particular, the negative coefficient on $\text{Post} \times \text{Overall Drug Life}_{f,2003}$ indicates that firms with a newer set of drugs as of 2003 proceed to introduce fewer new candidates into development in the post Part D period, suggesting that controlling for differences in firm development cycles is important. Perhaps surprisingly, the inclusion of $\text{Post} \times \text{Firm MMS}_{f,2003}$ in Column 6 does not matter much for our point estimates, suggesting that, in our sample, demand effects do not appear to increase development separately from cash flow effects.¹⁹ Going forward, we use Column 6 as our baseline specification.

The estimated magnitudes are also economically substantial. Focusing on Column 6, we can infer that a one standard deviation (0.41) increase in the main treatment variable leads to an 11% increase in the expected number of new drug candidates, relative to less treated firms. This corresponds to an elasticity of output to treatment of 0.40.²⁰ In Section 3.4, we interpret these magnitudes in terms of dollars for a subset of our firms.

Novelty of New Candidates

Next, we examine the novelty of the new drug candidates. Figure 5 and Table 5 summarize the results. The top panel of Figure 5 shows that the greatest increase in new candidates comes from an increase in candidates with Tanimoto similarity scores between 0.3 and 0.6. We see no increase in very similar “me-too” candidates, those with chemical similarity greater than 0.9. We also do not see increases in the number of drugs with similarity below 0.3. This is in fact because, as can be seen in Table 1, fewer than 8 percent of candidates have novelty scores in that range. To make these absolute patterns more interpretable, we also report the

¹⁹This finding may differ from drug market level estimates of the impact of demand on innovation because our firm-level analysis excludes the possibility of entry by new firms.

²⁰To arrive at this figure, we note that for a regression of the form $\log(1 + y) = bx + e$, the elasticity is given by $b \times \frac{1+y}{xy}$, where we evaluate at the mean of Medicare exposure in 2003 (0.54) and at the mean of drug output overall (0.55).

impact of financial resources on the number of drugs in each decile of similarity. This can be seen the bottom panel of Figure 5; again, we see a larger effect among more novel drug candidates and no significant increase in me-too candidates. These results suggest that the marginal drugs that firms develop in response to a cashflow shock tend to be more novel.

Event studies

One potential source of concern is that the differences in responses among the treatment and control group reflect pre-existing trends. To address this concern, Figures 6 and 7 show the accompanying event studies for the number of new and novel drugs, respectively. Focusing on Figure 6, we see that firms with different values of Medicare Drug Life_{*f*,2003} appear to be on parallel trends prior to the introduction of Part D. Following that, firms with high exposure begin to increase their drug output relative to firms with lower exposure starting in 2004, and this increase in drug development appears persistent, at least through the end of our data in 2014. Similarly, Figure 7 shows that the number of drugs in the bottom three quartiles of similarity (the top two panels and bottom left panel) increase following the introduction of Part D, but we see no such increase in output for the most chemically derivative drugs. To address any remaining concerns about pretrends, Appendix Table A.18 also shows that our main results are robust to including company year quarter linear trends.

The fact that we find a persistent effect should not be surprising because Medicare Part D was not a one time shock to firm cash flows. What is perhaps surprising is the fact that we observe a small increase in the number of new and novel drug candidates starting in 2004, even though Part D did not go into effect until 2006, meaning that firms would have expected increased cash flows in 2003, but would not have actually received them until 2006.

We believe the quick reaction appears in our data for two main reasons. First, because we focus on established firms with at least one approved drug in 2003, our sample consists of firms that very likely have a stock of drug candidates in the discovery phase at that time, making it easier for them to respond quickly. A change in expected cash flows may make firms more willing to support more of these candidates as they move through the development pipeline. Second, this is particularly plausible because, as discussed in Appendix Section A.2, investments in drug projects are staged. Pre-clinical and Phase 1 trials, while expensive compared to investments in R&D in other industries, are less costly than Phase 2 or Phase 3 trials. A firm that anticipates greater revenue in 2 to 3 years may choose to push its more novel discovery-stage candidates into the preclinical testing knowing that it would not need

to pay for the bulk of development costs for another few years and, moreover, would only need to make these payments if the drug candidate shows promise.

3.3 What types of drugs do firms develop?

A natural next step is to further examine the types of drugs that firms develop, and how these new drugs that firms develop fit into their existing portfolios. Table 6 shows that firms increase development for a wide variety of drugs, not just those that were more likely to be covered by Part D insurance. In this table, the outcome (log of one plus number of new compounds per company-quarter) is split by quartile of Medicare market share (MMS) that the new drugs fall into. Comparing elasticities across Columns (1) through (4), we see that firms are equally responsive in developing drugs across all MMS quartiles. This finding provides evidence that we are indeed identifying a firm response to a cash rather than demand shock: were we simply identifying the impact of Part D on demand for the development of drugs for seniors, we would expect the marginal candidates that firms develop to be in high MMS indications.

We next examine how these new drugs relate to the firm's existing portfolio of drug investments. Table 7 presents the results. Columns (1)-(3) focus on how new candidates compare to a firm's existing candidates on the basis of what disease indication they focus on. Column 1 shows that increased resources lead firms to develop drugs for indications they have not developed prior candidates for: a one standard deviation (0.41) increase in Medicare Drug Life increases the number of candidates in indications new to a firm by about 7 percent. Similarly, Column (2) shows that firms receiving a larger Medicare shock reduce the concentration of indications that they focus on, as measured by a decreasing indication-specific firm Herfindahl. Columns (3) and (4) show that this same pattern applies when considering candidates that act on new biological targets, as opposed to treating new disease-indications.

In sum, we see that treated firms invest in candidates across the MMS spectrum (and not just in drugs that target the elderly). In addition, we find some evidence that firms try to diversify their existing portfolio of drugs. The first finding partially validates our identification strategy. Specifically, the fact that firms are expanding their portfolios more broadly and not just in the areas that experience a demand shock as a result of Medicare Part D strongly indicates that our strategy is at least partially successful in isolating a cashflow shock from a shock to firms' investment opportunities. The second result is consistent with the idea that firms behave in a risk averse manner.

3.4 Discussion

Here, we discuss the interpretation of our findings and assess the quantitative significance of our findings relative to the existing literature.

Interpretation

Together, our baseline results suggest that firms may prioritize the development of me-too and other incremental drug candidates but with additional funding, it appears that they take on more risk by expanding their portfolio to include more chemically novel compounds. These results are unlikely to be driven by differences in development costs, since they are similar across novel and non-novel drugs (see Appendix A for more details).

Taken together, the facts we document are consistent with the presence of financing frictions in drug development. In particular, a central prediction of models with financing frictions is that, all else equal, an increase in internal funds will lead to more investment (see, e.g. [Froot et al., 1993](#); [Kaplan and Zingales, 1997](#)). In our setting, this implication would translate into firms developing a larger number of drug candidates following a shock to the availability of internal funds. Further, the fact that firms tilt their development towards more novel candidates may be interpreted as evidence for decreasing risk aversion, which is also a direct implication of models with financing frictions—even if the risks associated with the investment project are idiosyncratic. Specifically, firms anticipate the possibility that, in the future, they will need to raise external funds to finance new investment projects. As long as the costs of external finance are convex, firms will be reluctant to invest in risky projects today (see, e.g. [Froot et al., 1993](#)). A positive shock to their (current or future) cashflows will lower the amount that needs to be raised, and therefore make firms more risk tolerant.²¹ A closely related possibility is that having more internal funds allows the firm to invest in a more diversified portfolio of projects, which will lower the average riskiness of the firm’s cashflows, which is consistent with the results in Table 7.

At this point, it is worth recalling that our point estimates in Section 2.5 suggest that novel drugs don’t necessarily generate higher value for shareholders. Ignoring the several caveats

²¹A different version of the financial constraints hypothesis is that more novel drugs are more expensive to finance using external funds. One reason why this might be the case is that the degree of information asymmetries between the firm and external investors regarding the success probability of a novel drug candidate may be too large. Indeed, this may be the case if the average likelihood of success for a novel drug is sufficiently low (as we see in Section 2), but there is considerable heterogeneity in the *ex-ante* likelihood of approval—and more importantly, firm managers have some information about this likelihood that they cannot credibly share with outside investors. In this case, we would expect to see underinvestment in novel drugs by ‘high type’ firms that need to access external markets due to adverse selection. An increased availability of internal funds will lead these firms to develop more of these novel drugs.

inherent in this calculation, and assuming that this indeed the case, a natural question then is why do firms invest in novel drugs following an increase in the availability of resources. There are several possibilities. First, there may be value to pursuing novel drugs that our revenue and stock return measures do not capture; for example, firms may learn more from developing novel compounds or may advance their reputation as innovative, or these compounds may diversify their portfolio by being less correlated with the success of more similar drugs. Second, we focused mostly on the returns to shareholders. It is quite likely that firm executives may capture an important share of the returns to developing novel drugs, either in the form of higher compensation, or in other types of non-pecuniary benefits. Such indirect benefits could include, but are not limited to, developing their human capital and reputation, which may lead to an increase in their lifetime income. It is also possible that firm managers who undertake drug development decisions overestimate either the likelihood of success, or the drugs revenues upon FDA approval. This possibility is in line with the literature discussing the existence, and persistence, of managerial overconfidence (e.g., [DeBondt and Thaler, 1995](#); [Bernardo and Welch, 2001](#); [Malmandier and Tate, 2005](#); [Goel and Thakor, 2008](#); [Malmandier, Tate, and Yan, 2011](#))

Assessing the Magnitudes

Our analysis so far has been qualitative in nature. In particular, our main estimates that a one standard deviation change in pre-Part D Medicare drug life leads to an 11% percent increase in the development of new and novel drugs. To assess the magnitude of this effect and benchmark it to the existing literature, we need to express our estimates in terms of the implied elasticity of drug development with respect to firm R&D spending. Hence, we need a measure of how much firm resources increase as a result of this policy.

To assess the response of R&D investment to our main treatment variable, we match the public firms in our data to Compustat North America and Compustat Global. We are able to match approximately 50% of these firms. For these firms, we estimate our main specification, as defined by Equation (3), but with the log of firm profits and R&D spending as dependent variables. These results are reported in Table 8. Columns (1) and (2) show that firms with higher Medicare Drug Life in 2003 experienced growth in R&D and operating cashflows in the years following treatment. Columns (3) and (4) examine the response of firm-level borrowing in response to treatment: the expansion of Medicare Part D might have benefitted treated firms not only with an expansion of the flow in operating profits, but also via an expansion in their ability to borrow—as the value of installed assets increases. Though the point estimates

suggest this might be the case, the coefficients are too noisily estimated to conclude that the response is different from zero; we conjecture that the noisiness of these findings is also driven by the fact that pharmaceutical firms are less likely to use debt financing (see Section A.2 in the Online Appendix for a discussion). Panel B shows that these results are robust in limiting our sample to years prior to the financial crisis in 2008.

These results can be used to compute the elasticity of drug development with respect to firm R&D spending. Focusing on Column (1), we estimate an elasticity of treatment exposure to R&D expenditure of 0.53.²² If a one percent increase in treatment leads to both a 0.53 percent increase in R&D and a 0.40 percent increases in drug output, this suggests an elasticity of output to R&D of 0.75. If we apply this same calculation to our analysis by novelty bins, we find an elasticity of output to R&D of about 1.01 and 1.59 for drugs in the top 1 and 2 deciles of novelty, respectively, compared to an elasticity of 0.02 and 0.31 for the top 1 and 2 deciles of the most similar drugs, respectively.

There are several caveats to this analysis. Because some of our firms include large conglomerates (for instance firms such as Dow Chemical), our R&D figures include spending on sectors that may not be related to pharmaceuticals. More generally, we caution that while we estimate a causal impact of Medicare exposure on drug output, we cannot say that we estimate the associated productivity of R&D spending because lags between R&D expenditure and final commercial output are difficult to predict when it comes to drug innovation: a dollar spent today could lead to output in one year, two years, or ten years. Put another way, Medicare Part D cannot be thought of as an instrument that allows us to identify the causal effect of spending on outcomes because estimating such an elasticity would require both exogenous variation in cash flow and a way of linking that cash flow to specific drug outputs: while we have the former, we do not have the latter.

With those considerations in mind, our benchmark elasticity estimate appears sensible, given the wide range of related estimates that exist in the literature. One comparable analysis comes from [Henderson and Cockburn \(1996\)](#), who examine determinants of research productivity in the pharmaceutical sector. They find elasticities of R&D with respect to “important” patents of about 0.4 to 0.5. This analysis, however, is not highly comparable to ours as their data come from 1961–1988 and they employ a different production function estimation approach. Another more recent analysis by [Acemoglu and Linn \(2004\)](#) finds an elasticity of non-generic drug development to potential market size of 4, though this is not translated into R&D dollar terms. Our results are more comparable to [Azoulay, Graff-Zivin,](#)

²²This is taken from the coefficient, 0.975, multiplied by 0.54, the mean of treatment exposure in the pre-period.

Li, and Sampat (2016), which estimates the casual impact of *public* investments in biomedical research on patenting and drug development by private firms. They find elasticities of approximately 0.4–0.6; if firms are more responsive to their own spending, we would expect private elasticities to be greater than public elasticities.

3.5 Additional Results and Robustness Checks

Here, we provide a set of additional results and robustness checks. To conserve space, we briefly mention the results and refer the reader to the Tables in the Online Appendix for more details.

We begin by examining the decision to develop a new drug candidate versus acquire an existing drug from another firm. We find that firms primarily use marginal resources to push forward the development of their own earlier stage drug candidates, rather than by acquiring candidates from other firms (Table A.12 and Figure A.12 in the Appendix). In addition, the majority of new drugs that are developed were originated by that same firm, rather than acquired from another firm (Appendix Table A.12). Further, we find that larger firms account for the majority of the marginal drugs developed as a result of a finance shock, but, in looking at elasticities we find that smaller firms are just as, if not more, responsive (Table A.14 and Figure A.13 in the Appendix). We caution that our results cannot be fully extrapolated to the smallest pharmaceutical and biotechnology firms because our sample is limited to firms that had an approved drug on the market in 2003 (these are the firms for which we can calculate our key variable, Medicare Drug Share).

Next, we examine the robustness of our main results across several dimensions. First, our measures focus on chemical similarity as measured by Tanimoto scores. A limitation of this approach is that it can only be applied to small molecule drugs, and not to more complex biological entities, known as biologics, which has been a growing area of R&D focus in pharmaceuticals. Biologics include a broad class of biological products, usual derived or synthesized using tools from bioengineering rather than pharmaceutical chemistry: vaccines and insulins are both examples of biologics. Remicade (infliximab) for arthritis and Avastin (bevacizumab) for cancer are also examples of modern biologics. Understanding the impact of our shock on biologics is potentially important because, even though they make up a smaller fraction of overall pharmaceutical R&D, biologics have been a source of breakthrough innovation in drug development in recent years and are a priority research area for many pharmaceutical firms. If we were to find that our shock leads to decreases in biologic output, this would complicate our finding that access to financial resources increase novelty. In Table

A.17 in the Online Appendix, we show that this is not the case: more treated firms, especially those who have developed biologics prior to Part D, increase their biologic output more relative to less treated firms.

Second, we find our results are not driven by pre-existing firm-specific trends (Table A.18); are robust to alternative definitions of novelty, specifically novelty with respect to prior candidates for the same indication (Table A.16). Further, our results are robust to different empirical specifications (Table A.19 considers Poisson Count models; Table A.22 considers a binary outcome variable (does the firm have any new drugs); and Table A.20 considers a binary treatment). Our results are also robust to different definitions of treatment: Table A.21 shows that we can define Medicare Drug Life based on proportion of drugs with more than 7 and 10 years of remaining exclusivity (weighted by drug MMS). In Appendix Table A.23 we estimate alternative specifications wherein we control for the total years of remaining patent life times the post period indicator, as a proxy for both development cycle and firm size, in lieu of controlling for the overall *proportion* of drugs on patent. Last, our results are not driven by the extreme values in the Medicare market share variable shown in Figure A.8; Table A.24 shows that our results are similar if we exclude these firms.

4 Conclusion

In sum, we have developed a new measure of drug novelty based on the chemical similarity of a drug’s active ingredients. We show that our measure novelty is significantly positively correlated with measures of private and social value; however, novel drugs are less likely to be approved by the FDA, hence they represent a riskier investment. As a result, our point estimates suggest that novel drugs are unlikely to be a more valuable investment, compared to me-too drugs, in terms of shareholder value.

To further understand firm development decisions, we exploit a shock to firm cashflows as a result of the Medicare Part D expansion to show that firms which experience a positive shock respond by both increasing the number of drug candidates that they develop and by pursuing more novel drug candidates. The marginal drugs that are developed as a result tend to diversify the firm’s drug portfolio by pushing firms to develop candidates for different indications and acting on different biological targets.

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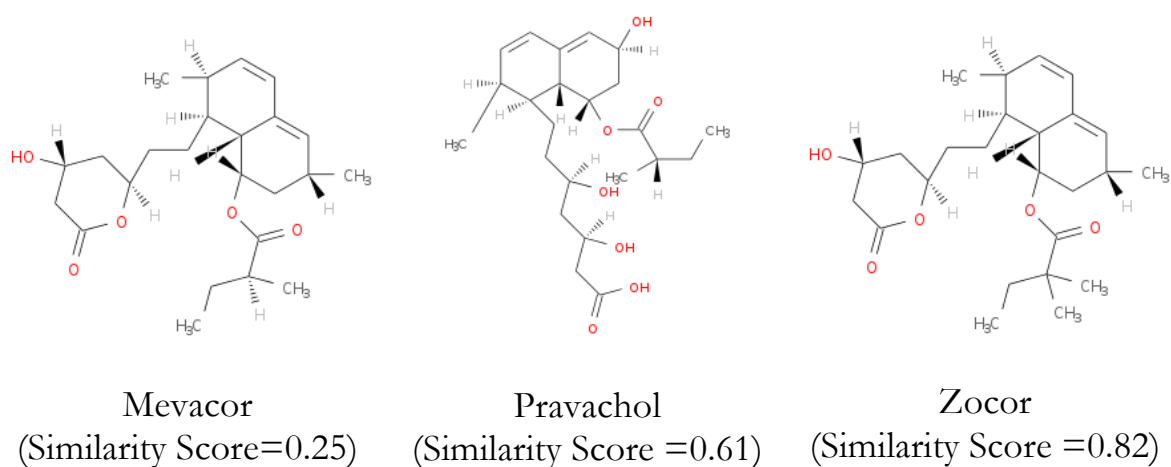
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Tables and Figures

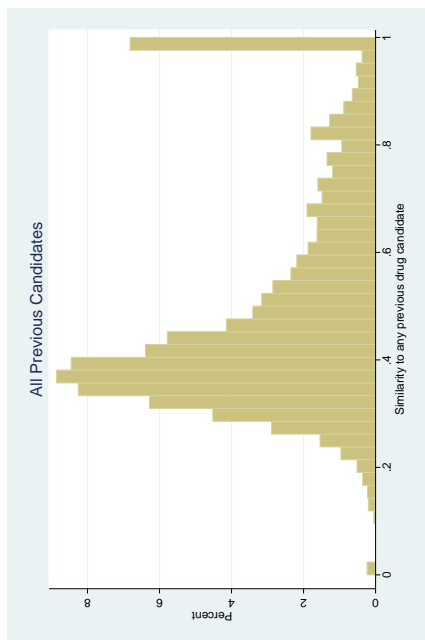
Figure 1: SIMILARITY FOR STATINS



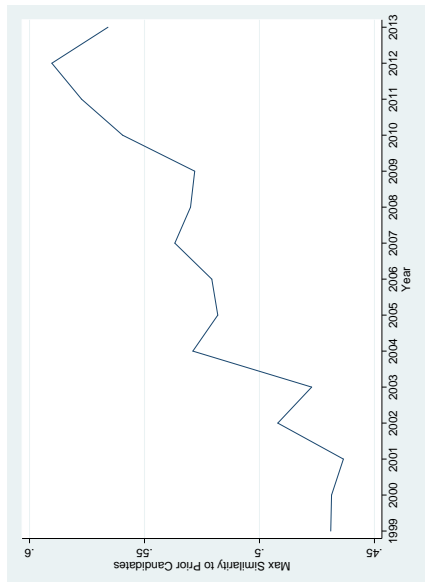
NOTES: Figure 1 provides the molecular structure and maximum similarity score of three early statins. Mevacor (Lovostatin) was the first FDA approved statin (approved in September 1987) and its Tanimoto similarity to prior molecules is 0.25. Pravachol (Pravastatin) is was the second such statin, approved in October 1991; its pair-wise similarity to Mevacor is 0.61 and its overall maximum similarity is also 0.61. Finally, Zocor (Simvastatin) was the third such statin, approved December 1991: its pair-wise similarity to Mevacor is 0.82 and its pairwise to Pravachol is 0.52. Zocor's overall maximum similarity to prior molecules is 0.82.

Figure 2: DRUG NOVELTY, DESCRIPTIVE STATISTICS

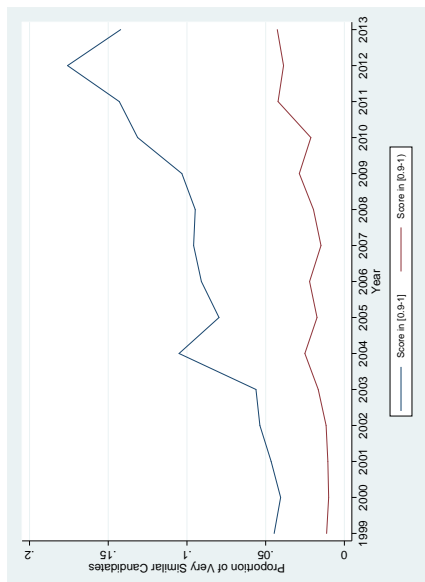
A. Distribution of Maximum Similarity to Prior Candidates



B. Average Similarity over time

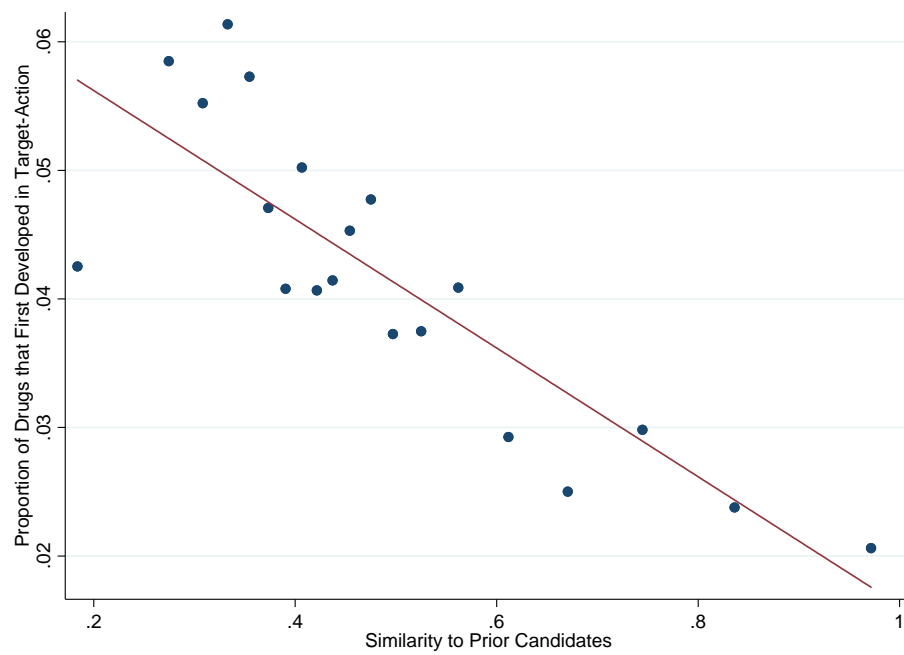


C. Proportion Very Similar Drugs



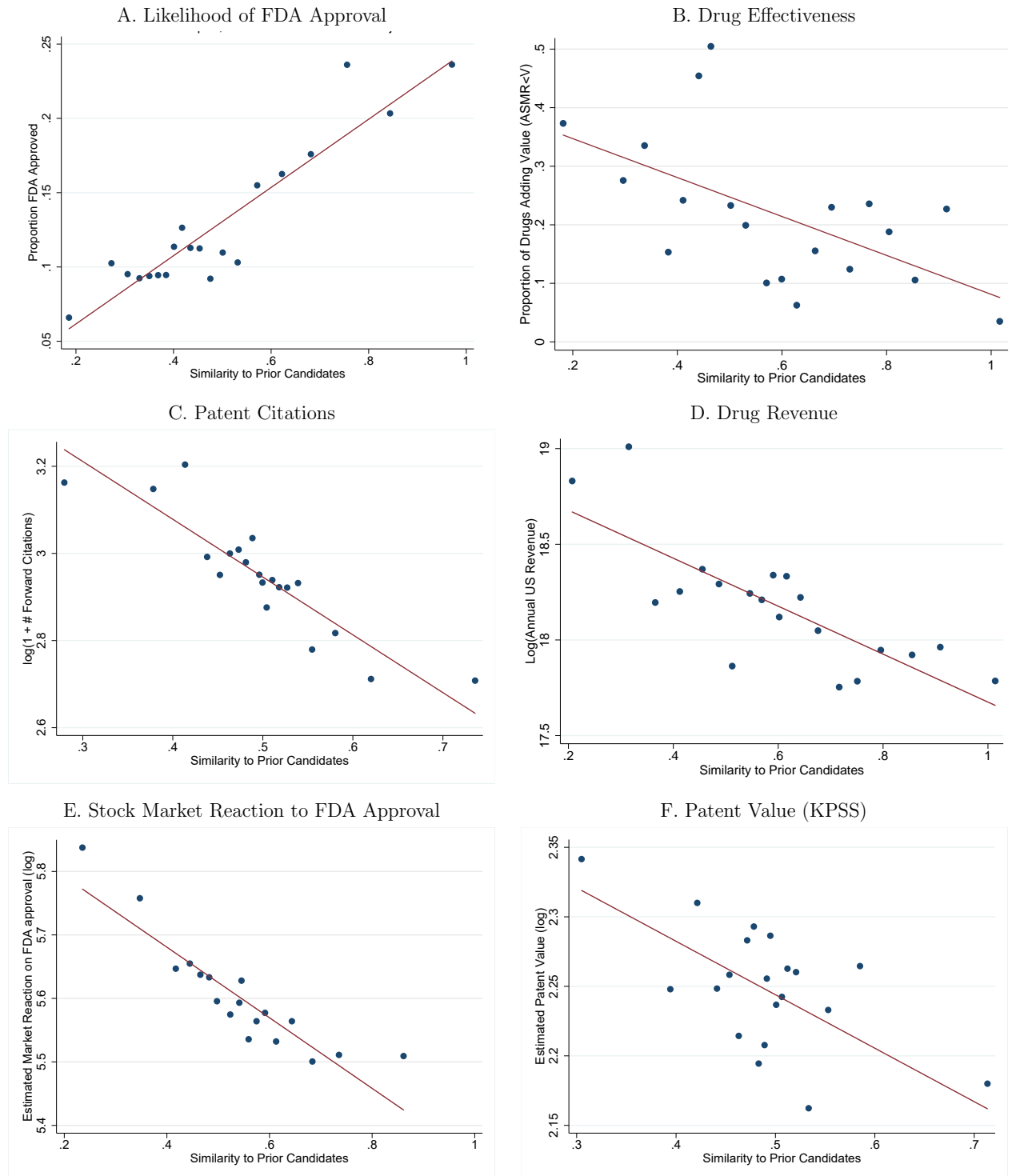
NOTES: Figure 2 displays descriptive statistics of our novelty measure. Panel A displays the distribution of our novelty measure. A drug's similarity is measured as its similarity to the most similar drug candidate that had previously entered Phase 1 clinical trials. For more details on this similarity measure, see Section 1.2. Panel B plots the trend in average drug candidate similarity over time. The line represents the average value of new drug candidates' maximum similarity to previously developed drugs, by year. Panel C displays the proportion of new drugs that are very similar. The blue line represents drugs with similarity scores greater than 0.9, which indicates over 90% overlapping chemical structures. The red line plots the same pattern, excluding drugs with similarity equal to one; this is to avoid counting combination therapies which may use the same molecule in conjunction with another molecule. Although our sample includes drug output in 2014, we plot up to 2013 in Panels B and C because our 2014 data do not include the entire year.

Figure 3: PROPORTION FIRST-IN-TARGET, BY DRUG SIMILARITY



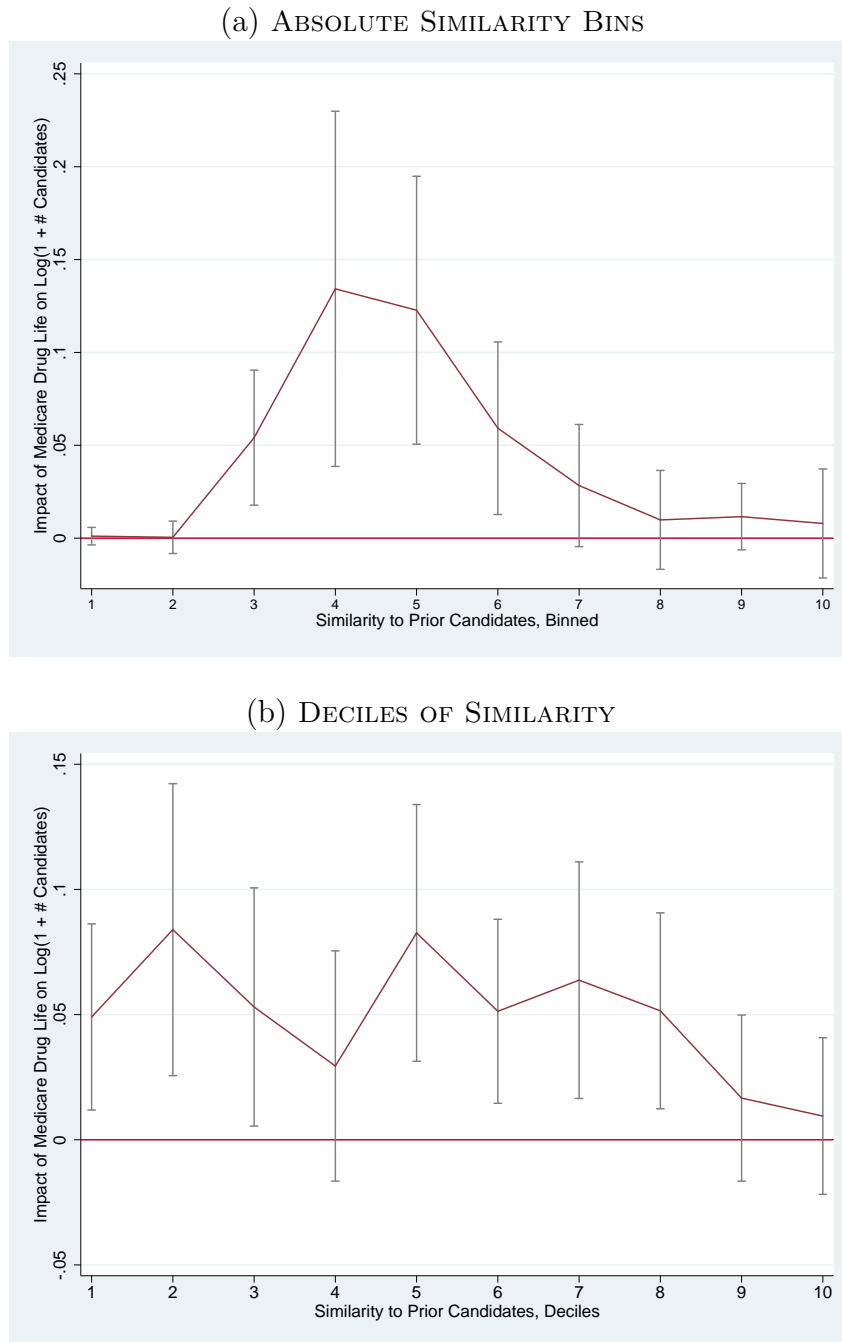
NOTES: Figure 3 presents a binned scatterplot of drug-level similarity against whether a drug is the first developed in its target-action. Each dot represents the proportion of candidates that are the first to be developed in their target-action, among all candidates within a given similarity score bin, conditional on disease (ICD9) and quarter of development fixed effects.

Figure 4: Drug Novelty and Risk, Social and Private Values



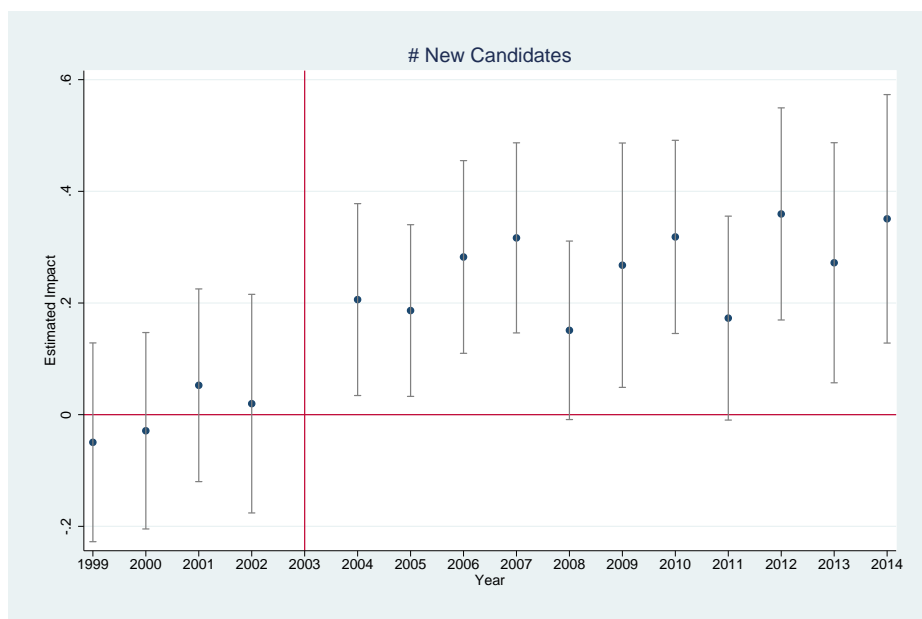
NOTES: Figure presents binned scatterplots of drug-level similarity against several drug characteristics. Panel A examines whether a drug is FDA approved. Panel B examines the drug's added benefit, which is derived from the French health system's clinical added benefits scores (ASMR), which range from one to five (I to V), with V indicating no value added. Panel C examines the logarithm of one plus the number of forward citations the patent receives. Panel D examines drug revenue. Panel E examines the logarithm of the estimated dollar reaction on the (first) approval of the drug by the FDA. Last, Panel F examines the logarithm of the ? estimated patent values. See Notes to Appendix Figures [A.2–A.7](#) for more details

Figure 5: IMPACT OF ADDITIONAL RESOURCES ON NOVELTY OF DRUG INVESTMENTS



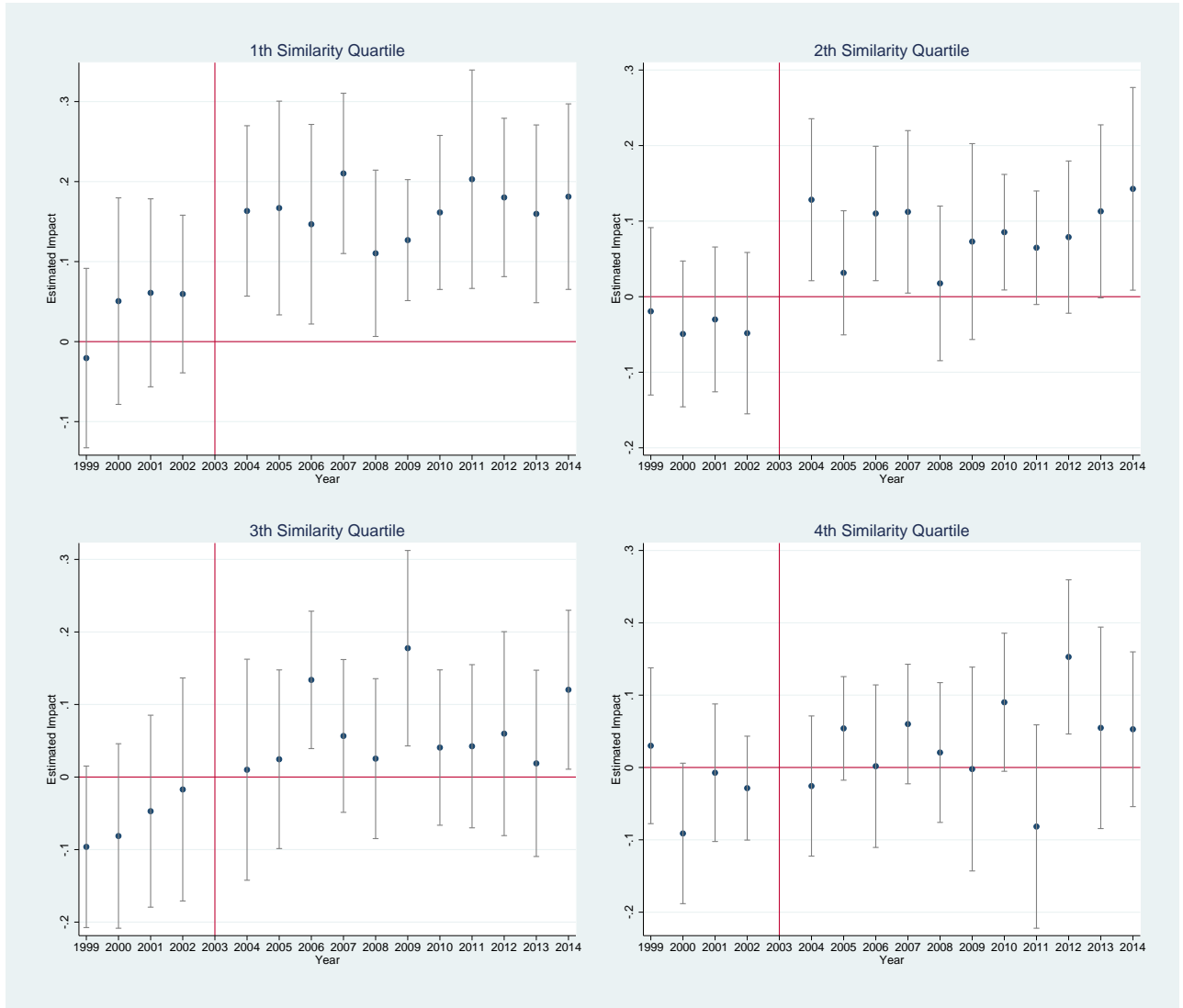
NOTES: Figure 5 plots the estimated coefficients on $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$ from our main regression specification defined by (3). Each point represents a different outcome variable: the number of new drug candidates in a given bin of similarity. In the top figure, bins are specified by absolute similarity scores: Bin 1, for example, counts the impact of our treatment on the number of drugs with similarity score between 0 and 0.1, while Bin 10 is the impact on drugs with similarity between 0.9 and 1.0. Because the number of drugs in each bin differ substantially, the bottom figure estimates the effect of our policy on the number of drugs in deciles of the novelty distribution. Bin 1 in this case is the impact of the policy on the number of drugs that fall into the bottom 10th percentile of similarity in our sample.

Figure 6: EVENT STUDIES: # OF NEW CANDIDATES



NOTES: Figure 6 reports the accompanying event study associated with Column 6 of Table 4. Each dot represents the coefficient on Medicare Drug Life_{*f*,2003} interacted with an indicator variable for that given year. 2003 is the omitted year, and 90th percentile confidence intervals are reported.

Figure 7: EVENT STUDIES: # OF NEW CANDIDATES, BY QUARTILES OF SIMILARITY



NOTES: Figure 7 reports event studies for number of novel drugs. In the interest of space, our outcome variables are the number of new candidates in different quartiles of similarity (rather than deciles as reported in Figure 5). Each dot represents the coefficient on Medicare Drug Life_{*f*,2003} interacted with an indicator variable for that given year. 2003 is the omitted year, and 90th percentile confidence intervals are reported. The upper left panel presents the event study associated with the (log of one plus the) number of drugs in the bottom quartile of similarity (the most novel drugs); the upper right presents the 25th-50th percentile quartile; bottom left the 50th to 75th percentile and, finally, the bottom right figure presents the impact on the most similar drugs.

Table 1: DRUG CANDIDATES SUMMARY STATISTICS

	All Drug Candidates 1999-2014	All Drug Candidates, Sample Firms 1999-2014
<i>Compound Characteristics</i>		
# Compounds	12,191	6,374
# US Phase 1 or above	3,043	1,894
# US Phase 2 or above	2,251	1,443
# US Phase 3 or above	988	756
# FDA Approved	392	356
Maximum Similarity to Prior Compounds	0.53	0.50
% between 0 and 0.1	0.20	0.06
% between 0.1 and 0.2	0.66	0.31
% between 0.2 and 0.3	6.60	6.48
% between 0.3 and 0.4	29.70	34.77
% between 0.4 and 0.5	21.97	23.25
% between 0.5 and 0.6	10.57	10.06
% between 0.5 and 0.6	7.65	7.08
% between 0.7 and 0.8	6.20	5.65
% between 0.8 and 0.9	5.96	4.88
% between 0.9 and 1.0	10.48	7.47
<i>Coverage Characteristics</i>		
# Target-Actions	2,211	1,448
# Disease Categories	430	363

NOTES: Table 1 reports characteristics of our full sample of drug candidates versus the sample of candidates associated with firms for which we are able to compute Medicare exposure in 2003. See Section A.1 for details about phases of drug approval in the United States. See Section 1.2 for details about how similarity is defined.

Table 2: FIRM-QUARTER SUMMARY STATISTICS

	Mean	p10	p25	p50	p75	p90
<i>Firm-Quarter Output</i>						
# New Drug Candidates	0.55	0	0	0	0	2
...own	0.36	0	0	0	0	1
...acquired	0.19	0	0	0	0	1
Average Max Similiarity Score	0.53	0.31	0.37	0.48	0.66	0.85
<i>Firm Characterisitics (2003)</i>						
Medicare Drug Life	0.54	0	0	0.54	1	1
Firm MMS	0.35	0.12	0.20	0.32	0.49	0.65
Overall Drug Life	0.57	0	0	0.60	1	1

NOTES: Table 2 reports characteristics of our firm-quarter analytic sample. A drug is considered a firm's own if it is assigned to that firm on the first date it enters development (as recorded in Cortellis); it is considered acquired if, on that date, it becomes associated with our focal firm even though it had previously been associated with another firm. Similarity is defined as the maximum similarity score, compared to all candidates that had previously entered development. We also compute distributions separately for prior candidates within the same indication or the same firm. Medicare drug life is the proportion of a firm's approved drugs in 2003 that had greater than 5 years of exclusivity left, weighted by the drug's Medicare Market Share (MMS). Firm MMS is the average MMS across that firm's approved drugs as of 2003. Overall drug life is the unweighted proportion of a firm's approved drugs in 2003 that had greater than 5 years of exclusivity left. Number of high patent life drugs is the total number of such drugs.

Table 3: Drug Novelty and Risk, Social and Private Values—Summary Table

	Risk	Measures of Social Value		Measures of Private Value		
		Drug Effectiveness (ASMR < V)	Patent Citations	Revenue	Stock Reaction to FDA Approval	Patent Value
	Likelihood of FDA Approval (1)	(2)	(3)	(4)	(5)	(6)
Maximum Similarity	0.272*** (0.024)	-0.332** (0.099)	-1.326*** (0.144)	-0.641*** (0.281)	-0.556*** (0.064)	-0.385** (0.183)
Appendix Table/Column	A.5.(2)	A.6.(4)	A.7.(4)	A.8.(4)	A.9.(3)	A.10.(4)

NOTES: Table 3 summarizes the relation between drug novelty and drug characteristics—specifically: risk (defined as the likelihood of FDA approval); proxies for social value (measured either using the AMR score, or the number of citations to related patents); and estimates of private value (measured either by drug revenues, the stock market reaction following a drug’s FDA approval, or via the [Kogan et al. \(2017\)](#) measure of value for the associated patents). The last row indicates the Appendix Tables referenced in this summary table (along with the relevant columns). For brevity, we report the coefficients on novelty (along with standard errors) using the most conservative specification. Please see the notes to the relevant Appendix Tables for more details. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 4: IMPACT OF RESOURCES ON # NEW CANDIDATES

	# New Candidates			Log(1 + New Candidates)		
	(1)	(2)	(3)	(4)	(5)	(6)
Post 2003 X Medicare Drug Life	0.211** (0.084)	0.860** (0.363)	0.847** (0.365)	0.057** (0.027)	0.268*** (0.096)	0.263*** (0.096)
Post 2003 X Overall Drug Life		-0.707* (0.366)	-0.694* (0.368)		-0.229** (0.098)	-0.225** (0.098)
Post 2003 X Firm MMS			-0.153 (0.140)			-0.049 (0.044)
R^2	0.556	0.556	0.557	0.594	0.595	0.595
Company FEs	Yes	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes	Yes
Overall Drug Life/Firm MMS						
Observations	16442	16442	16442	16442	16442	16442

NOTES: Table 4 examines the impact of additional resources on the number of new drug candidates. The dependent variable is the count of new drug candidates entering development (models 1-3), or the log of one plus the number of new drug candidates entering development. All models include a full set of company and quarter indicator variables to control for firm and calendar time fixed effects. Models 3 and 6 correspond to our main regression specification in defined by (3), with $\text{Post} \times \text{Overall Drug Life}_{f,2003}$ and $\text{Post} \times \text{Firm MMS}_{f,2003}$ both included as independent variables. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 5: IMPACT OF RESOURCES ON # NEW CANDIDATES, BY SIMILARITY

(A) ABSOLUTE SIMILARITY BINS										
Log(1 + New Candidates), by Similarity Bin										
	1	2	3	4	5	6	7	8	9	10
Post 2003 X Medicare Drug Life	0.001 (0.003)	0.000 (0.005)	0.054** (0.022)	0.134** (0.058)	0.123*** (0.044)	0.059** (0.028)	0.028 (0.020)	0.010 (0.016)	0.012 (0.011)	0.008 (0.018)
R^2	0.023	0.034	0.188	0.506	0.395	0.231	0.163	0.128	0.111	0.118
Company FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	16442	16442	16442	16442	16442	16442	16442	16442	16442	16442

(B) DECILES OF SIMILARITY										
Log(1 + New Candidates), by Similarity Decile										
	1	2	3	4	5	6	7	8	9	10
Post 2003 X Medicare Drug Life	0.049** (0.023)	0.084** (0.035)	0.053* (0.029)	0.029 (0.028)	0.083*** (0.031)	0.051** (0.022)	0.064** (0.029)	0.052** (0.024)	0.017 (0.020)	0.009 (0.019)
R^2	0.176	0.280	0.283	0.314	0.324	0.247	0.223	0.210	0.201	0.141
Company FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	16442	16442	16442	16442	16442	16442	16442	16442	16442	16442

NOTES: Table 5 reports the main specification coefficient for Post \times Medicare Drug Life_{*f*,2003}. In Panel A, the dependent variable varies by new drug candidates' absolute maximum similarity compared to all prior drug candidates that reached phase I trials (e.g. bin 6 represents all drugs with maximum similarity scores in the range 0.5-0.6). In Panel B, the dependent variable is split into bins that represent new drugs' deciles of maximum similarity score. All models include a full set of company and quarter indicator variables, with Post \times Overall Drug Life_{*f*,2003} and Post \times Firm MMS_{*f*,2003} both included as additional independent variables. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 6: PROPORTION OF NEW DRUGS ACROSS MMS QUANTILES

	Log(1+ New Candidates), by MMS Quartile			
	(1)	(2)	(3)	(4)
Post 2003 X Medicare Drug Life	0.085** (0.041)	0.084** (0.042)	0.110** (0.043)	0.115** (0.046)
R^2	0.337	0.343	0.366	0.358
Company FEs	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes	Yes
Observations	16442	16442	16442	16442

NOTES: Table 6 examines whether firms developing more drugs in response to cashflow shocks do so in areas that experience a greater increase in demand (proxied by MMS Share). The table reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. The dependent variable in each column corresponds to each quartile of the Medicare market share (MMS) distribution. All models include a full set of company and quarter indicator variables, with $\text{Post} \times \text{Overall Drug Life}_{f,2003}$ and $\text{Post} \times \text{Firm MMS}_{f,2003}$ both included as additional independent variables, but not reported in the table. Robust standard errors in parentheses, clustered around company identifiers. $*p < 0.10$, $**p < 0.05$, $***p < 0.01$.

Table 7: PORTFOLIO EXPANSION (CANDIDATES NEW TO FIRM)

	<u>New Indications</u>		<u>New Targets</u>	
	(1) Log(1+ #)	(2) Δ HHI	(3) Log(1+ #)	(4) Δ HHI
Post 2003 X Medicare Drug Life	0.160** (0.069)	-0.013* (0.008)	0.101* (0.060)	-0.020*** (0.007)
R^2	0.260	0.029	0.440	0.025
Company FEs	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes	Yes
Observations	16442	12220	16442	12220

NOTES: Table 7 reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. All models include a full set of company and quarter indicator variables, with $\text{Post} \times \text{Overall Drug Life}_{f,2003}$ and $\text{Post} \times \text{Firm MMS}_{f,2003}$ both included as additional independent variables, but not reported in the table. The first model reports the main effect of the Medicare Part D shock on the number of new (to the firm) indications entered. The second model reports how the the introduction of Part D impacted the change in firm project concentration, as measured by a Herfindahl-Hirschman index of projects by therapeutic indication. The dependent variables in the third and fourth models are number of new drug targets, and the change in project concentration across drug targets, respectively. Columns 2 and 4 have fewer observations than their counterparts in columns 1 and 3, because our Herfindahl index calculations only cover company-quarters for which the focal company was directly developing a drug (rather than via a subsidiary firm). Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 8: IMPACT ON R&D AND PROFITS

A. FULL SAMPLE				
	(1) Log(RD)	(2) Log(Profits)	(3) Log(Debt)	(4) Leverage
Post 2003 X Medicare Drug Life	0.975* (0.573)	1.046* (0.564)	0.967 (1.118)	0.108 (0.108)
R^2	0.934	0.930	0.800	0.463
Company FEs	Yes	Yes	Yes	Yes
Year of Development FEs	Yes	Yes	Yes	Yes
Observations	1774	1572	1657	1925
B. EXCLUDING THE FINANCIAL CRISIS (PRE-2008)				
	(1) Log(RD)	(2) Log(Profits)	(3) Log(Debt)	(4) Leverage
Post 2003 X Medicare Drug Life	1.098* (0.559)	1.189** (0.513)	1.281 (1.005)	0.103 (0.087)
R^2	0.949	0.937	0.800	0.582
Company FEs	Yes	Yes	Yes	Yes
Year of Development FEs	Yes	Yes	Yes	Yes
Observations	1110	978	1067	1218

NOTES: Table 8 examines the response of firm-level research spending, operating cashflow, and debt to our main treatment variable, $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. The dependent variable is either the logarithm of R&D spending; the logarithm of operating cashflows (Compustat: $\text{ib} + \text{dp}$); the logarithm of long-term debt (Compustat: dltt); and the logarithm of leverage (Compustat: dltt scaled by at). Panel A examines the full sample (years 1999–2013), while panel B only includes the years 1999–2008 in order to exclude the effects of the financial crisis. All specifications include a full set of company and quarter indicator variables, with $\text{Post} \times \text{Overall Drug Life}_{f,2003}$ and $\text{Post} \times \text{Firm MMS}_{f,2003}$ both included as additional independent variables, but not reported in the table. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.