

NBER WORKING PAPER SERIES

MISSING NOVELTY IN DRUG DEVELOPMENT

Joshua L. Krieger
Danielle Li
Dimitris Papanikolaou

Working Paper 24595
<http://www.nber.org/papers/w24595>

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
May 2018, Revised January 2019

Previously circulated as “Developing Novel Drugs.” We are grateful to Jason Abaluck, Leila Agha, Pierre Azoulay, Amitabh Chandra, Iain Cockburn, Leemore Dafny, Carola Frydman, Shane Greenstein, Tal Gross, Jonathan Gruber, Jennifer Kao, Borja Larrain, Monty Krieger, Patrick McCarren, Prescott Murphy, Ramana Nanda, Nicholson Price, Fiona Scott-Morton, Amit Seru, Kelly Shue, Ariel Stern, Michael Weisbach, Heidi Williams, Michael Serrano-Wu, Motohiro Yogo, Joshua Graff Zivin, and numerous seminar participants for helpful comments and suggestions. We also thank Descartes Holland, Jiaheng Yu, and Shumiao Ouyang for outstanding research assistance. We also thank Duncan Gilchrist and Bhaven Sampat for generously sharing drug patent data, as well as Laurie Jacquet and Léa Toulemon for sharing their data on Amélioration du Service Medical Rendu scores. Previous versions of this paper appeared under the titles “Financing Novel Drugs” and “Developing Novel Drugs.” Krieger and Li acknowledge funding from the National Institute on Aging under Award Number R24AG048059 to the National Bureau of Economic Research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or NBER.

NBER working papers are circulated for discussion and comment purposes. They have not been peer-reviewed or been subject to the review by the NBER Board of Directors that accompanies official NBER publications.

© 2018 by Joshua L. Krieger, Danielle Li, and Dimitris Papanikolaou. All rights reserved. Short sections of text, not to exceed two paragraphs, may be quoted without explicit permission provided that full credit, including © notice, is given to the source.

Missing Novelty in Drug Development
Joshua L. Krieger, Danielle Li, and Dimitris Papanikolaou
NBER Working Paper No. 24595
May 2018, Revised January 2019
JEL No. G31,I10,O3

ABSTRACT

This paper provides evidence that risk aversion leads pharmaceutical firms to underinvest in radical innovation. We define a drug candidate as novel if it is molecularly distinct from prior candidates. Using our measure, we show that firms face a risk-reward tradeoff when investing in novel drugs: while novel drug candidates are less likely to be approved by the FDA, they are based on patents with higher indicators of value. We show that—counter to the predictions of frictionless models—firms respond to a plausibly exogenous positive shock to their net worth by developing more of these riskier novel candidates. This pattern suggests that financial market imperfections may lead even large public firms to behave as though they are risk averse, therefore hindering their willingness to invest in potentially valuable novel drugs.

Joshua L. Krieger
Harvard Business School
jkrieger@hbs.edu

Danielle Li
MIT Sloan School of Management
100 Main St, E62-484
Cambridge, MA 02142
and NBER
danielle.li@mit.edu

Dimitris Papanikolaou
Kellogg School of Management
Northwestern University
2211 Campus Drive, Office 4319
Evanston, IL 60208
and NBER
d-papanikolaou@kellogg.northwestern.edu

Understanding the frictions that impede the development of new ideas is critical, especially in light of recent work documenting an apparent slowdown in innovation and productivity across a broad array of sectors (Jones, 2009; Gordon, 2016; Bloom, Jones, Reenen, and Webb, 2017). One possibility is that this slowdown reflects an underlying scarcity of good ideas: as knowledge advances, it becomes more difficult to discover new ideas. In such a world, slowdowns in innovation and productivity would be difficult to reverse. Yet other factors may also limit innovation. For example, good ideas may not be scarce but they may be riskier to develop, and firms may prefer to focus instead on safer, but more marginal, projects. In this world, by contrast, it would be possible to increase innovation by encouraging firms to take on more risk.

Using data from the pharmaceutical industry, we provide evidence that risk-aversion leads firms to under-invest in radical innovations. To arrive at this conclusion, we first develop a new measure of the molecular novelty of firms' new drug candidates. Using this measure, we show that firms face a risk-reward tradeoff when considering investments in novelty: novel drug candidates are less likely to be approved by the FDA, but they also appear to be more valuable in the sense that they are based on more valuable patents, and generate greater private and social returns conditional on approval. Having established that novel drugs appear to be economically viable investments, we then examine whether financing frictions impede firms' willingness to invest. Using variation based on the expansion of Medicare prescription drug coverage, we find that firms respond to plausibly exogenous increases in their net worth by developing riskier, more innovative drugs. This result—which holds even for profitable, publicly-traded firms—stands in contrast to the neoclassical frictionless benchmark in which a firm's willingness to take risks should depend only on the potential of its ideas, and not its net worth. Our results suggest, instead, that pharmaceutical firms both large and small behave as though they are risk averse, and that this behavior leads them to develop fewer novel drug candidates.

We begin by developing a new way to assess the novelty of drug candidates. To construct our measure, we compute a drug's pair-wise chemical similarity to prior drug candidates using a metric known as a "Tanimoto score" or "Jaccard coefficient." Tanimoto scores are designed to measure overlap in chemical substructures between two molecules, and are commonly used by pharmaceutical chemists to identify drugs with similar function (Wawer et al., 2014; Bickerton et al., 2012). We compute a drug's maximum Tanimoto similarity to prior candidates and define a drug to be novel if it is molecularly distinct from all prior drug candidates. Because our metric is based on properties observable when a drug candidate enters development, it can be defined for all candidates, and provides a measure of a firm's *ex-ante* willingness to invest in innovative drugs. By contrast, existing measures of pharmaceutical innovation count either the number of new drug candidates (which

ignores substantial variation in the novelty of drugs),¹ particularly promising candidates (which credits firms with innovating only when they succeed),² or number of entries into therapeutic areas or drug “classes” (which ignores innovation in common disease categories for which there already exist treatments),³ our approach takes advantage of advances in the field of chemical informatics to assess novelty on the basis of molecular structure.

Using our measure of novelty, we show that many new drug candidates are close chemical modifications of previous candidates: over 15 percent of newly developed candidates have a maximum similarity score of over 0.8, meaning that they share more than 80 percent of their chemical substructures with a previously developed candidate. As a benchmark, Figure 1 displays the chemical structures for Mevacor and Zocor, two very similar statins, which share an 82 percent overlap. Consistent with Bloom et al. (2017), among others, we document a decline in innovation among small molecule drugs over time. For instance, the proportion of highly derivative compounds—ones whose maximum similarity to prior candidates exceeds 0.9—has doubled from 1999 to 2014.

Next, we characterize the economic risk and returns associated with developing novel drugs. We show that novel candidates are riskier investments: relative to other drug candidates developed in the same quarter for the same disease indication, a one-standard deviation increase in novelty is associated with a 24 percent decrease in the likelihood that a drug candidate receives regulatory approval from the FDA. This risk, however, appears to be accompanied by potentially greater rewards: across a variety of metrics, we find that novel drugs are privately and socially more valuable. Conditional on approval, novel drugs generate more revenue, contribute more to a firm’s market value (as measured by event studies around the date of their approval), and are more likely to be classified as adding clinical value (following Kyle and Williams, 2017).

Novel drugs are also likely to be more valuable investments ex-ante, that is, based on their value early in the development process. We reach this conclusion by comparing patents associated with more versus less novel drug candidates. Because pharmaceutical firms have a strong incentive to patent potential therapies early—well before they enter clinical development—measures of patent value are useful indicators of a drug candidate’s expected worth to the firm. In particular, the value of a pharmaceutical patent incorporates not only a drug candidate’s value to the firm conditional on approval, but also the possibility that it may not be approved, as well as the value a firm may

¹Marcia Angell, a former editor of the *New England Journal of Medicine* argues that pharmaceutical output is a poor measure of innovation because firms increasingly concentrate their research on variations of top-selling drugs already on the market, sometimes 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>

²See Dranove, Garthwaite, and Hermosilla (2014). While these may be useful measures of research success, they are misleading measures of a firm’s willingness to *invest* in innovation ex-ante.

³See DiMasi and Paquette (2004); Dranove et al. (2014); DiMasi and Faden (2010); Lanthier, Miller, Nardinelli, and Woodcock (2013).

derive (e.g. learning) even if the candidate fails. We use two proxies for that value: future citations to the patent (following [Hall, Jaffe, and Trajtenberg, 2005](#)) and the patent’s contribution to the firm’s stock market value (following [Kogan, Papanikolaou, Seru, and Stoffman, 2017](#)). Our results show that the key patents associated with novel candidates generate greater contributions to stock market value and receive more citations. Specifically, a one-standard deviation increase in novelty is associated with approximately a 10 percent increase in the estimated value of associated patents and a 8–18 percent increase in future citations.

If novel drug candidates are more valuable, this raises the question of why firms invest in so many chemically derivative drugs. One answer is that viable novel drug candidates are scarce, and firms have exhausted the set of such candidates available for development. However, it is also possible that various frictions lead firms to under-invest in novelty. In the remainder of this paper, we explore the role that financial market imperfections—that is, costs of external finance, as in [Froot, Scharfstein, and Stein \(1993\)](#)—can play in shaping firms’ willingness to pursue exploratory R&D. We present a model in which firms favor more conservative development strategies because they internalize the possibility that novel candidates are more likely to fail and leave them with financing shortfalls in the future. In fact, firms may choose to develop safer but more derivative drug candidates, even when novel drug candidates are ex-ante more valuable. In our model, novel drugs are “missing” because concerns about managing cashflow risk discourage firms from investing in such candidates.

The second part of this paper explores this idea by examining how cashflow shocks impact firms’ development decisions. Absent financial frictions, firms should assess investments only on the basis of their expected value. In such a world, a firm’s R&D decisions would not depend on its cashflows. However, if firms face financing frictions, then an increase in their net worth may enable them to invest in more drug candidates than they were previously able to. Such a response would suggest that these marginal drugs were missing to begin with.

We construct shocks to firm net worth using the introduction of Medicare Part D, which expanded US prescription drug coverage for the elderly and increased the profitability of drugs targeting the elderly ([Friedman, 2009](#)). Medicare Part D (hereafter “Part D”) differentially benefited firms along two pre-existing dimensions: the extent to which they produce drugs for the elderly and the remaining market exclusivity on these drugs. Using both dimensions of variation allows us to control for confounders arising from each individual dimension. For example, firms with more existing drugs for the elderly may respond to Part D by investing in more or more novel drugs—not because they are responsive to cashflows, but because they may differentially see a greater increase in investment opportunities. Similarly, firms with longer remaining exclusivity periods on their products may have different development strategies than firms whose drugs face imminent competition, again,

even absent changes to cashflows. Our identification strategy thus compares firms with the same share of drugs sold to the elderly and the same remaining exclusivity periods across their overall drug portfolio, but that differ in how their remaining patent exclusivity is distributed across drugs of varying elder shares. This strategy allows us to identify the impact of differences in expected cashflow among firms with similar investment opportunities, and at similar points in their overall product life-cycle.

We find that treated firms develop more new drug candidates, and that this increase is driven by an increase in molecularly novel candidates. By contrast, we find no evidence that firms increase the development of very derivative, so called “me-too,” drugs. Using a back of the envelope analysis based on R&D spending among firms in Compustat, we show that these results imply an elasticity of drug development to firm R&D of between 1 and 1.6 for novel drugs, and of between 0 and 0.3 for me-too drugs.

Importantly, our results document “missing novelty” across a host of drug markets. Although our shock to net worth arises from an expansion in insurance coverage for elderly consumers, treated firms respond by developing more novel drugs for patients of all ages—including infants, children, and young adults. This finding also implies that our identification strategy is not simply picking up firms’ response to an increase in demand for drugs targeting elderly patients. Further, we also find some evidence that firm managers have a preference for diversification. Treated firms are more likely to pursue drugs that focus on different diseases, or operate using a different mechanism (target), relative to the drugs that the firm has previously developed. Taken together, these findings suggest that firms respond to increases in net worth by diversifying their portfolios and undertaking more exploratory development strategies at the margin. Moreover, since we show that novel drugs are based on more valuable patents, our results are unlikely to result from ‘empire-building,’ whereby managers deploy additional resources to pursue inferior projects.

Perhaps surprisingly, our findings hold even for large publicly traded firms, some of which hold substantial cash reserves. As such, it is unlikely that a scarcity of cash resources in the present is the main factor impeding innovation in our setting. Rather, our findings suggest that firms invest conservatively today because they are concerned about the prospect of facing R&D failure and uncertain cashflows in the future (Froot et al., 1993). Indeed, rather than being a sign of financial slack, the presence of large cash holdings can indicate that firms internalize the costs of potentially needing to raise external finance in the future. These concerns likely to be particularly salient in the pharmaceutical industry, where development costs are high, debt financing is more scarce due to difficulties collateralizing potentially unproven intellectual property, and where asymmetric information about project potential can make it costlier to raise equity.

Our work makes a distinct contribution to the literature studying the impact of financial frictions on firm investment decisions.⁴ While existing work typically observes the response of investment aggregated at the level of individual firms or geographic locations, we are able to characterize the risk and return of the marginal projects being undertaken as a result of ameliorating financial frictions. By observing the economic characteristics of specific projects, our work clarifies the mechanism through which financial frictions affect radical innovation and opens the door for a wider array of potential policy prescriptions. Specifically, documenting a positive relation between firm resources and innovation typically focuses attention on policies that stimulate R&D through subsidies. By identifying firm risk aversion as a limiting factor, our results also lend support to a different set of policies that reduce the relative risk of novel versus me-too investments, potentially at a lower cost to the taxpayer. Examples of such policies include: creating diversified portfolios of drugs, as proposed in [Fernandez, Stein, and Lo \(2012\)](#); providing convex incentive schemes to entrepreneurs, as done by venture capital firms; or by limiting reimbursements for derivative drugs.

Finally, our work also contributes to the literature studying the rate and direction of innovation. For instance, [Jones \(2010\)](#); [Bloom et al. \(2017\)](#) argue for the presence of decreasing returns to innovation. Consistent with this view, we find that drug novelty has decreased over time, although an important caveat is that our novelty measure cannot be computed for biologic drugs, which have been a vibrant research area in recent years. Our work also relates to research on how regulatory policies and market conditions distort the direction of innovation ([Budish, Roin, and Williams, 2015](#)), as well as work and how changes in market demand affect 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 passage of Medicare Part D, and find more innovation in markets that receive a greater demand shock (drugs targeted to the elderly). We use the same policy shock—but interact with the characteristics of firms’ patent portfolio—to ask a different question. Rather than looking at the impact of changes in demand on disease-level innovation, we study the impact of cashflow shocks on firm-level investment decisions—that is, we isolate a cashflow shock from the demand for new drugs. Indeed, our finding that treated firms increase drug development for pediatric and young adult conditions strongly suggests that we are identifying a cashflow shock rather than a shock to demand for drugs targeting the elderly.

⁴An incomplete list includes [Almeida, Campello, Laranjeira, and Weisbenner \(2011\)](#); [Frydman, Hilt, and Zhou \(2015\)](#); [Chodorow-Reich \(2014\)](#); [Duygan-Bump, Levkov, and Montoriol-Garriga \(2015\)](#); [Bond, Harhoff, and van Reenen \(2005\)](#); [Brown, Fazzari, and Petersen \(2009\)](#); [Hall and Lerner \(2010\)](#); [Nanda and Nicholas \(2014\)](#); [Kerr and Nanda \(2015\)](#); [Hombert and Matray \(2017\)](#); [Benmelech, Frydman, and Papanikolaou \(2017\)](#). [Kerr and Nanda \(2015\)](#) summarize the literature on financing frictions and R&D.

1 Measuring Drug Novelty

The first step in our analysis is to construct an ex-ante measure of drug novelty. To do so, we rely a core tenant of modern pharmaceutical chemistry, known as the “Similarity Property Principle,” which states that structurally similar molecules are more likely to have similar functional properties (Johnson and Maggiora, 1990). Chemists rely on this idea when they use molecular similarity calculations to build libraries for drug screening (Wawer et al., 2014), quantify the “drug-like” properties of a compound (Bickerton et al., 2012), or expand medicinal chemistry techniques (Maggiora et al., 2014). We use the relationship between physical and functional similarity to define a drug’s novelty based on its chemical similarity to all previously developed drug candidates. This approach is similar in spirit to recent research in microbial biochemistry, which uses chemical similarity to assess patterns of innovation in the discovery of bacterial and marine-derived natural products (Pye et al., 2017).

1.1 Data Overview

To conduct our analysis, we construct a panel dataset that tracks firm–quarter level drug development outcomes using data from a number of sources.

The primary data we use to construct drug output and novelty measures come from Clarivate Analytics’ Cortellis Investigational Drugs database. Cortellis assembles the data on drug candidates from public records (e.g., company documents, press releases, financial filings, clinical trial registries, FDA submissions) and then further processes the data to assign the proper classifications (e.g., therapeutic indications and drug targets).⁵ Hence, the earliest point of entry for a given drug candidate is generally the first time a patent is filed or when the drug candidate appears in documents describing a firm’s research pipeline. Our data will have near complete coverage for drugs that enter clinical trials—companies are required to file an Investigational New Drug (IND) Application with the FDA, and this will almost always be observed. We also observe many later stage pre-clinical drugs as most of these will be patented, but may miss early stage pre-clinical candidates that show no promise in the earliest screening experiments (these may never leave a paper trail for Cortellis to pick up). Among drugs that do enter our data, we are fairly confident that we have accurate development dates because Cortellis attempts to backfill information; for example, if Cortellis first becomes aware of a drug when it fills out an IND, Cortellis employees will work to ex-post determine the dates of its earlier clinical development.

⁵In 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. The Food and Drug Administration Modernization Act, passed in late 1997 and enacted in 1999, required the reporting of clinical trials to a centralized government registry. Even though we observe some drug candidates pre-1999, we believe that our data provides fuller coverage post 1999.

We supplement these data using a variety of other sources. We use ChemMine Tools, an open source program for chemical-informatics, to compute similarity scores.⁶ We obtain accounting information for a subset of the companies (those that we can match based on their name) from Compustat. We link approved drugs to their key patents and exclusivity dates using the FDA Orange Book and information from the Federal Register. We obtain patent value information from Kogan et al. (2017). Last, we use the Medical Expenditure Panel Survey (MEPS) to estimate drug revenue and Medicare market share (MMS).

1.2 Similarity Based on Chemical Structure

The first step in measuring novelty requires us to estimate the similarity of two molecules. We follow the chemical informatics literature and measure similarity using the Tanimoto distance (Jaccard coefficient) between two sets of chemical fragments (Nikolova and Jaworska, 2004),

$$T_{A,B} \equiv \frac{|A \cap B|}{|A \cup B|} = \frac{|A \cap B|}{|A| + |B| - |A \cap B|}. \quad (1)$$

The similarity measure in (1) takes values in $[0, 1]$ and returns the fraction of chemical features that are shared by the two chemical compounds. 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 orientation in space (stereosymmetry).⁷ We compute the distance metric (1) using ChemMine Tools.

We compute a drug candidate’s maximum pairwise similarity to previously developed candidates, and define a candidate to be novel if it has a low maximum similarity:

$$\text{Maximum Similarity}_i \equiv \max_{j \in P_i} T_{i,j}, \quad (2)$$

where P_i is the set of drug candidates that have reached Phase 1 clinical trials prior to the introduction of candidate i . We compare to prior drugs in Phase 1 and above rather than to all prior drugs in development to avoid mistakenly labeling a novel drug candidate as derivative if it was developed at approximately the same time as other novel (but pair-wise similar) candidates (DiMasi and Faden, 2011).

⁶Appendix C.2 provides more detail about the construction of similarity scores using the simplified molecular-input line-entry system (SMILES) and ChemMine Tools.

⁷For 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 orientations of the same molecule, each known as an enantiomer, whereas Nexium consists of a single enantiomer of this same molecule. Despite their differing orientation, we record the pair as having a Tanimoto score of 1.

Figure 1 illustrates an example of how our novelty measure works for several HMG-CoA reductase inhibitors—more commonly known as “statins”—used to treat heart disease. In September of 1987, Mevacor (Lovostatin) became the first statin to be approved by the FDA; its 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 candidate. Next, in December of 1991, a third statin, Zocor, 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).

1.3 Descriptive Statistics

We now describe the distribution and evolution of novelty in our data.

Panel A of Figure 2 shows the distribution of our maximum similarity measure. Recall that lower maximum similarity to prior candidates implies higher novelty. We see that the distribution of our ex-ante novelty score is somewhat bi-modal; the vast majority of drugs have maximum similarity scores in excess of 0.2, and most fall in the 0.3 to 0.6 range. However, there is a second peak close to 1 (zero novelty). Approximately 10 percent 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. Column 1 of Table 1 documents the underlying number of drug candidates in various bins of similarity, as well as by phase of development. In the second column, we show the characteristics of drug candidates that are included in our firm-level analysis in Section 3, which we will discuss in Section 3.3.

Panel B of Figure 2 shows that the novelty of the average new drug candidates has declined over time. Part of this increase may reflect an increasing difficulty of finding new ideas when there is a larger stock of existing knowledge. However, part of this increase may also be an artifact of our truncated sample. A me-too drug that enters development in 1999 may appear more novel simply because we observe less data on prior candidates, relative to a me-too drug that enters development later in our sample period. To explore whether this is the main factor behind this trend, we also plot the average novelty of new drug candidates where the comparison group is restricted to those which entered Phase 1 over the last five years. We can see that even in this case the average novelty of new drugs has declined over time. Panels C and D of the same figure also document an increase in the fraction of new drug candidates that are very similar to prior candidates, those with maximum Tanimoto scores of over 0.9. We refer to such candidates as “me-too” or “derivative” drugs because they represent only a small modification from existing drugs. Regardless of whether we include combination drugs (Panel C) or not (Panel D), we see that the proportion of such drugs

is increasing. 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, Carter, and Mossialos, 2015) and is also consistent with the presence of decreasing returns to scale in innovative activity (Jones, 2010; Bloom et al., 2017).

1.4 Validation and Caveats

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

First and foremost, there is no perfect correspondence between structural and functional similarity. 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 exceptions, chemical informatics research has shown that Tanimoto similarity measures are nonetheless useful for identifying drug qualities and novelty on average (O’Hagan et al., 2015; Baldi and Nasr, 2010; Bickerton et al., 2012; Pye et al., 2017). We also independently verify that our measure of chemical similarity captures a sense of functional similarity. Appendix Table A.2 shows that pairs of drugs which share the same biological target action are approximately 2.2 times more similar than the average pair; sharing the same indication also increases similarity by over 25 percent. Figure 3 further shows that 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 that enter development in the same quarter, we find that a one standard deviation increase in novelty (-0.21) increases a drug’s chances of being the first in its broad target class by over 40 percent.⁸

Second, we can only measure novelty with respect to prior molecules in the Cortellis data. Hence, our measure of novelty is an upper 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, which are disproportionately candidates that enter development toward the start of our sample. To control for cohort differences, we will include fixed effects for the quarter of a candidate’s earliest development date in all of our empirical analysis.

Finally our novelty measure cannot be applied to more complicated drug therapies whose chemical structure is more difficult to characterize. Specifically, 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.

⁸Appendix Table A.3 shows that these results are robust to other specifications and controls.

Although biologics make up for only 20 percent of drug development, their share is increasing and are often considered to be a source of innovation in the drug industry (Ralf Otto, Alberto Santagostino, and Ulf Schrader, 2014). In Section 3.7 we show that a positive cashflow shock also leads to greater development of biologics.

2 Risk and Return of Investing in Novel Drugs

In this section, we explore the risk and return of developing novel drugs. The main risk in drug development is FDA approval; hence, we first examine the relation between novelty and likelihood of FDA approval. Meanwhile, measuring the return of investing in novel drugs is somewhat more challenging, and we will examine several proxies of private and social value. Some of these proxies are at the drug level, and are therefore only available for approved drugs. To measure the ex-ante return of investing in novel drugs we will instead focus on outcomes at the drug patent level. The advantage of focusing on drug patents is that they are typically filed well before the drug approval decision is made, which allows us to assess the value of drugs that have not been approved, including that of early stage pre-clinical candidates.

2.1 Drug Novelty and Risk: Likelihood of FDA Approval

We first examine how novelty relates to a drug candidate’s likelihood of FDA approval using linear probability models that relate a candidate’s approval status ($Outcome_i$) to its ex-ante novelty, given by its maximum similarity score:

$$Outcome_i = a + b \text{Maximum Similarity}_i + c Z_i + \varepsilon_i. \quad (3)$$

We saturate our specification with a battery of controls, including quarter of development, disease (ICD-9 indication), and firm fixed effects. We cluster the standard errors by indication. We estimate Equation (3) for all drug candidates, but also report results separately conditioning on different stages in development. We will estimate versions of Equation (3) for a variety of other outcomes, discussed in later sections.

Novel drugs are significantly less likely to be approved by the FDA, as we can see in Column 1 of Table 2 and Panel A of Figure 4. Compared to drugs of similar age, that targeting the same disease (ICD-9 indication), and are developed by the same firm, a one standard deviation increase in drug novelty (-0.21) is associated with a $-0.21 \times 0.208 = 4.4$ percentage point decrease in the likelihood of FDA approval. Given that the unconditional likelihood of FDA approval for candidates in our

data is 18 percent, this estimate represents a 24 percent decrease in the likelihood of developing a successful drug candidate.

Further, this negative relationship between novelty and approval persists throughout the development pipeline, as we can see in Figure A.2 and Table A.4 in the Online Appendix—though the magnitude of the association attenuates as the drug progresses further along the approval process. Focusing on our preferred specification with the full set of controls, we find that conditional on reaching Phase 1 or Phase 2, a one standard deviation increase in novelty is associated with an approximately 5 percentage point reduction in the likelihood of ultimate approval. However, conditional on reaching Phase 3, there are no statistically significant differences in approval probabilities between more and less novel drugs.

2.2 Novelty and Measures of Value for Approved Drugs

Even if novel drugs are less likely to be approved by the FDA, they may still be valuable investments if their expected value is high. To explore whether this is the case, we develop several measures of the value of drugs that make it to market. We focus on the relation between the novelty of a drug and its revenue, contribution to firm value and clinical value added.

We relate the different measures of drug candidate value $Outcome_i$ to our novelty measure using specifications similar to Equation (3). Depending on the measure of value, $Outcome_i$ takes either binary values (to identify whether the drug is deemed clinically important), or consists of the logarithm of revenues, or estimated contributions to firm value. To ensure that we are comparing otherwise similar drugs, we control for a drug’s age (development quarter or year) and disease (ICD9 indication) fixed effects.

Drug revenue

We begin by examining the relation between our novelty measure and revenue. To obtain data on drug revenue, we use the expenditures reported in the Medicare Expenditure Panel Survey (MEPS) from 1996–2012. To match drugs to Cortellis, we employ a name-matching procedure. Appendix C.3 provides further details on the data construction and matching procedure. The data is at the drug-indication-calendar year level. After restricting attention to drugs for which we can compute a similarity score, we are left with 11,256 observations. We relate novelty to a drug’s log revenues using a panel version of Equation (3), which now also includes calendar year fixed effects.

Novel drugs generate greater revenue, on average. Column 3 of Table 2 reports the estimated coefficient b from our baseline specification with our full set of controls. The economic magnitudes are significant: a one standard deviation increase in novelty is associated with an increase in annual

revenue of approximately 0.14 log points. Given that the unconditional standard deviation of log revenues is approximately 2.1 log points, our estimates imply that novelty can account for a non-trivial fraction of this variation. Panel D of Figure 4 provides a binned scatter plot of the results, and Appendix Table A.5 reports results using different combinations of controls.

Measuring a drug’s private value using revenue has some disadvantages. First, it ignores the costs of production. Markups may be systematically related to the novelty of a drug; if firms charge higher markups for novel drugs, revenue estimates would understate the relation between novelty and private value.⁹ Drug-level revenues also ignore potential spillovers on other drugs in a firm’s portfolio. These spillovers can be positive if the firm markets some drugs jointly, or negative, if the new drug cannibalizes older drugs. As a result, a more appropriate measure of the (private) value of a drug is its contribution to the firm’s market value; we explore this idea next.

Stock market reaction to FDA approval

To measure the market value of a drug, we exploit information contained in the stock market’s reaction to news about a drug’s FDA approval. Specifically, we closely follow the methodology of Kogan et al. (2017). This approach, which we discuss in more detail in Appendix C.4, allows for stock price movements that are unrelated to the value of the approved drug, and adjusts our estimates to account for the fact that markets may react more strongly to the approval of novel drugs not because they are more valuable but because the news is more surprising. After restricting the sample to drugs with similarity scores that we can match to the CRSP dataset, we are left with 34 firms and 462 announcement days, focusing our attention on the first approval date for each drug.

We find that novel drugs generate more market value upon approval. Specifically, we estimate a version of Equation (3), where the dependent variable is the logarithm of the estimated contribution to firm value. We include controls for drug development year, indication, firm fixed effects and the year the drug is approved. Column 3 of Table 2 reports the estimated coefficient b from our preferred specification that includes the full set of controls. Panel E of Figure 4 provides the associated scatter plot; Appendix Table A.6 reports estimates using different combination of controls. In terms of magnitudes, a one standard deviation increase in novelty is associated with approximately 20 percent larger stock price increase. This correlation is robust to varying the set of controls. Panel E of Figure 4 shows the associated binned scatter plot (with the full set of controls); this relation appears to be monotone across the full distribution of drug similarity.

⁹Further, revenues are potentially mis-measured because we do not observe the presence of pharmaceutical rebates, discounts given to buyers, relative to a drug’s listed price. These discounts are negotiated, and often depend on whether a buyer can claim a credible alternative (e.g. a generic or close substitute). To the extent that novel drugs are less likely to have substitutes, we may expect unobserved discounts for novel drugs to be smaller. This would further bias us away from finding a positive relation between revenue and novelty.

Drug effectiveness

Next, we consider how novelty correlates with drug effectiveness. To do so, we follow [Kyle and Williams \(2017\)](#) and use the data from the French Haute Autorité de Santé (HAS), which assigns scores based on drug’s clinical contributions. 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 and I indicating the highest improvement relative to existing drugs. We match our data on developed drugs to their ASMR scores; the details are discussed in [Appendix C.5](#).

We find that novel drugs contribute greater clinical benefits. To see this, we estimate Equation (3), where now the definition of the dependent variable is either the raw ASMR score, or a binary variable that takes the value of one if the drug has been deemed of adding sufficient clinical value (ASMR scores below a threshold). Column 2 of [Table 2](#) reports results using our baseline specification, which examines whether a drug is assigned a score less than V (denoting it has some clinical benefit) and controls for the age of the drug, as measured by the launch year, company, and indication fixed effects. Comparing drugs of the same age, launched by the same firm that treat the same indication, a one-standard deviation increase in novelty is associated with a 5 percentage point increase in the likelihood that a drug is classified as adding any value ($ASMR < V$). These magnitudes are substantial, given that only 24 percent of drugs are classified as having any clinical value-added. [Panel B of Figure 4](#) provides a binned scatter plot. [Appendix Table A.7](#) reports results using additional specifications.

2.3 Novelty and Measures of Value for Drug Candidates

We next turn our attention to the relation between novelty and value for all drug candidates, regardless of whether they obtain FDA approval. To do so, we examine the characteristics of patents that are related to more or less novel drug candidates. Drug companies aim to patent all molecules that they suspect may have any pharmacological value. These patents are taken out very early in the pre-clinical testing processes, generally long before serious development begins on a drug. As such, measures of the economic value of a patent are likely informative of the *ex-ante* value of a drug candidate.

Measuring the economic value of a patent has received considerable attention in the literature. [Hall et al. \(2005\)](#) argue that patent citations are significantly related to economic value, based on the relation of firm valuation ratios and their patent portfolio. [Harhoff, Narin, Scherer, and Vopel \(1999\)](#) and [Moser, Ohmstedt, and Rhode \(2011\)](#) provide complementary evidence regarding the positive relation between patent citations and economic performance, and [Abrams and Sampat \(2017\)](#) specifically documents a relation between citations to drug patents and various measures of

private and social value. [Kogan et al. \(2017\)](#) provides a direct estimate of the market value of a patent based on the firm’s stock market reaction around a patent grant.

We therefore focus on two patent-level outcomes: the number of forward citations and the [Kogan et al. \(2017\)](#) contribution of the patent to the firm’s stock market value. We restrict our attention to key patents—that is, patents that are issued prior to any FDA approval. These patents are more likely to be related to a drug’s active ingredients, rather than to auxiliary innovations such as a drug’s manufacturing or mechanism of delivery. We link drug candidates to patents using the process described in [Appendix C.6](#). The resulting dataset has information on 31,915 patents, out of which 3,955 are issued by the USPTO and the rest are international patents.¹⁰ Since a drug may be associated with multiple main patents, our analysis in this section is at the drug-indication-patent level.

Patent citations

We begin by examining citations received by patents associate with more or less novel drug candidates. We estimate [Equation \(3\)](#) where now the dependent variable is equal to the logarithm of (one plus) the number of citation a patent receives. [Column 5 of Table 2](#) reports the results from our most conservative specification, which includes controls for the year the patent is granted interacted with the country where the patent is issued; the indication (ICD9) treated by the drug; company and drug age (year of development) fixed effects. [Panel C of Figure 4](#) provides a binned scatter plot of the results. [Panel A of Appendix Table A.8](#) examines how the choice of controls impacts our results.

We find that patents associated with novel drugs on average receive a larger number of forward citations. The correlation between our measure is both statistically and economically significant. Our estimates imply that a one-standard deviation increase in drug novelty is associated with an increase of 0.15 patent citations, which is economically significant when evaluated at the median number of citations a drug-related patent receives (2). As a robustness check, we replicate our analysis by restricting attention to patents issued in the US. [Panel B of Appendix Table A.8](#) displays the full set of results. We find that, using the full set of controls, the relation between novelty and future citations is statistically significant and comparable to the full sample: a one-standard deviation increase in novelty is associated with 0.36 more citations—relative to the median of number of citations in US patents in the sample (2). In this case, however, our estimates are sensitive to the choice of controls: omitting firm dummies results in estimates that are not statistically significant from zero.

¹⁰We scrape priority dates and the citation data for these 31,915 patents from Google Patents. We extend the analysis of [Kogan et al. \(2017\)](#) to all the US patents in our sample, which ends in September 2016.

Stock market reactions to patent grants

As further evidence that novel drugs generate higher economic benefits in expectation, we next examine the correlation between novelty and the [Kogan et al. \(2017\)](#) measure of patent values. Because patent approval occurs early in a drug’s development, market reactions to patent approval incorporate the likelihood that the drug candidate does not ultimately make it to market. 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 restriction reduces the sample to 5,130 drug-patent-indication observations, corresponding to 231 firms and 701 drug candidates. As before, we estimate a version of Equation (3), where now the dependent variable is the logarithm of the estimated contribution to firm value. We use the same set of controls as before. Column 6 of Table 2 reports the estimated coefficient b from our preferred specification that includes the full set of controls. Panel F of Figure 4 shows the associated binned scatter plot; Appendix Table A.9 reports estimates using different combinations of controls.

In brief, we find that patents of novel drug candidates are likely to contribute more to firm value than patents associated with me-too drugs. The economic magnitude of the estimated effects is substantial: a one-standard deviation increase in novelty is associated with an approximately 9.8 percent increase in the (estimated) value of associated patents. Since these point estimates incorporate the likelihood that the drug does not make it to market, they are considerably lower than the ones in Section 2.2 which condition on drug approval (20 percent). Given that it is unlikely that the patent office applies a higher threshold for patents associated with novel drugs, it is unlikely that our estimates of value are biased upwards for novel drugs.

2.4 Discussion and Caveats

Our results so far strongly suggest that novel drug candidates are riskier but higher expected return investments. Further, novel drugs are more likely to be commercially successful conditional on regulatory approval. However, given the difficulties associated with measuring value, several important caveats are in order. First, it is possible that novel drugs are more expensive to develop. 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 may work on multiple projects. One potential (though noisy) proxy for development costs are the number of patients enrolled in clinical trials and the number of trials associated with drugs. Since clinical trials are so expensive, recruiting patients and running trials constitutes a substantial proportion of a drug’s development cost. In Table A.10 and Figure A.8 in the Appendix, we consider how the number of patients and number of trials associated to a compound vary by its chemical novelty. We

find no consistent relationship between these proxies of development cost and drug novelty. Further, the stock market reaction to FDA approvals, or patent issues, should already incorporate production costs.

Second, the value of a drug candidate to the developing firm may also take into account its impact on a firm’s future portfolio through the unobserved value of learning, even in the case when a drug fails. However, it is likely that firms learn more from developing novel drugs, rather than derivative ones. For example, working on more cutting edge science may allow a firm (and its key talent) to gain skills more quickly, or learning that a newly hypothesized mechanism does not work may allow the firm to more efficiently allocate research funds to other approaches, which may lower the cost of future drug development. In these cases, our estimates would in fact understate the relative value of investing in novel drug candidates, relative to derivative candidates.

Comparing estimates of the value of *patents* associated with novel versus me-too drugs addresses many of these criticisms. The contribution of a patent to firm value incorporates the likelihood that the drug will be approved by the FDA; any benefits to the firm from drugs that are not approved; and production and other costs associated with bringing the drug to market. However, one may be concerned that our measures of patent value are estimated based on stock price movements. In particular, the relation we document between patent values and drug novelty may be spurious if it is driven by an unobservable firm characteristic that affects both the distribution of firm returns as well as drug development choices.

To verify that the link between novelty and patent values, we perform a series of placebo experiments. In each placebo experiment, we randomly generate a different issue date for each patent within the same year the patent is granted to the firm. We repeat this exercise 5,000 times and then reconstruct the [Kogan et al. \(2017\)](#) measure using the placebo grant dates. In [Appendix Figure A.9](#), we plot the distribution of the t -statistics corresponding to the point estimate of the relation between novelty and patent values, using the specification in [Column 6 of Table 2](#). We see that the distribution of t statistics across the placebo experiments is centered at zero. Our estimates lie on the tail of the distribution; only 2.3 percent of the simulations produce estimates that are of the same sign and greater statistical significance as ours. This suggests that it is unlikely that our results are spurious.

Keeping these caveats in mind, our estimates suggest that novel drug candidates are on average more valuable investments than me-too candidates. While novel candidates are less likely to obtain FDA approval, this is a diversifiable risk from the perspective of the firm’s shareholders, and should therefore not influence firm investment decisions in a frictionless market. By contrast, our results in [Section 1.3](#) indicate that firms devote substantial resources toward developing drug candidates that are derivative and that, in fact, the proportion of “me-too” drugs in development has been

steadily rising. This raises the question of why firms are behaving in this way. If novel drugs are indeed more valuable, why do firms develop so many me-too drugs? One possibility is that novel drug candidates are scarce and firms are already pursuing all valuable opportunities. Another view is that excessive risk aversion—for instance, due to the presence of financial frictions—constrains firms’ willingness to take risks and develop novel drug candidates. The next section explores this idea more fully.

3 Cashflow Shocks and Drug Development

We begin by discussing the channel through which shocks to firm cashflows affect drug development decisions. We then outline our empirical strategy and document our findings on the link between cashflow shocks and drug development decisions.

3.1 Theoretical framework

In the absence of financial frictions, shocks to cashflows that are orthogonal to the firm’s investment opportunities should have no effect on the firm’s drug development decisions. In such a world, all drug candidates that are deemed (ex-ante) profitable should be undertaken; the firm’s net worth or current cash reserves are irrelevant since the firm can raise external funds for all projects at no additional cost. By now, the literature on corporate financing decisions has concluded that this frictionless benchmark is not consistent with the data and has argued for the importance of financial frictions (see, e.g. [Kerr and Nanda, 2015](#), for a summary of the literature on financing frictions and R&D).

We present a simple, yet tractable, model of investment in (potentially) innovative drugs. The goals of the model are twofold. First, it provides intuition about how the presence of financing can lead firms to develop not only fewer drugs, but also even fewer novel drugs—relative to a frictionless benchmark. Second, the model clarifies how firms drug development decisions may respond to a cashflow shock. Our model builds on [Bolton, Chen, and Wang \(2011\)](#), which provide a tractable framework to study dynamic investment, financing, and risk management decisions for financially constrained firms in continuous time. To simplify exposition, we outline the main ingredients of the model and then discuss its key predictors. All technical details are provided in [Appendix B](#).

Model setup and solution

Firms grow by developing new drugs. We denote the scale of the firm by K , which here can be thought of as the firm’s customer base. Each period, with probability λdt the firm gets an opportunity to develop a new drug candidate. Drug candidates are characterized by their probability

of success p (e.g., their ex-ante likelihood of FDA approval) and their contribution to the firm's customer base (that is, their value) given by χ , conditional on approval. When a firm receives a development opportunity, it draws a pair (p, χ) from a distribution $G(p, \chi)$. Given (p, χ) , the firm decides whether to develop the drug or not, $I \in \{0, 1\}$. Developing a drug costs fK . If developed, the drug is approved with probability p . If the firm foregoes that opportunity, we assume that it cannot pursue it in the future. The evolution of firm scale K_t is therefore given by

$$\frac{dK_t}{K_t} = \chi I_t \tilde{S} dN_t - \delta dt. \quad (4)$$

Here, dN_t is a Poisson variable with intensity λdt that counts the number of opportunities the firm has received in the past; \tilde{S} is an random variable denoting drug success, with $E[\tilde{S}|p, \chi] = p$. When drugs are successful ($\tilde{S} = 1$), the firm's customer base increases proportionally by a factor χ . If they are unsuccessful, there is no increase in the customer base; in either case, the firm's customer base depreciates at a rate δ .

The firm's flow operating revenue over an instant dt is given by $K_t dA_t$, where dA_t is an i.i.d. shock to profits, that could arise either due to changes in productivity or demand,

$$dA_t = \mu dt + \sigma dZ_t. \quad (5)$$

Here, Z_t is a standard Brownian motion. The parameters μ and σ govern the mean, and volatility, of the profitability shock dA_t . Firm profits depend its scale of operations or customer base, K_t .

The firm's operating cashflows—revenue minus development costs—are therefore equal to

$$dY_t = K_t dA_t - I_t f K_t dN_t. \quad (6)$$

Firms can fund drug development through accumulated cash or external financing. External financing has a fixed and variable cost. First, to access finance, a firm needs to pay a cost equal to $\Phi_t = \phi K_t$. Denote by H_t the firm's cumulative external financing up to time t , and hence by dH_t the firm's incremental external financing over time interval $(t, t + dt)$. In addition to a fixed cost, there is a marginal cost of external financing equal to γdH_t . Similarly, let X_t denote the cumulative costs of external financing up to time t , and dX_t the incremental costs of raising incremental external funds dH_t . The cumulative external equity issuance H and the associated cumulative costs X are stochastic controls chosen by the firm.

Given our assumptions, the firm's cash holdings evolve according to

$$dW_t = dY_t + (r - c)W_t dt + dH_t - dU_t, \quad (7)$$

where $r - c$ is the return on the firm's cash holdings, dH_t is external financing, and dU_t denotes payments from the firm to investors.

Finally, the firm makes investment and finance decisions to maximize its value to its owners,

$$V(W_t, K_t) = \max_{H, U, I} E_t \int_t^\infty e^{-r(s-t)} \left(\underbrace{K_s dA_s - I_s f K_s dN_s + (r - c) W_s ds - dX_s}_{dU_s - dH_s} \right),$$

subject to (4)–(5). That is, the firm is maximizing its net payout to investors after financing costs.

Given our assumptions, the value of the firm can be written as

$$V(W_t, K_t) = v(w_t) K_t, \quad w_t \equiv \frac{W_t}{K_t}, \quad (8)$$

where the function $v(w)$ solves the Hamilton-Jacobi-Bellman equation (B.9) in Appendix B.

Model predictions

Given the form of the firm's value function (8), the key variable that determines firm policies is its cash holdings to scale ratio w . Figure 5 plots the level and the gradient of the firm's value function, $v(w)$, as a function of w .

We see that $v(w)$ is concave for $w \in [0, \bar{w}]$, which implies that the firm exhibits risk aversion. This concavity arises from the presence of external financing costs that the firm incurs when its cash balances drop to zero. The firm internalizes this, and will therefore be reluctant to take risks that increase the likelihood that it needs to raise costly finance in the future. Further, for $w \in (0, \bar{w})$, the marginal value of cash $v'(w)$ exceeds one. This implies that when a firm with limited cash balances will retain earnings, rather than paying dividends to investors. Firms does so because cash provides them with the funds to invest in potential drugs without having to raise as much external capital. At the point $w = \bar{w}$ the firm has sufficient cash balances, so that it pays any amount of cash in excess of \bar{w} as dividends to its shareholders. Because the firm raises cash at $w = 0$ and pays excess cash at $w = \bar{w}$, w will fall between 0 and \bar{w} in equilibrium.

We next turn to drug development decisions. In a world without external financing costs, the value of the firm is independent of its cash holdings, and therefore $v(w)$ is constant and equal to \bar{v} . In that case, the firm will develop all drugs i whose expected payoff exceeds their development cost,

$$\bar{v} p_i \chi_i \geq f. \quad (9)$$

By contrast, in the presence of financing frictions, the firm decision rule is given by

$$p_i (1 + \chi_i) v \left(\frac{w - f}{1 + \chi_i} \right) + (1 - p_i) v (w - f) - v(w) \geq f. \quad (10)$$

The first term is the firm’s new value function if its drug is approved, which it is with probability p_i . In the case it is not, with probability $1 - p_i$, the firm’s new value function is instead given by the middle term. The last term, $v(w)$ is simply the firm’s starting value.

Comparing (10) to the frictionless case (9), yields three key insights which follow directly from the concavity of $v(w)$. First, the threshold for developing a new drug is higher in the presence of frictions, so fewer drugs will be developed. Second, the left hand side of (10) is increasing in w : the same drug is more likely to be developed at a firm with more cash than in a firm with less cash. Last, this effect differs with the a drug’s probability of success p_i —which summarizes its level of risk. Holding constant a drug’s expected payoff $p_i \chi_i$, increases in riskiness (decreases in p_i), will decrease a firm’s expected payoff. Thus, the firm will apply a higher threshold to riskier projects than safer projects, even if a drug’s expected value is unchanged. The magnitude of this distortion will decrease with the level of cash balances to firm scale, w

Figure 6 illustrates these tradeoffs. In Panel A, we plot the acceptance threshold, as a function of cash balances, for two drugs with the same expected value, $p \chi$, but different levels of risk (captured by the acceptance probability p). The blue line represents a safer drug, and the red line represents a riskier one. First, we see that different firms will make different development decisions for the same drug: firms with cash above a certain threshold w^i will develop drug i , while those with cash below this threshold will pass. Second, we see that the exact threshold differs for safe (m) versus risky drugs (n). In particular, the safer drug has a lower acceptance threshold than the riskier drug, $w^m < w^n$. That is, ceteris paribus, safer drugs are more likely to get funded than riskier drugs.

Panel B illustrates the implications for the development threshold associated with more or less risky drugs. The x -axis tracks a drug’s likelihood of success, with riskier drugs closer to the origin. The y -axis tracks a drug’s expected value $p \chi$. The lines plot how the firm’s threshold for investing in a drug relates to the drug’s riskiness. In a frictionless world, firms apply the same threshold regardless of risk: they will invest in all drugs whose expected value $p \chi$ exceeds a threshold that is independent of their probability of success p . When firms face financing frictions, however, they become sensitive to risk. Firms apply a higher threshold for risky drugs than for less risky drugs. The overall level threshold is higher as well, indicating that fewer drugs get developed.

Panels C and D illustrate how these frictions may impact the novelty of drugs that are developed. To illustrate which predictions are robust, we consider two cases: one in which the distribution of expected value among novel drugs is better, and one in which it is worse. Panel C illustrates

the case where novel drugs have higher expected value on average: the blue line represents less novel drugs and the red line represents more novel ones. In a frictionless world, firms invest in all drugs, novel or not, developing all drugs with expected value $p\chi$ to the right of the frictionless benchmark v^{fb} , equating the expected values of the marginal novel and not novel drug. When there are financing frictions, however, firms impose a higher threshold v^n for novel (which we have shown to be more risky) drugs than for less novel v^m (less risky) ones. The shaded blue area represents less-novel drugs that are ‘missing,’ that is drugs that would have been developed in the absence of financing frictions but which are not. Similarly, the shaded red area represents missing novel drugs. Similarly, Panel D illustrates the same phenomenon under a different set of assumptions about the distribution of expected value among novel and less novel drugs.

What would happen if firms received more cash—that is, if w increases exogenously? This would lead firms to decrease the threshold they apply for both novel and less novel drugs closer to the frictionless benchmark v^{fb} . This model makes two unambiguous predictions about how a firm facing financing frictions will respond to cashflow shocks. First, it will develop weakly more novel drugs, and weakly more me-too drugs. The model also predicts that the value of marginal novel drugs will be higher than that of marginal derivative drugs. These predictions can be seen in Panels C and D: in both cases, relaxing financial frictions will increase drug development, and the marginal novel drug will always be weakly more valuable than the marginal non-novel drug because the acceptance threshold for novel drugs is always weakly higher than for me-too drugs.

The model, however, does not make general predictions about how an increase in cash would impact the *relative number* of novel vs me-too drugs. In general, this would depend on the number and distribution of potential candidates of each type. To see this, note that in Panel C, there would be more marginal novel drugs than marginal me-too drugs, whereas the opposite is true in Panel D. This means that the model does not make predictions about either the overall novelty or value of the marginal drugs a firm invests in, relative to their inframarginal investments. Nevertheless, as long as the distribution of potential drug candidates is not too different, we are likely to see a greater increase among novel drug candidates.¹¹

¹¹One such example is AbbVie, which had the world’s top selling drug (Humira) from 2012–2017. With the profits from Humira, a biologic that sells for roughly \$5,000 for a prescription, AbbVie made some big risky bets in some notoriously difficult drug development areas. The company invested more than \$200 million in an R&D partnership with Alector to develop immunotherapies for Alzheimer’s disease, and another \$250 million in a deal with Google’s Calico to take on multiple new drugs in neurodegeneration and cancer. While these therapeutic areas are undeniably huge, both partnerships are incredibly risky given the rough track record of developing drugs for neurological diseases, and the relative inexperience of the partner companies. (<https://www.fiercebiotech.com/partnering/updated-abbvie-partners-google-s-calico-on-1-5b-r-d-operation-focused-on-aging>, <https://www.reuters.com/article/us-abbvie-alzheimers/abbvie-bets-on-alzheimers-immunotherapy-with-big-biotech-deal-idUSKBN1CT1NT>)

Discussion of Modeling Assumptions

The key assumption in the model is the presence of external costs of external finance. Theoretical foundations for these frictions include asymmetric information (Myers and Majluf, 1984) or limited enforcement (see e.g., Tirole, 2010, for a textbook treatment). Indeed, these frictions are likely to be particularly relevant for pharmaceutical firms, given the likely information asymmetry between the firm and outside investors regarding the potential of a new drug candidate, or the difficulty of collateralizing intellectual property before its value has been proven (Hall and Lerner, 2010). The central prediction of models with financing frictions is that such frictions induce risk averse behavior on the part of firms (see, e.g. Froot et al., 1993). Firms want to avoid states of the world in which they need to access costly external funds; a shock to either current or future profits makes such states less likely—since firms will have a larger buffer of internal funds available tomorrow—and therefore induces more risk-taking behavior on the part of firms.

In the interest of tractability we have made some simplifying assumptions. These assumptions allow us to illustrate the economic forces at play and are not driving our results.

First, we assume that production and financing costs scale with firm size. This assumption greatly simplifies the solution of the model—constant returns to scale imply that the only relevant state variable for firm decisions is the firm’s cash balances to firm scale, w . In the absence of constant returns, we would need to keep track of two state variables K and W separately, which greatly complicates the solution of the model. This assumption does not affect the main implications of the model: firms will be risk averse and discriminate against riskier (novel) drugs. Shocks to firm net worth will ameliorate this risk aversion. Nevertheless, this discussion reveals that our model will be not very useful in comparing the behavior of large versus small firms. A richer model that relaxes the constant returns to scale assumption and allows for more firm heterogeneity—for example, differences in firm investment opportunities (λ)—is an interesting extension of our model that we leave for future work.

Second, the model has i.i.d. shocks to firm profitability. This means that cashflow shocks in our model are unanticipated, so that firms effectively respond to changes in current cash balances induced by profit shocks. In our empirical analysis, our identifying variation will generate a shock to expected future cashflows. The same intuition will continue to hold in this case: firms are risk averse because they want to avoid states of issuing costly external finance in the future; a positive shock to future cashflows makes those states of the world less likely and will therefore induces firms to take on more risk, just as a shock to current cashflows would.

Model Interpretation

The key economic mechanism that generates risk aversion in the model is that decision makers wish to avoid states of the world in which project cashflows are low—even when these returns are idiosyncratic. In the model described above, this result arises due to the presence of costly ‘external’ finance.

Our notion of ‘internal’ versus ‘external’ capital allows for several interpretations. As we discussed above, asymmetric information between a firm and its potential outside investors can generate a wedge between the cost of financing a project with internal cashflows and the cost of raising outside funds (Myers and Majluf, 1984). Here, the notion of internal versus external is defined by the boundary of the firm. Our model, however, also applies to cases in which similar boundaries exist within the firm. For instance, a senior manager in charge of cancer research may be allocated a budget by firm headquarters; if she pursues a risky project that fails, she will have to seek additional funds from headquarters to continue her division’s work. However, just as there may be asymmetric information between a firm and the market, firms may not perfectly observe the effort of their employees. Knowing this, a division manager may choose to pursue safer projects to avoid states of the world in which she will have to explain failure to the CEO or members of the board.

More broadly, the presence of agency frictions within the firm may lead managers to choose projects that maximize their own utility rather than the shareholder value of the firm. For example, a firm’s senior managers may hold a significant fraction of their wealth in their own firm, and hence be poorly diversified (see, e.g. Smith and Stulz, 1985). In this case, a positive shock to *firm* net worth may lead to greater investment in (idiosyncratically) riskier projects—not by alleviating the firm’s own risk aversion—but rather by reducing the effective risk aversion of the firm’s senior managers.

3.2 Identification Strategy

To identify the causal impact of a shock to firm cashflows on drug development, we exploit the introduction of Medicare Part D, a provision of the 2003 Medicare Modernization Act that expanded prescription drug coverage for elderly Americans to include prescription drugs taken at home. Previous work has shown that the passage of Part D (and its implementation in 2006) led to an increase in sales of drugs to elderly consumers, a decrease in their price, and an overall increase in the market value of the firms that produce high elderly-share drugs (Lichtenberg and Sun, 2007; Duggan and Scott Morton, 2010; Friedman, 2009). To identify a shock to cashflows we utilize an additional source of pre-existing variation—the remaining life of a firm’s patents. In particular, the

extent to which a firm benefits from the introduction of Part D depends not only on the types of drugs it sells (elderly share), but also on the amount of market exclusivity remaining on those drugs. Our empirical strategy makes use of both these sources of variation in order to isolate the impact of Part D that comes through a shock to a firm’s cashflows in particular.

First, the extent to which firms benefit from Part D depends on whether its customers are in the Medicare population. A firm with drugs for osteoporosis would expect an increase in cashflows because Part D ensures that its potential customers will now be reimbursed for their purchase of its products. By contrast, a firm that only sells drugs for pediatric conditions should not expect to see an increase in sales, except possibly through secondary factors such as wealth effects. 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. Appendix C.3 describes the matching process. We define a drug’s MMS as the share of revenues generated by patients over 65 in 2003, just prior to the introduction of Part D. We then construct a firm-level Medicare exposure by aggregating these drug-specific MMS values into Firm MMS $_{f,2003}$, which is the firm-average of drug level MMS.

Second, the extent to which firms benefit from Part D also depends on the amount of market exclusivity remaining on their current drug portfolios. A drug’s exclusivity period is determined by the amount of time remaining on its patents (generally 20 years from the filing date), as well as the existence of any federally legislated FDA extensions to this term.¹² Firms with greater remaining exclusivity on their drugs in 2003 would expect to benefit more from the introduction of Part D, because of their longer horizon for charging monopoly prices. To determine remaining exclusivity for each firm’s drugs, we match drugs approved as of 2003 to their associated patents and, where possible, link the drugs to their key patent expiration dates and FDA exclusivity extensions. 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. Since our data on exclusivity periods is somewhat noisy, we minimize measurement error

¹²The FDA will grant extensions on a drug’s market exclusivity period, beyond the relevant patent expiration date, under a number of scenarios that are outlined in legislation (as opposed to extensions being negotiated with firms on a case by case basis). For example, the Orphan Drug Act of 1983 incentivizes the development of drugs for rare (“orphan”) diseases through different provisions, including a guarantee of seven years of market exclusivity. Other legislation also sets aside market exclusivity for additional drug designations (e.g., five years for New Chemical Entities, and six months for Pediatric Exclusivity). For more information on our drug-to-patent data and patent expiration dates see the Online Appendix, Section C.6

using a cutoff rule. In our baseline results we define long exclusivity as 5, or more, years, which is close to the median remaining life in our sample. Our results are robust to alternative cutoffs of 7 and 10 year thresholds, as shown in Appendix Table A.23.

We incorporate both the elderly share and market exclusivity sources of variation into a new firm-specific measure of exposure to Part D:

$$\text{Medicare Drug Life}_{f,2003} = \sum_{i \in A_f} \left[\frac{\text{Drug MMS}_{i,2003}}{\sum_{j \in A} \text{Drug MMS}_{j,2003}} \mathbb{I}(\text{on patent in } X \text{ yrs})_{i,2003} \right] \quad (11)$$

Here, firm f 's Medicare Drug Life in 2003 is defined as the proportion of its approved drugs ($i \in A_f$) with long remaining exclusivity as of 2003, weighted by their drug-level MMS. Firms with the highest Medicare Drug Life are those with long exclusivity on high MMS drugs.

We note that simply comparing high vs. low Medicare Drug Life firms does not isolate the impact of expected cash flow. Firms with high Medicare Drug Life may change their investment behavior following Part D for three reasons: a) they expect greater cashflows due to increased demand for their existing drugs (this is the effect we would like to identify); b) they expect increased returns to future investments (we call this the demand channel); and c) their future development decisions differ not because of Part D, but because high Medicare Drug Life firms have a younger portfolio of drugs in general, and so may differ in their taste for exploratory work because they are at different points in the product development cycle. To isolate the first channel, we estimate the following regression, which takes advantage of variation in Medicare Drug Life, *holding constant* a firm's overall elderly share and its overall drug life:

$$\begin{aligned} \text{New Drug Candidates}_{ft} = & a_0 + a_1 \text{Post} \times \text{Medicare Drug Life}_{f,2003} & (12) \\ & + a_2 \text{Post} \times \text{Overall Drug Life}_{f,2003} \\ & + a_3 \text{Post} \times \text{Firm MMS}_{f,2003} + \delta_f + \delta_t + e_{ft} \end{aligned}$$

Our main coefficient of interest is a_1 , which captures the *cashflow* impact of our main treatment variable defined in Equation (11). We control for an interactions with the post Part D period for both Overall Drug Life and Firm MMS $_{f,2003}$. In our baseline specification we include firm- and quarter-dummies to 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.20 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.

In Equation (12), our identifying variation for a_1 comes from firms that have the same share of elderly drugs, and the same overall remaining market exclusivity but which differ in how this remaining exclusivity is allocated across high and low elderly share drugs. To see this, consider a simple example. There are 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). Both firms have one drug that will expire soon and another that will not. Since both firms have the same Firm MMS and the same overall drug life, 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 that these firms differ in which of its drugs will remain on patent: drug H_A for Firm A , but drug L_B for Firm B . In this case, despite their other similarities, we would intuitively expect Firm A to receive a greater cashflow shock as a result of Part D because its high MMS drug is the one that will remain on patent. This is what the identifying variation in Equation (12) is based on: holding constant firm MMS and Overall Drug Life, 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 $\frac{75}{75+50} \times 0 + \frac{50}{75+50} \times 1 = 0.4$.¹³

Before continuing, we note that this empirical strategy requires that we observe the MMS and remaining exclusivity of a firm's marketed drugs, as of 2003. As a result, the firms in this analysis tend to be larger and more established than the full set of firms we observe when we examined the characteristics of novel drugs in Section 2.2. The type of selection can be seen in Table 1: our original sample included over 12,000 drug candidates from 3,108 firms while our cashflow analysis sample consists of approximately 6,000 candidates from 270 firms. This sample change is explained by the fact that many firms in our descriptive sample have never had a successful approved drug; indeed, 1,525 firms have only one drug candidate. By contrast, our sample restrictions do not significantly impact the number of approved drugs that we observe: 356 out of 392 approved drugs are represented in this cashflow analysis sample, consistent with the intuition that our empirical strategy selects for larger, more established firms.¹⁴

¹³Table 3 describes the distribution of this 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 only one approved drug on the market as of 2003, so that their treatment values can only be 0 or 1. Appendix Figure A.10 shows a smoother distribution of Medicare Drug Life for firms with non extremal values and we show in Appendix Tables A.22 and A.26 that our results are robust to restricting to this subsample, or to using a binary treatment measure.

¹⁴The descriptives that we report in Section 2.2 continue to hold for drugs associated with firms in our cashflow analysis sample. Indeed, our analysis on the relationship between novelty and measures of value for approved drugs is largely the same because 90 percent of these drugs are associated with firms in our natural experiment sample.

3.3 Results

Table 3 contains summary statistics of our dataset at the company–quarter level. 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. We therefore use the logarithm of one plus the number of new, or the number of novel drugs, as our primary outcome measures. In the Appendix, we show that our findings are robust to using alternative specifications, including count models (see A.21).

New Candidates

Table 4 examines the causal impact of a financial shock, as described in Equation (12), on the total number new drug candidates under development by our sample firms. Columns 1 to 3 focus on the count of new candidates; Columns 4 to 6 focus on the logarithm of one plus the number of new candidates, which is our preferred outcome 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). 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 materially affect our point estimates, suggesting that (in our sample) demand effects do not appear to increase development separately from cash flow effects.¹⁵ For the remainder of our analysis, we use Column 6 as our baseline specification.

The estimated magnitudes are 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 percent increase in the number of new drug candidates. This corresponds to an elasticity of output to treatment of 0.40.¹⁶ In Section 3.6, we translate these magnitudes in terms of dollars for a subset of our firms.

¹⁵This finding may differ from drug market-level estimates of the impact of demand on innovation because our firm-level analysis does not capture the innovation impact of entry by new firms.

¹⁶To 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).

Novelty of New Candidates

Next, we examine the novelty of the marginal drug candidates that are developed as a result of the cash flow shock we identify. Panel A of Figure 7 reports estimates of Equation (12) where the outcome variable is the number of drug candidates with a given similarity score. We see that the greatest increase in new candidates comes from an increase in candidates with maximum similarity scores between 0.3 and 0.6. We see no increase in very similar (me-too) candidates, defined as those with chemical similarity greater than 0.9. We also do not see increases in the number of drugs with similarity below 0.3, perhaps because fewer than 8 percent of candidates have novelty scores in that range (see Table 1).

Since the number of drugs in each bin does vary, we also report the estimates across novelty deciles in Panel B of Figure 7. Again, we see that the increase in overall drug development that we document is driven by relatively more novel drugs. The response for highly similar drugs, those in the top quintile of similarity, are smaller in magnitude and not statistically different from zero.

Taken together, our findings are consistent with the presence of financing frictions in drug development, as described by our model, or as in other models such as Froot et al. (1993). We see that a relaxing of financing concerns increases total drug development and, in particular, leads to the development of more novel drugs. Interestingly, we do not find an increase in the development of more me-too drugs, even though our model allows for the possibility that firms may invest in these types of drugs as well. Our finding therefore suggests something about the shape of the distribution of potential drugs available to them, as schematically illustrated in Panels C and D of Figure 6. At least at the margin of the cashflow shock we identify, it appears that the number of “missing” novel drugs is substantially greater than the number of missing me-too drugs.

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 8 and 9 show how the estimated effect of the cashflow shock on the number of new and novel drugs, respectively, vary over time. Focusing on Figure 8, 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. This suggests that their development opportunities and patterns were largely similar prior to the policy. 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. Similarly, Figure 9 shows that the number of drugs in the bottom three quartiles of similarity (shown in the top two panels and bottom left panel) increases following the introduction of Part D. By contrast, we see

no such increase in output for the most chemically derivative drugs. To address any remaining concerns about preexisting trends, Appendix Table A.20 also shows that our main results are robust to including company-year-quarter linear trends.

In Figure 9, we also 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 January 1, 2006, suggesting that firms' development decisions were responsive to positive shocks to net worth arising from higher expectations of future cashflows.¹⁷ The fact that firms can quickly alter their development pipeline is not particularly surprising for our sample of firms, those with an approved drug in 2003. Since these firms are more established, they likely have a stock of potential drug candidates in the discovery phases of development at any given point in time. Indeed, the majority of drug candidates that entered development in 2004 or 2005 are based on at least one patent application that was filed prior to the introduction of Medicare Part D in late 2003 (86 and 66 percent, respectively).

In addition to developing new candidates, treated firms may also advance existing drug candidates to later stages of development, and the timing of these responses may differ by stage: pre-clinical, Phase 1, Phase 2, and Phase 3. Figure 10 plots event studies for the impact of cashflow on the number of new drug candidates entering each stage of development. We find the largest and most immediate response for drugs entering pre-clinical development. We find smaller—and more delayed—impacts on the number of new drugs entering Phase 1, and even more delayed results for Phase 2, where we don't find any significant changes until 2012. These patterns are consistent with treated firms engaging in more early stage experimentation—knowing that the bulk of development costs are only incurred in later phases, and only for candidates that end up showing promise. Indeed, the delayed increase in Phase 1 and Phase 2 trials that we see may in part reflect the later success of some of the earlier stage investments that we observe initially.

3.4 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 fit into firms' existing portfolios.

¹⁷The model in Section 3 has i.i.d. cashflow shocks. However, the same intuition applies if firms were anticipating a shock to future profits: firms would internalize that the likelihood that they need to raise costly external finance would fall, which would imply that they are more willing to take risks today. Further, some firms may have seen actual cashflow increases earlier than 2006, as a result of Medicare's Drug Discount and Transitional Assistance Programs, which operated from 2004 to 2006. These programs spent about \$1.5 billion over an 18 month time period (Huh and Reif, 2017).

Portfolio diversification

If risk aversion is an important determinant of drug development decisions, then we would expect firms to take steps to reduce the overall risk of their drug portfolio. In particular, firms receiving a cashflow shock may want to use these marginal funds to help diversify its existing portfolio of drugs.

Our empirical results support this prediction. Table 5 considers how these new drugs relate to the firm’s existing portfolio of drug investments. Columns 1 and 2 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 for which they have not developed candidates in the past. 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 within-firm Herfindahl. Columns 3 and 4 show that firms also diversify their portfolios by investing in drugs with different biological targets.

Drug development across patient age groups

A potential concern with our empirical design is that firms which experience a greater shock to their net worth as a result of Medicare Part D may also experience a greater increase in investment opportunities arising from increased demand for elderly share drugs. If our identification strategy is not fully successful in isolating a cashflow shock from increased demand for new drugs covered by Part D, then we would expect the increase in drug development that we observe to be driven by an increase in drugs that target elderly patients (high MMS drugs).

We find that this is not the case. Although we identify an expected cashflow shock that comes from an expansion of coverage for elderly patients, we find that firms respond to this increase by developing new drugs for patients of all ages. In Panel A of Table 6, we split our outcome variable (log of one plus number of new compounds) by the quartile of Medicare market share (MMS) that the new drugs fall into. Comparing the elasticities across Columns 1 through 4, we see that firms are equally responsive in developing drugs across all MMS quartiles. In Panel B, we narrow our focus on drugs that are explicitly targeted toward younger consumers, an area that definitely did not experience any demand shock as a result of Medicare Part D. In Columns 1 and 2, we show that treated firms increase their development of drugs for conditions in which fewer than 5 or 10 percent of patients are elderly. In Column 3, we consider the development of drugs for pediatric conditions—those defined as indications for which an above median share of drug trials require enrollees to be newborns, infants, pre-school aged children, or simply just children. Column 4

expands this definition to include indications in which drug trials often explicitly require adolescents or young adults. In all cases, we observe a relative increase in development for more treated firms.

One may be concerned that increases in cashflows may spur additional development, but only increases in demand lead to investments in innovation. Table 7 shows that this is not the case. Examining Panels A through C, we see that firms respond to increased net worth by developing more novel—as opposed to “me-too”—drugs for the non-elderly market: we consistently see more novel drugs for below median MMS conditions, pediatric conditions, and conditions primarily afflicting children and young adults. The overall shift toward more novel drugs that we observe is therefore not driven solely by innovation in high elderly share categories.

Collectively, these results indicate that financial frictions lead to missing drugs—in particular, missing novelty—across a broad array of patient groups. The fact that firms are developing new drugs that target younger patients, and not just drugs in the market that experienced a positive demand shock as a result of Medicare Part D, further indicates that our identification strategy is at least partially successful in isolating a shock to the profitability of current assets from a shock to firms’ investment opportunities.

3.5 Firm Heterogeneity

We next examine how the impact of cashflows on drug development decisions varies across firms. One might expect firms that are more financially constrained are more responsive. It is important to note, however, that identifying which firms are likely to be financially constrained is challenging (Farre-Mensa and Ljungqvist, 2016). Financial constraints are a function both of a firm’s financing cost, and of its investment opportunities. Hence, financial frictions may not matter for some small firms because they have no investment opportunities. Conversely, financial frictions may be more salient for certain large public firms with valuable investment opportunities. Further, a firm’s cash holdings are (partly) a choice variable; large cash holdings may indicate that firms are less constrained, but they may also be an endogenous response on the part of firms that are constrained. As such, neither size nor the level of cash holdings are likely to be appropriate measures of financial constraints.

With these caveats in mind, we explore whether a given dollar increase in cashflows is likely to be more relevant for firms that had low prior profits than for firms with high prior profits. As a proxy for prior profitability, we create a measure of the firms’ total revenues generated by drug candidates that are approved prior to 2003. We then estimate Equation (12) separately across the firms that are below or above the median prior firm revenue in 2003.

Table 8 presents the results. We see that the estimated coefficient a_1 on the main treatment effect is statistically significant for the firms with low prior revenue (Column 3). For the firms with higher past revenue (Column 2), the point estimates are larger, but less precisely estimated. In terms of elasticities, firms with low past revenue display a larger response: a one percent increase in the main treatment variable is associated with a 0.64 vs 0.30 percentage increase in the number of drug candidates across low- and high-revenue firms, respectively. By contrast, we find no meaningful differences in the impact of cashflows between these two sets of firms on their propensity to develop novel vs me-too drugs—see Appendix Figure A.12.

In sum, we find that firms with low past revenues are more sensitive to the treatment than firms with high past revenues—though the difference is not statistically significant. These results, however, should be interpreted with caution because our measure of firm size conflates prior revenue with firm experience. More experienced firms likely have more opportunities to develop novel drugs than less experienced firms. Thus, the lack of differential response of across the two sets of firms is not particularly surprising; there is simply not enough variation in the data to separate past cashflows from investment opportunities.

3.6 Magnitudes

Our analysis so far has been qualitative in nature. Our central finding is 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 percent of our sample firms. For these firms, we estimate our main specification, as defined by Equation (12), but with the log of firm profits and R&D spending as dependent variables. These results are reported in Table 9. Columns 1 and 2 show that firms with higher Medicare Drug Life in 2003 experienced higher growth in R&D and operating cashflows in the years following treatment.¹⁸

¹⁸Columns 3 and 4 examine whether treated firms responded by increasing their borrowing—an alternative explanation for why firms appeared to increase their drug development before Part D cashflows were realized. Our point estimates suggest this may be the case, but our coefficients are too noisily estimated to conclude that the response is different from zero. Part of this may be due to the possibility the fact that pharmaceutical firms are significantly less likely than other firms to use debt financing (see, e.g. Table A.1 in Appendix) given the relative difficulty of collateralizing their IP.

These results can be used to compute the elasticity of drug development with respect to firm R&D spending. Using the point estimate (0.98) from Column 1 multiplied by the mean of treatment exposure in the pre-period (0.54) yields an elasticity of treatment exposure to R&D expenditure of 0.53. 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 similarity, respectively. These magnitudes are broadly consistent with the literature.¹⁹

3.7 Additional Results and Robustness

Here, we provide a brief description of some additional results. We refer the reader to Appendix D for remaining robustness and specification checks.

In Section 3.3 we showed that firms that experienced an increase in cashflows developed more novel drugs. A natural question is whether these new candidates were developed in-house or acquired by another firm. We find that the increase in development we see is primarily accounted for by an increase in in-house development, rather than acquisitions (Table A.12 and Figure A.14 in the Appendix). 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.15 and Figure A.15 in the Appendix). In interpreting this result, 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 Life).

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

¹⁹There 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. With those considerations in mind, our benchmark elasticity estimate is consistent with the range of estimates that exist in the literature. For instance, Henderson and Cockburn (1996), 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. If firms are more responsive to their own spending, we would expect private elasticities to be greater than public elasticities. More recently, Azoulay, Graff-Zivin, Li, and Sampat (2016) estimate the casual impact of *public* investments in biomedical research on patenting and drug development by private firms and find elasticities of approximately 0.4–0.6. Dubois, de Mouzon, Scott-Morton, and Seabright (Dubois et al.) uses variation in demographic trends, and finds a smaller elasticities of innovation to market size of 0.23. We may find a larger impact in part because the increase in novel drug development that we document may reflect the development of pre-existing research ideas—which were unexplored by choice (for instance, due to risk aversion).

is that it can only be applied to small molecule drugs, and not to more complex biological entities, known as biologics, which make up a smaller fraction of pharmaceutical output but which have been a growing area of R&D focus. 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.18 in the 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. In Table A.19, we also look at alternative measures of novelty based on a hierarchical classification used to classify drugs' molecular targets. These less precise alternative novelty definitions also yield qualitatively similar results: more treated firms disproportionately increase their investments in novel drugs.

4 Conclusion

We introduce a new measure of drug novelty based on molecular structure and investigate firms' decisions to develop novel vs. derivative drug candidates. Our analysis of the economic characteristics of novel drug candidates indicates that firms face a risk-reward tradeoff when deciding whether to pursue more exploratory research. Novel candidates are less likely to be approved by the FDA but, across a range of measures, appear to be better investments ex-ante (based on proxies for the value of their underlying patents) and ex-post, if they are approved (based on measures of clinical value-added and private market returns).

In the second part of the paper, we show that—contrary to models of investment without financial frictions—firms experience greater shocks to their net worth respond by developing more drugs in general and more novel drugs in particular. These marginal drugs target a range of conditions—including pediatric conditions—and are not simply a response to an increase in demand for elderly drugs. Our results suggest that increased cashflows lead to more innovation by reducing firms' effective risk aversion, and therefore enabling them to invest in high-value exploratory research. Because novel drugs are based on more valuable patents ex-ante, our results are less consistent with a model in which managers or firms spend additional resources on wasteful empire building.

Overall, our results suggest that risk aversion arising from financial frictions leads firms to invest too conservatively, resulting in a pattern of missing novelty across a variety of research areas. By proposing a specific mechanism—risk aversion—we also point to a wider array of potential policy responses. Specifically, rather than supporting policies that increase pharmaceutical profits, our paper lends support for policies that alter the relative risk/reward tradeoff associated with investing in novel vs. me-too drugs. For example, creating larger portfolios of drug candidates may allow firms to bear more idiosyncratic risk by decreasing aggregate risk. Such an idea has been suggested

by [Fernandez et al. \(2012\)](#) and is also similar to the strategies of venture capital firms, who are able to invest in and encourage risk taking in small biotech firms because this risk is part of a larger portfolio of investments. Our results also lends support to efforts to encourage innovation by either increasing the risks or lowering the benefit associated with developing derivative drugs—for example by limiting reimbursement for drugs that show little value relative to existing treatments. Our paper therefore points toward a variety of avenues for future research.

References

- Abrams, D. and B. Sampat (2017). What’s the value of patent citations? evidence from pharmaceuticals. *Working Paper*.
- Acemoglu, D. and J. Linn (2004). Market size in innovation: Theory and evidence from the pharmaceutical industry. *The Quarterly Journal of Economics* 119(3), 1049–1090.
- Almeida, H., M. Campello, B. Laranjeira, and S. Weisbenner (2011). Corporate Debt Maturity and the Real Effects of the 2007 Credit Crisis. *Critical Finance Review* 1, 3–58.
- Azoulay, P., J. Graff-Zivin, D. Li, and B. Sampat (2016). Public r&d investments and private-sector patenting: Evidence from nih funding rules.
- Backman, T. W. H., Y. Cao, and T. Girke (2011, 05). Chemmine tools: an online service for analyzing and clustering small molecules. *Nucleic Acids Research* 39(suppl_2), W486–W491.
- Baldi, P. and R. Nasr (2010, 07). When is chemical similarity significant? the statistical distribution of chemical similarity scores and its extreme values. *Journal of Chemical Information and Modeling* 50(7), 1205–1222.
- Benmelech, E., C. Frydman, and D. Papanikolaou (2017, March). Financial frictions and employment during the great depression. Working Paper 23216, National Bureau of Economic Research.
- Berndt, E. R., I. M. Cockburn, and K. A. Grépin (2006). The impact of incremental innovation in biopharmaceuticals. *PharmacoEconomics* 24(2), 69–86.
- Bickerton, G. R., G. V. Paolini, J. Besnard, S. Muresan, and A. L. Hopkins (2012, 02). Quantifying the chemical beauty of drugs. *Nat Chem* 4(2), 90–98.
- Bloom, N., C. I. Jones, J. V. Reenen, and M. Webb (2017). Are ideas getting harder to find? working paper, Stanford University.
- Blume-Kohout, M. E. and N. Sood (2013). Market size and innovation: Effects of medicare part d on pharmaceutical research and development. *Journal of Public Economics* 97, 327 – 336.
- Bolton, P., H. Chen, and N. Wang (2011). A unified theory of tobin’s q , corporate investment, financing, and risk management. *The Journal of Finance* 66(5), 1545–1578.
- Bond, S., D. Harhoff, and J. van Reenen (2005). Investment, r&d and financial constraints in britain and germany. *Annals of Economics and Statistics* (79-80), 433–460.
- Brown, J. R., S. M. Fazzari, and B. C. Petersen (2009). Financing innovation and growth: Cash flow, external equity, and the 1990s r&d boom. *The Journal of Finance* 64(1), 151–185.

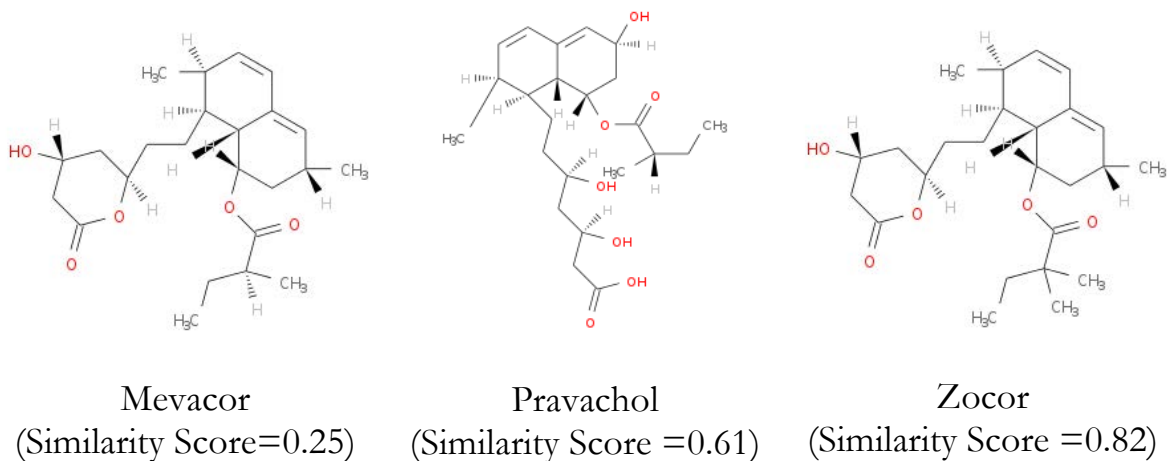
- Budish, E., B. N. Roin, and H. Williams (2015, July). Do firms underinvest in long-term research? evidence from cancer clinical trials. *American Economic Review* 105(7), 2044–85.
- Chodorow-Reich, G. (2014). The employment effects of credit market disruptions: Firm-level evidence from the 2008-09 financial crisis. *Quarterly Journal of Economics* 129(1), 1–59. Lead article.
- DiMasi, J. and R. Chakravarty (2016). Competitive development in pharmacologic classes: Market entry and the timing of development. *Clinical Pharmacology and Therapeutics* 100(6), 754–760.
- DiMasi, J. A. and L. B. Faden (2010). Competitiveness in follow-on drug r&d: A race or imitation? *Nature Reviews Drug Discovery* 10(23).
- DiMasi, J. A. and L. B. Faden (2011, 01). Competitiveness in follow-on drug r&d: a race or imitation? *Nat Rev Drug Discov* 10(1), 23–27.
- DiMasi, J. A., H. G. Grabowski, and R. W. Hansen (2016). Innovation in the pharmaceutical industry: New estimates of r&d costs. *Journal of Health Economics* 47, 20 – 33.
- DiMasi, J. A. and C. Paquette (2004, Oct). The economics of follow-on drug research and development. *PharmacoEconomics* 22(2), 1–14.
- Dranove, D., C. Garthwaite, and M. Hermosilla (2014). Breakthrough or me-too? the impact of medicare part d on biotech innovation.
- Dubois, P., O. de Mouzon, F. Scott-Morton, and P. Seabright. Market size and pharmaceutical innovation. *The RAND Journal of Economics* 46(4), 844–871.
- Duggan, M. and F. Scott Morton (2010, March). The effect of medicare part d on pharmaceutical prices and utilization. *American Economic Review* 100(1), 590–607.
- Dumas, B. (1991). Super contact and related optimality conditions. *Journal of Economic Dynamics and Control* 15(4), 675 – 685.
- Duygan-Bump, B., A. Levkov, and J. Montoriol-Garriga (2015). Financing constraints and unemployment: Evidence from the Great Recession. *Journal of Monetary Economics* 75(C), 89–105.
- Farre-Mensa, J. and A. Ljungqvist (2016). Do measures of financial constraints measure financial constraints? *The Review of Financial Studies* 29(2), 271–308.
- Fernandez, J.-M., R. M. Stein, and A. W. Lo (2012, 10). Commercializing biomedical research through securitization techniques. *Nature Biotechnology* 30(10), 964–975.
- Friedman, J. (2009). The incidence of the medicare prescription drug benefit: Using asset prices to assess its impact on drug makers.
- Froot, K. A., D. S. Scharfstein, and J. C. Stein (1993, December). Risk Management: Coordinating Corporate Investment and Financing Policies. *Journal of Finance* 48(5), 1629–58.
- Frydman, C., E. Hilt, and L. Y. Zhou (2015). Economic effects of runs on early "shadow banks": Trust companies and the impact of the panic of 1907. *Journal of Political Economy* 123(4), 902 – 940.
- Gordon, R. (2016). *The Rise and Fall of American Growth: The U.S. Standard of Living since the Civil War*. The Princeton Economic History of the Western World. Princeton University Press.
- Hall, B. H., A. B. Jaffe, and M. Trajtenberg (2005). Market value and patent citations. *The RAND Journal of Economics* 36(1), pp. 16–38.
- Hall, B. H. and J. Lerner (2010). Chapter 14 - the financing of r&d and innovation. In B. H. Hall and N. Rosenberg (Eds.), *Handbook of The Economics of Innovation, Vol. 1*, Volume 1 of *Handbook of the Economics of Innovation*, pp. 609 – 639. North-Holland.

- Harhoff, D., F. Narin, F. M. Scherer, and K. Vopel (1999). Citation frequency and the value of patented inventions. *The Review of Economics and Statistics* 81(3), 511–515.
- Henderson, R. and I. Cockburn (1996). Scale, scope, and spillovers: The determinants of research productivity in drug discovery. *The RAND Journal of Economics* 27(1), 32–59.
- Hochberg, Y. V., C. J. Serrano, and R. H. Ziedonis (2016). Patent collateral, investor commitment, and the market for venture lending.
- Hombert, J. and A. Matray (2017). The real effects of lending relationships on innovative firms and inventor mobility. *The Review of Financial Studies* 30(7), 2413–2445.
- Huh, J. and J. Reif (2017). Did medicare part d reduce mortality? *Journal of Health Economics* 53(Supplement C), 17 – 37.
- Johnson, M. A. and G. M. Maggiora (1990). *Concepts and applications of molecular similarity*. Wiley.
- Jones, B. F. (2009). The burden of knowledge and the "death of the renaissance man": Is innovation getting harder? *The Review of Economic Studies* 76(1), 283–317.
- Jones, B. F. (2010). Age and great invention. *The Review of Economics and Statistics* 92(1), 1–14.
- Kerr, W. R. and R. Nanda (2015). Financing innovation. *Annual Review of Financial Economics* 7(1), 445–462.
- Kogan, L., D. Papanikolaou, A. Seru, and N. Stoffman (2017). Technological innovation, resource allocation, and growth*. *The Quarterly Journal of Economics* 132(2), 665–712.
- Kyle, M. and H. L. Williams (2017, January). Is american health care uniquely inefficient? evidence from prescription drugs. Working Paper 23068, National Bureau of Economic Research.
- Lanthier, M., K. L. Miller, C. Nardinelli, and J. Woodcock (2013). An improved approach to measuring drug innovation finds steady rates of first-in-class pharmaceuticals, 1987–2011. *Health Affairs* 32(8), 1433–1439. PMID: 23918488.
- Lichtenberg, F. R. and S. X. Sun (2007). The impact of medicare part d on prescription drug use by the elderly. *Health Affairs* 26(6), 1735–1744.
- Light, D. W. and J. R. Lexchin (2012). Pharmaceutical research and development: what do we get for all that money? *BMJ* 345.
- Maggiora, G., M. Vogt, D. Stumpfe, and J. Bajorath (2014, 04). Molecular similarity in medicinal chemistry. *Journal of Medicinal Chemistry* 57(8), 3186–3204.
- Mann, W. (2016). Creditor rights and innovation: Evidence from patent collateral.
- Moser, P., J. Ohmstedt, and P. Rhode (2011). Patents, citations, and inventive output - evidence from hybrid corn.
- Myers, S. C. and N. S. Majluf (1984). Corporate financing and investment decisions when firms have information that investors do not have. *Journal of Financial Economics* 13(2), 187–221.
- Naci, H., A. W. Carter, and E. Mossialos (2015). Why the drug development pipeline is not delivering better medicines. *BMJ* 351.
- Nanda, R. and T. Nicholas (2014). Did bank distress stifle innovation during the great depression? *Journal of Financial Economics* 114(2), 273 – 292.
- Nikolova, N. and J. Jaworska (2004). Approaches to measure chemical similarity—a review. *QSAR & Combinatorial Science* 22(9-10), 1006–1026.

- O'Hagan, S., N. Swainston, J. Handl, and D. B. Kell (2015). A 'rule of 0.5' for the metabolite-likeness of approved pharmaceutical drugs. *Metabolomics* 11(2), 323–339.
- Pye, C. R., M. J. Bertin, R. S. Lokey, W. H. Gerwick, and R. G. Linington (2017). Retrospective analysis of natural products provides insights for future discovery trends. *Proceedings of the National Academy of Sciences* 114(22), 5601–5606.
- Ralf Otto, Alberto Santagostino, and Ulf Schrader (2014, December). Rapid growth in biopharma: Challenges and opportunities. *McKinsey & Company*.
- Smith, C. W. and R. M. Stulz (1985). The determinants of firms' hedging policies. *The Journal of Financial and Quantitative Analysis* 20(4), 391–405.
- Tirole, J. (2010). Princeton University Press.
- Wawer, M. J., K. Li, S. M. Gustafsdottir, V. Ljosa, N. E. Bodycombe, M. A. Marton, K. L. Sokolnicki, M.-A. Bray, M. M. Kemp, E. Winchester, B. Taylor, G. B. Grant, C. S.-Y. Hon, J. R. Duvall, J. A. Wilson, J. A. Bittker, V. Dančik, R. Narayan, A. Subramanian, W. Winckler, T. R. Golub, A. E. Carpenter, A. F. Shamji, S. L. Schreiber, and P. A. Clemons (2014, July). Toward performance-diverse small-molecule libraries for cell-based phenotypic screening using multiplexed high-dimensional profiling. *Proceedings of the National Academy of Sciences* 111(30), 10911–10916.

Tables and Figures

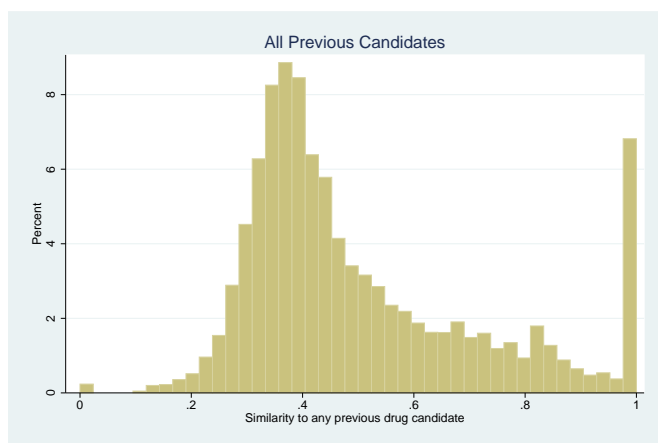
Figure 1: SIMILARITY FOR STATINS



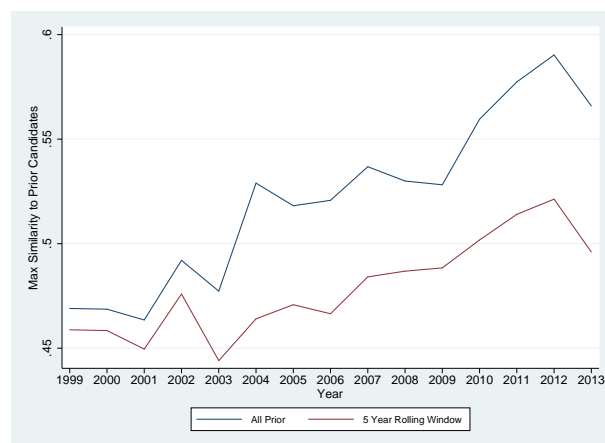
NOTES: Figure 1 provides the molecular structure and maximum similarity score of three early statins. Mevacor (Lovostatin) was the first FDA approved statin (approved in September 1987) and its Tanimoto similarity to prior molecules is 0.25. Pravachol (Pravastatin) is was the second such statin, approved 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

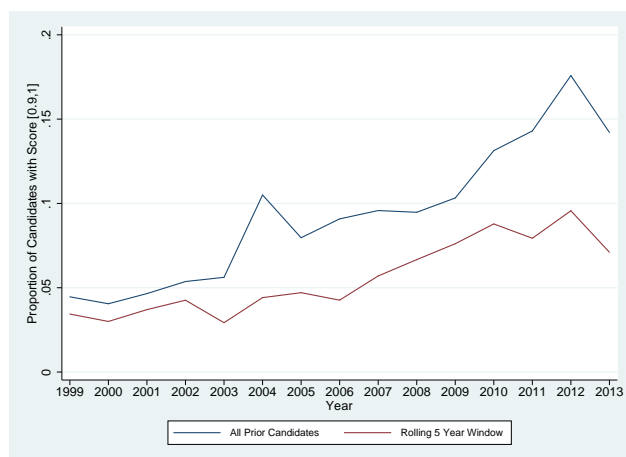
A. DISTRIBUTION OF SIMILARITY



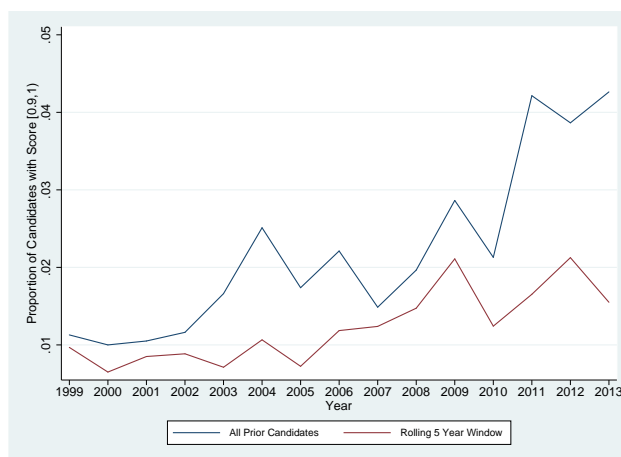
B. AVERAGE SIMILARITY OVER TIME



C. PROPORTION > 0.9

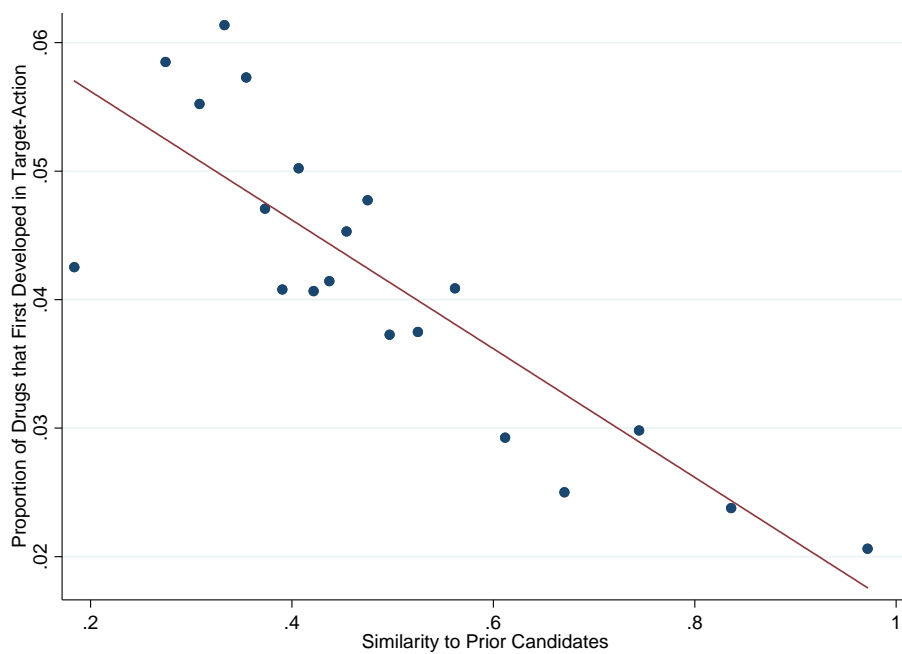


D. PROPORTION > 0.9, EXCL. COMBINATION



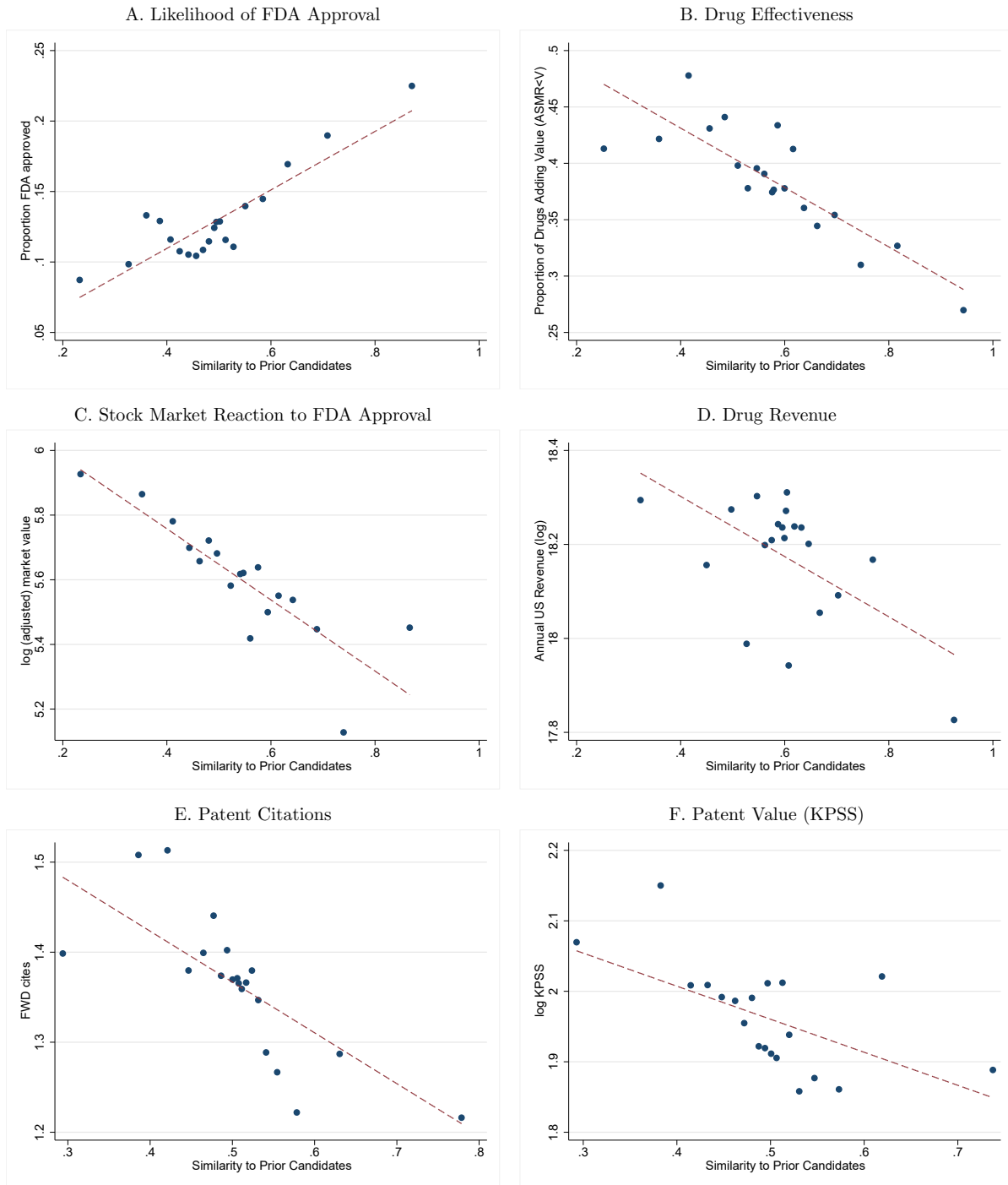
NOTES: Figure 2 displays descriptive statistics of our novelty measure. Panel A displays the distribution of our drug similarity measure. A drug's similarity is measured as its similarity to the most similar drug candidate that had previously entered Phase 1 clinical trials. For more details on this similarity measure, see Section 1.2. Panel B plots the trend in average drug candidate similarity over time. The blue line represents the average value of new drug candidates' maximum similarity to previously developed drugs, by year. To control for the fact that the number of prior drugs rises mechanically with time, the red line plots average similarity when comparing a drug candidate only with drug candidates that have entered Phase 1 trials in the 5 years prior. Panel C displays the proportion of new drugs that have greater than 0.9 similarity, comparing to both all prior drugs and drugs in a 5 year rolling window. Panel D plots the same figure as Panel C, 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



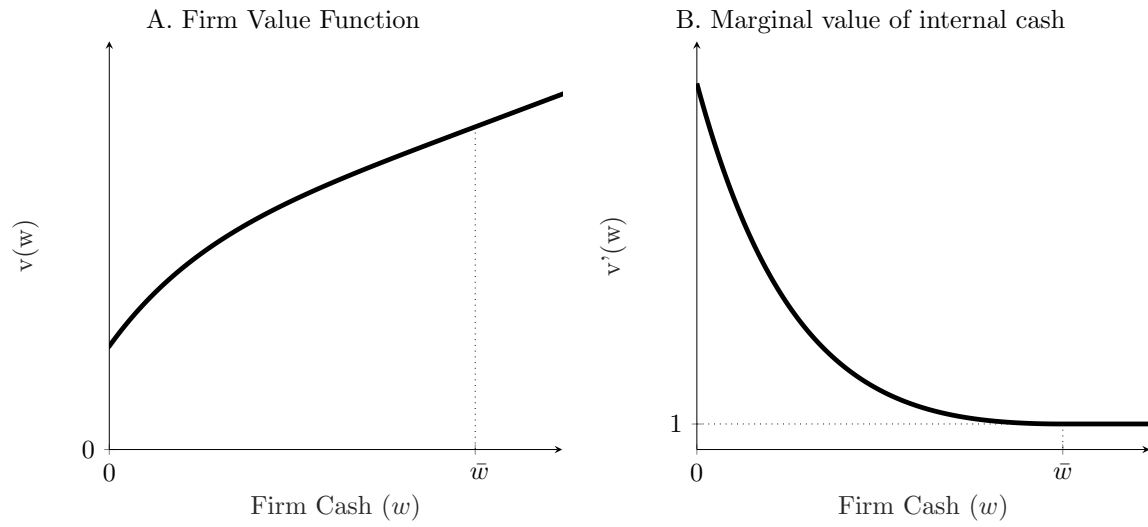
NOTES: Figure 3 presents a binned scatterplot of drug-level similarity against whether a drug is the first developed in its target-action. Each dot represents the proportion of candidates that are the first to be developed in their target-action, among all candidates within a given similarity score bin,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

Figure 4: Drug Novelty: Risk and Return



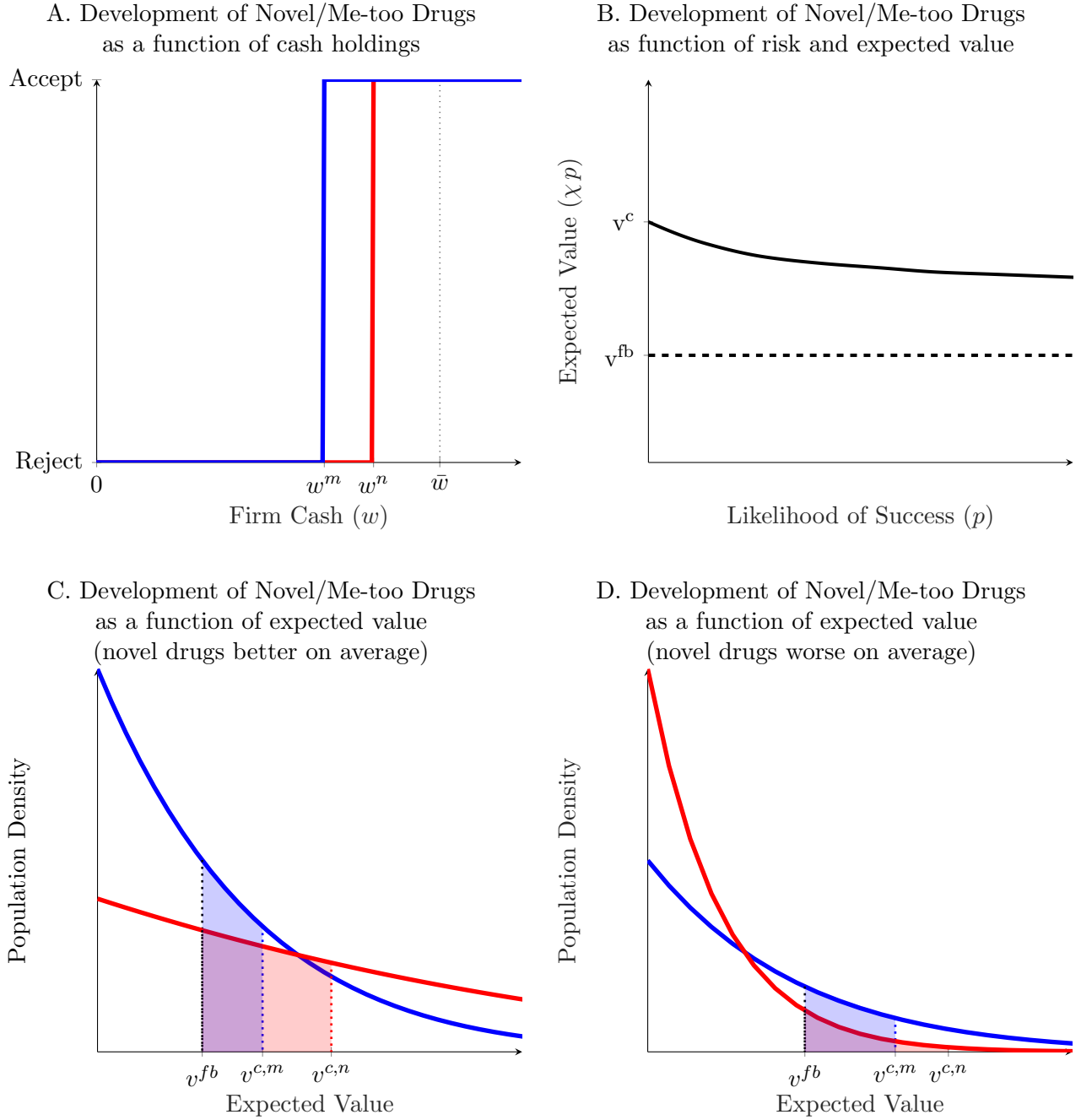
NOTES: Figure 4 presents binned scatterplots of drug-level similarity against several drug characteristics. Panel A examines whether a drug is FDA approved. Panel B examines the drug’s added benefit, which is derived from the French health system’s clinical added benefits scores (ASMR), which range from 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 [Kogan et al. \(2017\)](#) estimated patent values. All panels include fixed effects for drug development year; indication (ICD9); and company. Panels E and F also include controls for patent priority and issue year, respectively. See Notes to Appendix Figures [A.2–A.7](#) for more details.

Figure 5: Model Solution



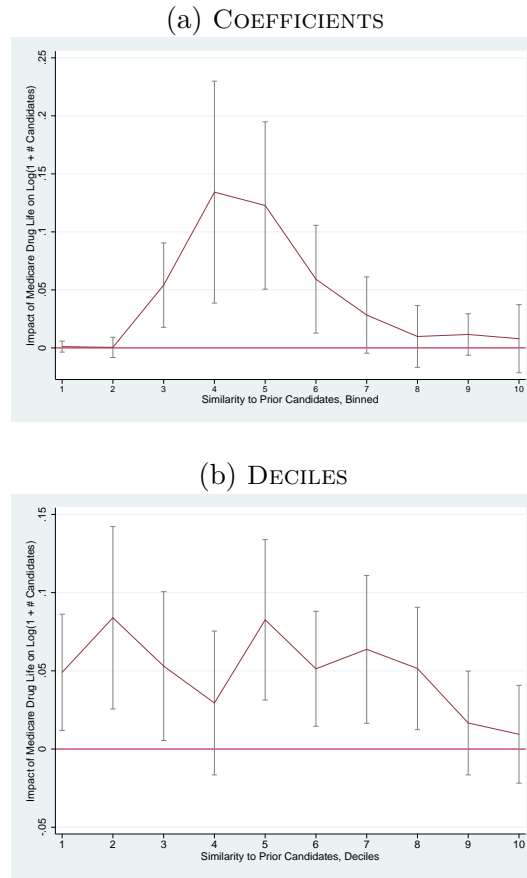
NOTES: Figure 5 plots the solution to the model in Section 3.1, specifically the properties of the firm's value function $V(K, W) = v(w)K$, where $w \equiv W/K$. See Appendix B for details.

Figure 6: Model and Drug Development Decisions



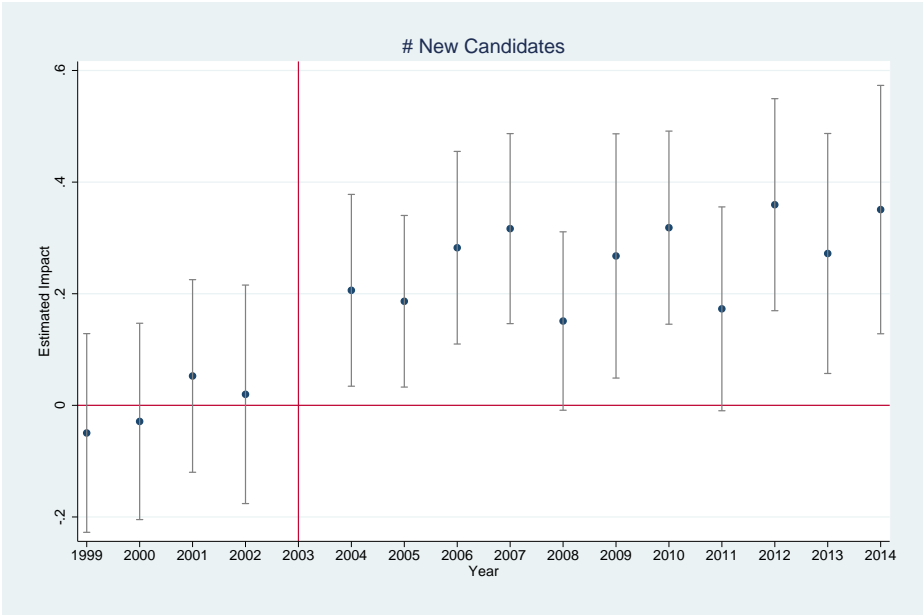
NOTES: Figure 6 illustrates how the drug development thresholds in the model described in Section 3.1 vary with cash holdings (Panel A) and the drug's expected value and likelihood of success (Panel B). w^m and w^n denote cash thresholds for safe (m) and risky drugs (n), respectively. Panels C and D illustrate two examples in which relaxing financing frictions (to the first-best level) affects the development threshold for drugs of different levels of riskiness. Red line denotes a novel (high-risk) drug, blue line denotes a me-too (low-risk) drug. v^{fb} is the frictionless benchmark expected value investment threshold. $v^{c,m}$ and $v^{c,n}$ are the investment thresholds for safe and risky drugs, respectively.

Figure 7: IMPACT OF ADDITIONAL RESOURCES ON NOVELTY OF DRUG INVESTMENTS



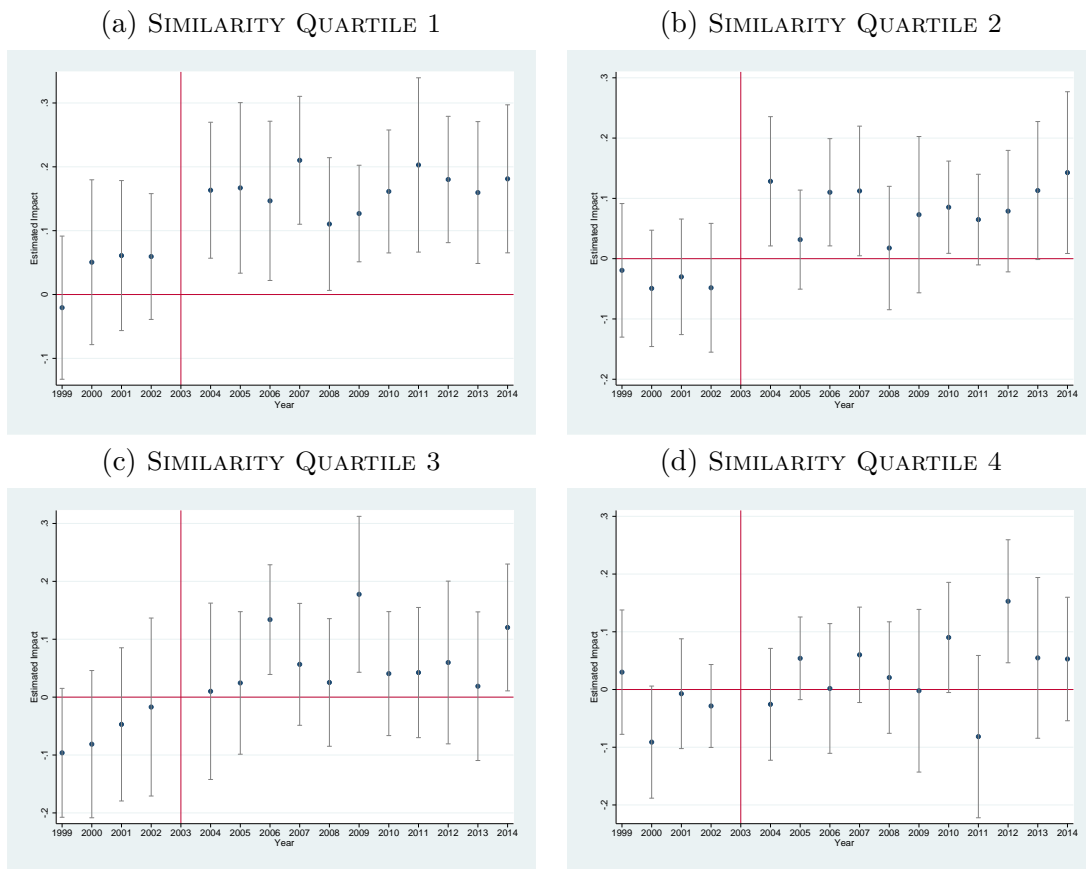
NOTES: Figure 7 plots the estimated coefficients on $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$ from our main regression specification defined by (12). Each point represents a different outcome variable: the number of new drug candidates in a given bin of similarity. Bins are specified by 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. The bottom figure reports the estimated response for drugs in each novelty decile bin.

Figure 8: EVENT STUDIES: # OF NEW CANDIDATES



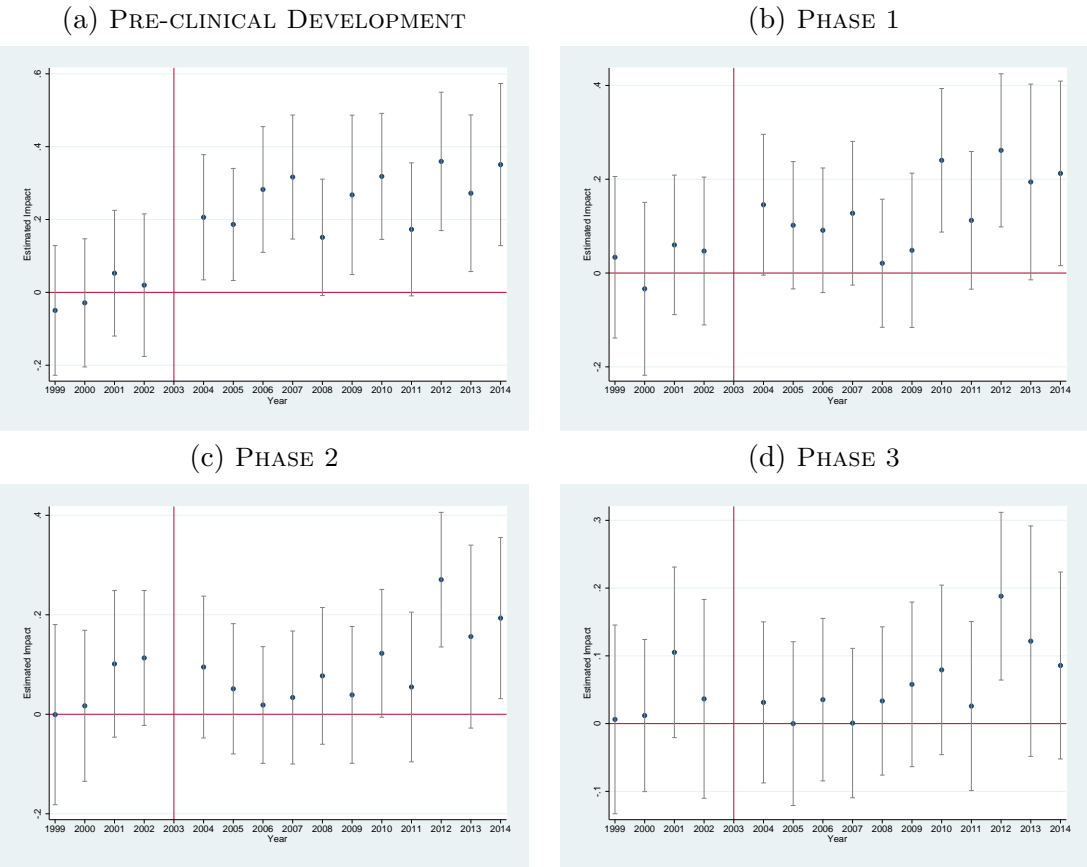
NOTES: Figure 8 reports the accompanying event study associated with Column 6 of Table 4. Each dot represents the coefficient on Medicare Drug Life_{*f*,2003} interacted with an indicator variable for that given year. 2003 is the omitted year, and 90th percentile confidence intervals are reported.

Figure 9: EVENT STUDIES: # OF NEW CANDIDATES, BY SIMILARITY QUARTILE



NOTES: Figure 9 reports event studies coefficients where the outcome variables are the number of new candidates in each quartile of similarity. 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 10: EVENT STUDIES: # OF NEW CANDIDATES, BY STAGES OF DEVELOPMENT



NOTES: Figure 10 reports event studies for number of novel drugs. Our outcome variables are the number of new candidates in different stages of development for each quarter. 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.

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 0.6 and 0.7	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: Drug Novelty and Risk, Social and Private Values—Summary Table

	Risk	Measures of Value Approval			Measures of Value, unconditional	
	Likelihood of FDA Approval (1)	Drug Effectiveness (ASMR < V) (2)	Revenue (3)	Stock Reaction to FDA Approval (4)	Patent Citations (5)	Patent Value (6)
Maximum Similarity	0.208*** (0.025)	-0.263** (0.053)	-0.641*** (0.293)	-0.977*** (0.299)	-0.238*** (0.098)	-0.469** (0.196)
Observations	19,127	1,778	11,230	399	116,611	5,031
Appendix Table/Column	A.4.(3)	A.7.(2)	A.5.(4)	A.6.(3)	A.8.(4)	A.9.(4)

NOTES: Table 2 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 ASMR 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, which, whenever possible, control for disease (indication); drug age (drug launch or patent issue year); company; Please see the notes to the relevant Appendix Tables for more details. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 3: 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 Characteristics (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 3 reports characteristics of our firm-quarter 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 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
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 (models 4-6). 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 (12), 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: PORTFOLIO EXPANSION (CANDIDATES NEW TO FIRM)

	New Indications		New Targets	
	(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 5 examines whether firms choose to diversify their drug portfolio, by pursuing candidates that are sufficiently different that their existing portfolio. We report 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 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. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 6: DRUG DEVELOPMENT ACROSS ELDERLY AND NON-ELDERLY DRUGS

(A) PROPORTION OF NEW DRUGS ACROSS MMS QUARTILES				
	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

(B) DRUGS FOR PEDIATRIC AND YOUNG ADULT CONDITIONS				
	Log(1+ New Candidates), Non-Elderly Conditions			
	(1)	(2)	(3)	(4)
	< 5% MMS	< 10% MMS	Pediatric	Youth
Post 2003 X Medicare Drug Life	0.076** (0.038)	0.090** (0.041)	0.192** (0.080)	0.138** (0.066)
R^2	0.317	0.344	0.532	0.517
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 (depending on whether these drugs target elderly or non-elderly patients). The table reports the main specification coefficient for Post \times Medicare Drug Life $_{f,2003}$. In Panel A, the dependent variable in each column corresponds to each quartile of the Medicare market share (MMS) distribution. In Panel B, the dependent variables are the number of drugs developed for (primarily) non-elderly conditions. Columns 1 and 2 define non-elderly as low MMS conditions, while Columns 3 and 4 use clinical trial patient selection criteria from to define conditions as “pediatric” or “youth.” We assign a condition the “pediatric” label if that condition’s drug trials have an above median share requiring enrollees to be newborns, infants, pre-school children or children. The “youth” category is assigned similarly, but expands this definition to include adolescents and young adults. 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, 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: NOVELTY FOR NON ELDERLY DRUGS

(A) BELOW MEDIAN MMS DRUGS				
	Log(1+ Non Elderly Candidates), by Similarity Quartile			
	(1)	(2)	(3)	(4)
Post 2003 X Medicare Drug Life	0.062** (0.029)	0.060** (0.030)	0.060** (0.028)	0.016 (0.019)
R^2	0.233	0.303	0.238	0.179
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

(B) DRUGS FOR PEDIATRIC CONDITIONS				
	Log(1+Pediatric Candidates), by Similarity Quartile			
	(1)	(2)	(3)	(4)
Post 2003 X Medicare Drug Life	0.093** (0.043)	0.084** (0.039)	0.084** (0.035)	0.040 (0.030)
R^2	0.322	0.407	0.311	0.237
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

(C) DRUGS FOR PEDIATRIC AND YOUNG ADULT CONDITIONS				
	Log(1+Youth Candidates), by Similarity Quartile			
	(1)	(2)	(3)	(4)
Post 2003 X Medicare Drug Life	0.081** (0.037)	0.058* (0.030)	0.062* (0.033)	0.026 (0.027)
R^2	0.292	0.377	0.295	0.231
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 7 reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$ but focuses only on novelty among drugs not targeted toward the elderly. The dependent variable in each column corresponds to each quartile of the compound similarity distribution. Panel A excludes “elderly” drug candidates, by removing drugs developed for conditions for which trials are above the median in likelihood of limiting patient selection to “elderly” or “aged” adults. Panel B limits the drug candidates outcomes to “pediatric” drugs—drugs developed for conditions whose trials are more likely to target newborns, infants and children. “Youth” candidates in Panel C are defined as drugs developed for conditions above the median in terms of limiting trial participation to newborns, infants, children, adolescents and young adults. 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 8: EFFECT OF CASHFLOWS ON NUMBER OF DRUG CANDIDATES, BY FIRM SIZE

	Log(1 + New Candidates), by Size		
	(1) All	(2) Top 50	(3) Bottom 50
Post 2003 X Medicare Drug Life	0.263*** (0.096)	0.299 (0.214)	0.192* (0.100)
R^2	0.595	0.641	0.209
Company FEs	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes
Observations	16442	5950	6207

NOTES: Table 8 examines how the treatment effect of cashflows on number of developed drugs varies by firm size. We measure firm size as the sum of revenue generated by approved drugs prior to 2003. We split firms into equal sized groups based on their size as of 2003; the number of observations differs due to firm exit. We report the main specification coefficient for Post \times Medicare Drug Life $_{f,2003}$. We estimate the model with the full set of company and quarter indicator variables, including Post \times Overall Drug Life $_{f,2003}$ and Post \times Firm MMS $_{f,2003}$, separately across groups. All control variables are allowed to vary across specifications, but are not reported in the table. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table 9: IMPACT ON R&D AND PROFITS

	(1)	(2)	(3)	(4)
	Log(RD)	Log(Profits)	Log(Debt)	Leverage
Post 2003 X Medicare Drug Life	0.975*	1.046*	0.967	0.108
	(0.573)	(0.564)	(1.118)	(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

NOTES: Table 9 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). Sample period is 1999–2013. 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. Standard errors clustered by firm are reported in parentheses. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Online Appendix to “Missing Novelty in Drug Development”

Joshua Krieger
Harvard University

Danielle Li
MIT & NBER

Dimitris Papanikolaou
Northwestern University
& NBER

A A Primer on Drug Development

Here, we provide a brief description of the process of drug development by pharmaceutical firms, while also emphasizing the potential role of financial market imperfections in drug development.

A.1 Development Process

The drug development process is typically divided into five stages: discovery / pre-clinical research; Phase 1, 2, and 3 of human clinical trials; and post-approval monitoring and clinical trials (Phase 4). From start to end, this process may take anywhere from 5 to 15 years. In the first stage of this process, discovery, researchers identify biological mechanisms that impact diseases and symptoms. For example, they may want to develop a drug that inhibits the functioning of a particular target, such as an enzyme or the gene that encodes it. Having identified a potential target, developers then screen potential compounds looking for structures that have some desired action on this target. At some point during this first stage of development, firms will apply for patents on promising candidates.²⁰

Having identified a set of promising compounds, researchers focus next on testing its pharmacokinetic and pharmacodynamic properties: how the body impacts the drug (its absorption, bioavailability, etc.) and how the drug impacts the body (drug actions, toxicity, etc.), respectively. If a drug performs well in animal models, firms may choose to file an Investigational New Drug (IND) application with the FDA to begin human clinical trials. Clinical trials have three phases. Phase 1 clinical trials mainly test for toxicity and help set dosage levels, using a few dozen healthy patients. Phase 2 trials involve hundreds of patients with the conditions of interest, and are typically randomized. Phase 3 trials are randomized controlled trials on a focused subset of patients likely to show the greatest response to the drug. These trials often include thousands of patients and involve tracking outcomes over long periods to assess both safety and efficacy. At the end of Phase 3, firms may submit a New Drug Application (NDA) to the FDA that includes the results of all trials and preclinical testing. After a formal review process, the FDA decides whether or not to approve the drug.

Throughout the development process, firms make many decisions about what types of compounds to invest in. These decisions are important for the ultimate novelty of drugs that are brought to market. For instance, firms may choose to develop drug candidates that act on known targets through known channels, or they can attempt to develop drugs that differ in either their mode of action.

²⁰Firms typically apply for broad patents that would cover a collection of similar compounds, rather than a single compound itself. This set of claims is described by a “Markush structure,” which is a generalized molecular structure used to indicate a collection of similar compounds.

One aspect of drug pipeline decisions that has attracted a lot of attention is the issue of “me-too” innovation. The idea behind “me-too” or “copycat” drugs is that firms prefer to modify existing drugs or create similar compounds in order to avoid the costs and uncertainty of more novel drug development. Developing such drugs has the benefit of providing doctors with a menu of valuable alternatives if a patient is not responding or having an adverse reaction to a specific drug. For example, [Berndt, Cockburn, and Grépin \(2006\)](#) find that drugs that gained supplemental approvals for new dosages, formulations and indications account for a large portion of drug utilization and economic benefits. A common critique of these type of drugs, however, is that they yield only marginal clinical improvements while increasing drug costs and diverting resources from the development of truly innovative therapies. For example, Joseph Ross, a professor of medicine and public health at Yale University School of Medicine, describes me-too drugs as those that “may have some unique niche in the market, but they are fairly redundant with other therapies that are already available” (New York Times, 2015). It is also worth noting that two similar drugs that are both brought to market may have been developed in parallel (“racing”) rather than through a scenario in which one drug imitated the other in order to capture a piece of the same, or similar, pie ([DiMasi and Chakravarthy, 2016](#)).

A.2 Development Costs and Financing

Drug development is financed through a number of different mechanisms, both public and private. First, an important input into drug development is the scientific knowledge that enables researchers to identify biological targets, and which enables the development of tools and techniques used in drug discovery. This type of “basic” research is usually funded by the government, most often through the National Institutes of Health. Translational research, in which insights from basic research are advanced toward medical applications and commercialization, may also involve public funding. For example, early stage biotechnology firms working on a proof-of-concept for a new type of drug may receive capital from the government’s Small Business Innovation Research (SBIR) program, as well as from private foundations and venture capital. In general, however, the direct public funding of private-sector drug development is limited.

The direct cost of drug discovery to firms themselves is substantial: [DiMasi, Grabowski, and Hansen \(2016\)](#) estimate that the direct cost of developing a single approved drug is over \$1.4 billion and has been increasing over time.²¹ This total cost of development is spread unevenly across the stages of drug development, with discovery and preclinical costs accounting for one third and clinical costs accounting for the remaining two thirds. Phase 3 trials, in particular, can be extremely

²¹This estimate is subject to some debate. See for instance, <http://www.nytimes.com/2014/11/19/upshot/calculating-the-real-costs-of-developing-a-new-drug.html>.

costly and involve multiple thousands of patients over several years. Because of this escalating cost structure, investments in drug development are essentially staged, with firms putting in smaller amounts of money in early stages and making greater capital commitments only if the drug shows promise.

One possible reason why firms, especially smaller ones, may not choose to invest in novel drugs is because these drugs may be more costly to develop. 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.10 and Figure A.8, we consider how the number of patients and number of trials associated to a compound vary by its chemical novelty. In general, we find no consistent relationship between these proxies of development cost and drug novelty. The left hand side panels of Figure A.8, 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. Further, to the extent that novel drugs are less likely to survive to later stages, our evidence suggests that their initial expected cost is likely to be weakly lower.

Accessing external finance for such costly and uncertain projects can be particularly challenging. In general, the pecking order theory (Myers and Majluf, 1984) predicts that using internal funds is the cheapest form of financing, followed by debt and then equity. By now, a broadly accepted view in corporate finance is that information asymmetries and moral hazard frictions make it particularly costly for both public and private firms to raise external equity finance. For several reasons, these frictions may be particularly salient for innovative firms (see, e.g. Kerr and Nanda, 2015; Hall and Lerner, 2010, for a review of the literature).

Financing drug development with debt is also difficult because few pharmaceutical firms have assets that can be reliably used as collateral. Patents for drug candidates, for instance, are taken out early in the development process, making their use as collateral something of a Catch 22—in order to know whether the patent is valuable as collateral, a bank would have to lend the firm the money to put it through testing, which is what the firm wanted the loan for in the first place.²²

²²A growing set of papers have shown, however, that pharmaceutical patents are sometimes pledged as collateral by public firms, although this phenomenon is small compared to the use of patents in electronics or medical devices

Consistent with this view, firms in the pharmaceutical industry have indeed lower leverage ratios than comparable firms in other industries (see Appendix Table A.1 for more details).

B Model Solution

Here, we discuss the model solution. We begin by describing the frictionless benchmark and then discuss the solution to the model with financing costs.

Frictionless benchmark

We start with the frictionless benchmark—the model without any financing costs. In this case, the only state variable at the firm level is K . So, the firm’s value function is $V(K_t)$. When the firm decides to invest in a new project or not, it will trade off its expected benefit versus its cost. A drug of type i will get developed as long as

$$p_i \left(V(K_t + \chi_i K_t) - V(K_t) \right) - f K_t > 0. \quad (\text{B.1})$$

Since the firm’s financial policy is irrelevant, we can assume that the firm pays all operating profits to investors. Hence, the firm’s value function is equal to

$$\begin{aligned} V(K_t) &= E_t \int_t^\infty e^{-r(s-t)} K_s \left(dA_s - f I_{i,s} dN_s \right) \\ &= K_t, E_t \int_t^\infty e^{-(r+\delta)(s-t)} \exp \left(\int_t^s \log(1 + \chi_i I_{i,u}) dJ_{i,u} \right) \left[\mu - \lambda f I_{i,u} \right] du \end{aligned}$$

Given our constant-returns assumption, we can conjecture (and verify later) that the investment decision for drug i independent of firm scale K . In that case, since demand shocks are i.i.d., we have that investment decision for drug i independent of firm scale K . In that case, since demand shocks are i.i.d., we have that

$$V(K_t) = K_t, \underbrace{E_t \int_t^\infty e^{-(r+\delta)(s-t)} \exp \left(\int_t^s \log(1 + \chi_i I_{i,u}) dJ_{i,u} \right) \left[\mu - \lambda f I_{i,u} \right] du}_{v_0 = \text{constant}}$$

which therefore implies that the decision to invest in a given drug (p_i, χ) is indeed independent of K :

$$v_0 p_i \chi_i \geq f. \quad (\text{B.2})$$

Put differently, the firm invests in all positive NPV projects.

(Mann, 2016). Hochberg, Serrano, and Ziedonis (2016) conduct a similar analysis examining the use of debt in venture financing; their study includes some medical devices firms but few if any biopharmaceutical firms.

Financing Frictions

Profits minus investment equals

$$dY_t = K_s dA_s - f I_{i,s} K_s dN_t \quad (\text{B.3})$$

Combining free cashflows and the firm's financing decisions, we can write the evolution of firm's stock of cash as

$$dW_t = dY_t + (r - c)W_t dt + dH_t - dU_t \quad (\text{B.4})$$

where the last term dU_t is payments to investors ('dividends').

The objective of the firm equals

$$V(W_t, K_t) = E_t \int_t^\infty e^{-r(s-t)} (dU_t - dH_t - dX_t) \quad (\text{B.5})$$

which is what we had before, since in that case net payout was

$$dU_t - dH_t = K_s dA_s - f I_{i,s} K_s dN_s \quad (\text{B.6})$$

and there are no financing costs. This is a fixed cost problem. Most of the time the firm will not raise external funds and use internal cashflow to finance development. In that region, the evolution of the firm's value function satisfies the following HJB equation:

$$\begin{aligned} rV(W, K) = & V_W [K\mu + (r - c)W] + \frac{1}{2} V_{WW} \sigma^2 K^2 - \delta V_K K + \\ & + \lambda \max_I \left\{ \int_p \int_\chi (pV(W - fKI, K + \chi IK) + (1 - p)V(W - fKI, K) - V(W, K)) G(p, \chi) d\chi dp - fIK \right\} \end{aligned}$$

The firm's decision problem to invest in drug i now depends on the concavity of the value function: it will invest as long as

$$p_i V(W - fK, K + \chi_i K) + (1 - p_i) V(W - fK, K) - V(W, K) > fK \quad (\text{B.7})$$

To make further progress, we can exploit the homotheticity of the problem. Conjecture that

$$V(W_t, K_t) = K_t p(w_t), \quad w_t \equiv \frac{W_t}{K_t}. \quad (\text{B.8})$$

The HJB equation thus becomes

$$0 = v'(w)(\mu + (r - c)w) + \frac{1}{2}v''(w)\sigma^2 - \delta v(w) - rv(w) + \\ + \lambda \max_{I(p,\chi)} \int \int \left[p \left((1 + \chi I)v \left(\frac{w - fI}{1 + \chi I} \right) - v(w) \right) + (1 - p) \left(v(w - fI) - v(w) \right) - fI \right] G(p, \chi) dp d\chi. \quad (\text{B.9})$$

and the firm will invest in drug i iff

$$p_i(1 + \chi_i)v \left(\frac{w - f}{1 + \chi_i} \right) + (1 - p_i)v(w - f) - v(w) > f \quad (\text{B.10})$$

To finish the characterization of the solution, we need to determine the payout region $w > \bar{w}$ and the region where the firm issues new securities, $w < \underline{w}$. These arguments are straightforward and follow the logic in [Bolton et al. \(2011\)](#). That is, the point at which the firm pays out dividends is the point at which the firm value function becomes linear and the marginal value of cash equals one:

$$v'(\bar{w}) = 1. \quad (\text{B.11})$$

The above can be seen as the limiting case of

$$v(w) = v(\bar{w}) + (w - \bar{w}), \quad w > \bar{w}. \quad (\text{B.12})$$

In addition, we also need the super-contact condition ([Dumas, 1991](#)),

$$v''(\bar{w}) = 0. \quad (\text{B.13})$$

We next discuss the behavior at the issuance boundary. The firm will issue an endogenous amount $mK > 0$ whenever it runs out of cash ($w = 0$). The value of the firm needs to be continuous before and after equity issuance, so

$$V(0, K) = V(mK, K) - \phi K - (1 + \gamma)m, K \quad (\text{B.14})$$

or after re-normalization,

$$v(0) = v(m) - \phi - (1 + \gamma)m. \quad (\text{B.15})$$

Here, not that if the firm, for whatever reason, ends up in a negative position, the above still holds, except that

$$v(z) = v(m) - \phi - (1 + \gamma)(m - z). \quad (\text{B.16})$$

for $z < 0$. This will be useful if the firm is investing close to the boundary. At the boundary, the firm will optimize over m , which implies that at $w = 0$, we have

$$v'(m) = 1 + \gamma. \quad (\text{B.17})$$

This equation pins down the size of the intervention.

In sum, this is a classic impulse control problem. There is an inaction region $w \in (0, \bar{w})$, in which the HJB equation holds. Whenever the firm reaches the boundaries, it either pays out cash or issues new securities so that w remains in $(0, \bar{w})$.

We next give a sketch of the numerical algorithm which is based on finite differences on a grid.

1. Start with a guess v^0 defined on the grid for w . We allow for the grid to take negative values. Denote the point k which corresponds to $w_k =$.
2. Find the amount of issuance for points $n < k$, which consist of maximizing over $v^0(m(n)) - (1 + \gamma)(m(n) - w_n)$ for $n \leq k$.
3. Solve the HJB which corresponds to grid point n as a function of its neighbours. Call that \hat{v}_n .
4. Start from the bottom. For points $n = 1 \dots k$, set

$$v_n^1 = v^0(m(n)) - \phi - (1 + \gamma)(m(n) - w_n). \quad (\text{B.18})$$

given the $m(n)$ above.

5. For each point v_n^1 , $n > k$ update it as

$$v_n^1 = \hat{v}_n \quad (\text{B.19})$$

6. After updating check whether the firm should start paying dividends at grid point n :

$$\hat{v}_n \leq \hat{v}_{n-1} + (w_n - w_{n-1}) \quad (\text{B.20})$$

If so, update $\bar{w} = w_n$ for point n^* , and set

$$v_m^1 = \hat{v}_{n^*-1} + (w_m - w_{n^*-1}) \quad (\text{B.21})$$

7. Update the firm's drug development policy $I_n(p, \chi)$ for all points. Since they never actually spend time in negative regions of w (we just need these to compute the investment policy in the $n \geq k$ region, assume $I_n(p, \chi) = 0$ for $n < k$).
8. Repeat until convergence

C Data Construction

Here, we describe the construction of the data in more detail.

C.1 Drug Development Histories

Our drug development data primarily comes from the Cortellis Investigational Drugs and Clinical Trials databases.²³ For drugs in the Cortellis data, we have information on characteristics, as well as associated companies and clinical trials. Most notably, Cortellis uses information from patents, regulatory filings, press releases, public press and company materials (e.g., pipeline “tables” and company website) to derive key dates for each drug’s development history by company, therapeutic indication and country. For example, Cortellis might list an earliest “discovery” date based on the scientific publication or patent that describes a drug candidate’s use for a particular disease, followed by dates corresponding to the start of clinical trials of each phase, and finally an approval or market launch date.

In our various analyses, we distinguish between a drug-indication’s earliest development date with any company, its first development milestone with a non-originating company that acquired the drug, and the drug candidate’s entry dates into phase I/II/III clinical trials. We calculate our primary drug novelty measures by taking the maximum a new drug candidate’s chemical structure similarity (at the time of earliest entry) to all prior drug candidates that ever reached phase I clinical trials. While we also tested alternative definitions of novelty that compare new drugs to all prior developed drug candidates of any stage, we prefer to compare to the phase I drugs because doing so reduces the likelihood of comparing a new drug candidate to another compound that was developed independently and simultaneously, but by chance was disclosed (or captured by Cortellis) at a slightly earlier date.

C.2 Chemical Similarity Scores

Section (1.2) in the paper provides a basic summary of our method for calculating drug similarity scores. This section provides more details on the mechanics of gathering pairwise similarity scores, and then calculating our novelty measures. The starting point for these scores is information on the drug candidate’s chemical structure. Cortellis contains information about the chemical structure of small molecule drugs, when that information is available. Chemical structure information is not available for vaccines and biologic drugs, which involve more complex mixtures of substances generated through biotechnology. Often, the chemical structure is also not available for drugs that

²³At the time of our data access agreement, Cortellis was owned by Thomson Reuters. In October 2016, Thomson Reuters sold Cortellis to Clarivate Analytics.

never progress out of very early stage drug development stages. Roughly 36% of Cortellis drug entries contain information on drug structure. This percentage is higher for small molecule drugs (53%), and for small molecule drugs that reach clinical trials (70%). When the chemical structure is known, Cortellis provides standardized chemical identifiers such as the simplified molecular-input line-entry system (SMILES). SMILES codes represent chemical structures as ASCII strings, with components of the string identifying atoms, bonds, branching, order and shape of a compound. These SMILES strings serve as the inputs to our similarity calculations.

In practice, calculating Tanimoto distance requires an algorithm that can convert a chemical identifier like a SMILES string into its component fragments and compare to other compounds. This process is both complex and computationally intensive. We used features of ChemMine Tools (publicly available at <http://chemmine.ucr.edu/>) a system developed by chemical informatics researchers at the University of California, Riverside (Backman, Cao, and Girke, 2011) in order to process and calculate pairwise Tanimoto scores. We used the R package version of ChemMine (ChemmineR) to batch submit similarity calculation requests for the unique SMILES codes represented in our drug development data from Cortellis. For data management purposes, we only kept pairwise similarity score results for pairs of compounds that had a Tanimoto distance greater than or equal to 0.1.

After generating all the pairwise similarity score data, we merge in the key development dates (e.g., earliest, phase I/II/III) for each drug, and calculate our novelty measures by drug candidate, as of the drug candidate’s earliest development date, and based on the maximum similarity score to all previously developed drugs, all drugs that previously reached phase I, all drugs that previously reached phase I etc..

C.3 Matching Drugs to MEPS

An important data step for our analyses is matching our drug development history and novelty data with the Medical Expenditure Panel Survey (MEPS). The MEPS program is run by the Agency for Healthcare Research and Quality at the U.S. Department of Health & Human Services, and tracks data on health services use and cost for a large nationally representative sample of households. For 2003, the year congress approved Medicare Part D, the MEPS consolidated data file includes 11,929 household identifiers.

Our matching process (described below) serves two purposes: 1) to estimate drug-specific Medicare market share (“elderly share”), and 2) to estimate relative drug revenues. We aggregate the former up to the firm-level to calculate one of the two components of our main “treatment” variable (Medicare drug Life, see Section 3.2), and the latter helps us describe the correlation between our novelty measure and private value to drug developers (see Section 2.2).

To match our drug development and novelty data to the MEPS data, we use all the drug names affiliated with Cortellis drug identifiers, and merge them with drug names represented in MEPS. After finding all the perfect name matches, we manually inspect any potential matches using a “fuzzy” name matching algorithm. Matching drug names from the MEPS prescription data to Cortellis can also be challenging due to inconsistencies in the naming of drugs. For example, a common antibiotic prescription may be listed as “Zithromax ,” “Zithromax Z-Pak,” or “Zithromax 250 Z-PAK.”

If a drug is not matched in the 2003 MEPS data, we attempt to match it to observations in the 2002 survey; 2001 if that is also not available, and so forth. For drugs we are unable to match, we infer the drug’s MMS using information on MMS for the other drugs in MEPS that share the same therapeutic indications. Therapeutic level MMS is computed in MEPS by taking the average share of revenues coming from elderly patients for all approved drugs in a particular ICD9 class in the year 2003. For example, if a drug is used to treat two different conditions, we assign that drug the average of the Medicare shares associated with each of these conditions, weighted by the relative importance of the conditions. The weights assigned to ICD9s are the share of total revenue in the 2003 MEPS data that come from drugs associated with that ICD9.

For drug revenue, we use all the years in our MEPS data (1996–2012) and adjust dollar expenditures to 2015 dollars using the Consumer Price Index for All Urban Consumers (CPI-U). After matching to the Cortellis drug development data, we then estimate the correlations between our drug novelty measure and annual drug revenue, controlling for sales year, the drug’s approval year, and therapeutic area (see Section 2.2).

C.4 Measuring Market Value of Approved Drugs

To construct an estimate of the drug’s private value, we closely follow the methodology of [Kogan et al. \(2017\)](#). 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. Similar to [Kogan et al. \(2017\)](#), we also allow for the possibility that this return window also incorporates stock price movements that are unrelated to the value of the approved drug.

Specifically, we closely follow [Kogan et al. \(2017\)](#) and assume that the cumulative return of the firm in that 5-day window equals

$$R_j = v_j + \varepsilon_j, \tag{C.1}$$

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. 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 34 firms and 462 announcement days.

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.

Consequently, our estimate of the stock market change as a result of the drug’s FDA approval is equal to

$$\hat{\Delta V} = E[v_j|r_j] M_j, \tag{C.2}$$

where M_j is the firm’s stock market capitalization at the end of the day prior to the FDA approval.

However, the firm’s stock market change following the drug’s FDA approval is a composite of both the contribution of the drug to the firm’s market value and the likelihood that the FDA approval was a surprise to the market. 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

$$\Delta V = (1 - q_j) \xi_j, \tag{C.3}$$

where ξ_j is the private value of the drug (in dollars). But, novel drugs are less likely to be approved, so q_j varies with novelty. Hence, it is important to adjust these estimates. To do so, we linearly approximate C.3 as $\log \Delta V = \log \xi_j + \log(1 - q) \approx \log \xi_j - q_j$. The point estimates from Column (9) of Table A.4 imply that the approval probability $\hat{q}_j = q_0 + 0.123 \text{maxsim}_j$, where the constant incorporates, year, indication, and firm fixed effects.

Putting the pieces together, our estimate of the log contribution of drug j to firm value is equal to

$$\widehat{\log \xi_j} = \log \hat{\Delta V}_j - 0.123 \text{maxsim}_j. \tag{C.4}$$

That is, we have adjusted (C.3) for the differential likelihood that a more novel drug is approved by the FDA—conditional on having reached Phase 3.

C.5 ASMRS

We merge our drug-level data using both established drug naming conventions and manual matching. 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. The ASMR scores are assigned only to approved drugs that are available for reimbursement from the French Government health system. After limiting our attention to 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. In 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.

C.6 Drug Patents

In order to build our firm-level measure of drug patent life, we start by gathering patent expiration and market exclusivity information for drugs that had been approved prior to the passage of Medicare Part D in 2003. To maximize our drug patent life coverage, we combine multiple data sources. As a starting point, we use information from the Federal Register on the key patents for approved drugs, along with the patents’ expiration dates and market exclusivity extensions. Extensions are usually the result of FDA rules that grant additional exclusivity after marketing approval for new chemical entities, pediatric drugs, antibiotics, and orphan drugs.²⁴ When we could not match an approved drug to the Federal Register data, we used the patent expiration dates of the drugs’ affiliated “Orange Book” patents listed by the FDA.²⁵

After identifying exclusivity periods for approved drugs, we use drug names to merge this information into our Cortellis drug data. We first match on exact names, then use a “fuzzy” match technique to identify potential additional matches and reviewed that set manually. Once merged to Cortellis entries, we can aggregate remaining exclusivity into a firm-level measure of drug patent life as of 2003.

C.7 Matching Drugs to Companies

One of the challenges in studying drug development pipelines is assigning drug candidates to their developer firms in a given point in time. The reason for this issue is that multiple firms may be

²⁴We thank Duncan Gilchrist for sharing this Federal Registrar data.

²⁵The Orange Book covers all FDA approved drugs; however, a key limitation of Orange Book patents is that they are designated by the producing firm and are subject to patent challenges.

connected with a single drug development project. Firms may team up to develop a drug through joint ventures, financing partnerships, or web of licensing and subsidiary arrangements. Ideally, one would assign ownership weights for a given drug (e.g., Firm A owns 30% and Firm B owns 70%). But due to complicated licensing and royalty arrangements, the outside analyst cannot easily infer such weights.

As a result, we are left with two distinct options: a) allow a single drug candidate to count as a (full or equal weighted) member of multiple firms’ portfolios, or b) determine which company is likely the central company in the development alliance, and assign that firm as the sole “lead” developer. We use the former method—allowing multiple firms to get credit for a single drug candidate or approved therapy. But when possible, we limit the set of assigned companies to those that were most recently “active” with the drug in the Cortellis data.

C.8 Public Firms

A number of our analyses require data on public firms in our drug development data. To identify public companies in the Cortellis drug development data, we started by running all Cortellis company names through Bureau Van Dijk’s Orbis software, which matches strings to company identifiers (including ticker and cusip CUSIP identifiers for publicly traded firms). To ensure that the Orbis process did not miss any notable public firms, we checked the match against historical lists of public pharmaceutical firms (e.g., Nasdaq and Standard & Poor’s pharmaceutical indices) to make sure we had positively matched major firms. In total, we match over 600 tickers to Cortellis company identifiers. When we limit to publicly traded firms in our main analysis sample of 17,775 small molecule drugs, we are left with 140 public firms. While this may seem like a small number given that we have over 3,585 distinct company identifiers linked to drugs in the sample, we also see that these 140 public firms are responsible for more than half of the drug development activity in the sample. After linking to public company identifiers (tickers and CUSIPS), we are able to download daily stock data from The Center for Research in Security Prices (CRSP), as well as historical profits and R&D spending from Compustat. Out of these firms, approximately 71 are in the United States and are publicly traded at some point (appear in CRSP). When estimating the market reaction to an FDA approval, we further restrict the set to firms that were publicly traded at the time of the drug’s first approval, we have 462 first-time approvals from 35 unique firms.

D Additional Specification Checks

We examine the robustness of our results with respect to an alternative measure of novelty, specifically, the novelty of a drug’s biological target—this analysis includes both small molecule

drugs and biologics. Table A.19 in the Appendix, shows the results of this analysis for four different biological criteria for target–novelty. First, whether a drug is the first using its target-action (e.g., Beta secretase 1 inhibitor, Cyclooxygenase-2 inhibitor). Second, whether a drug is the first in its target, defined more coarsely based on the sixth level of the Cortellis target “tree” (e.g., Beta secretase 1, Cyclooxygenase).²⁶ Next, we use an even broader definition of target based on the fifth level of the Cortellis tree (e.g., Beta secretase inhibitors are part of a larger class of Hydrolase enzymes, and Cyclooxygenase-2 inhibitors fall within a group of Oxidoreductase targets). Finally, we also developed a scoring system that assigns a “target novelty” value to a drug according to its targets’ locations in the tree and their entry order.²⁷ These results show that treated firms differentially develop more drug candidates aimed at new biological targets.

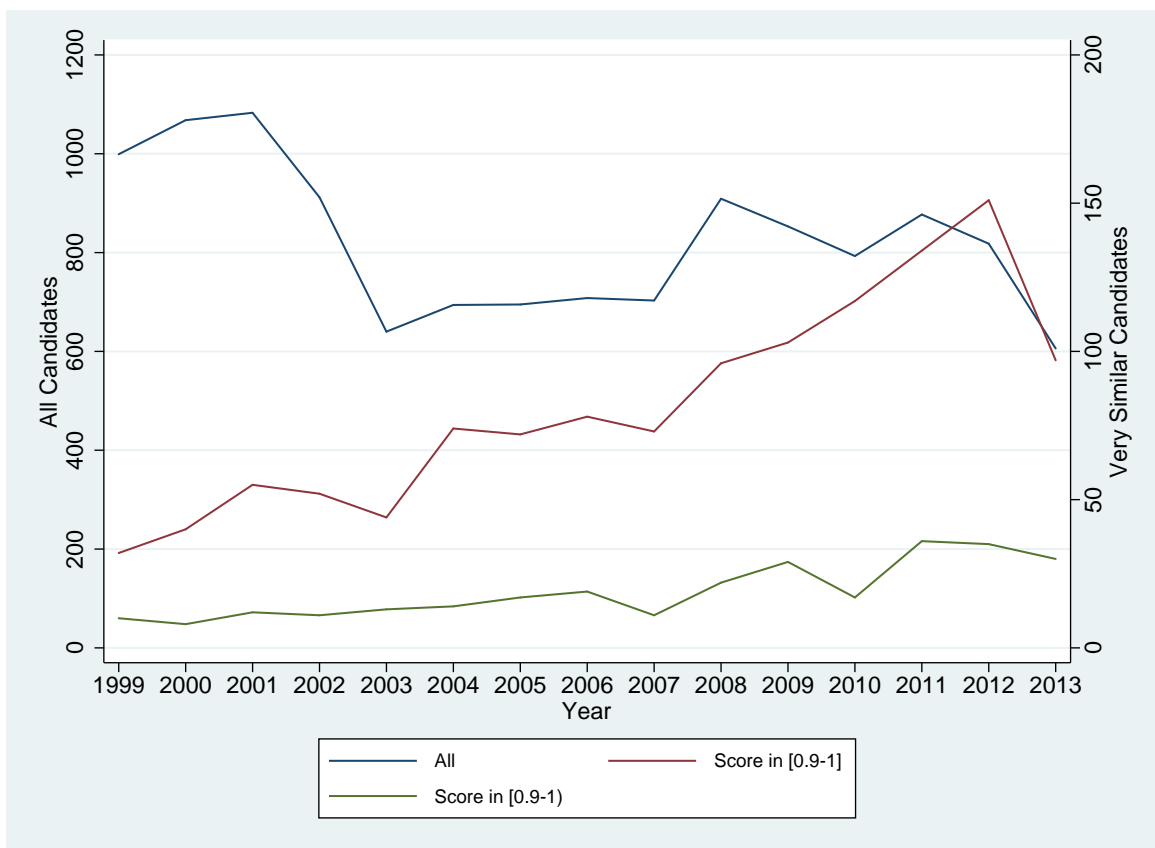
In addition, we find that our results are not driven by pre-existing firm-specific trends (Appendix Table A.20), and are robust to alternative definitions of novelty, specifically novelty with respect to prior candidates for the same indication (Appendix Table A.17). Further, our results are robust to different empirical specifications: Table A.21 in the Appendix considers Poisson count models, Table A.24 considers a binary outcome variable (based on whether the firm have any new drugs), and Table A.22 considers a binary treatment. Our results are also robust to different definitions of treatment: Table A.23 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.25 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.10; Table A.26 shows that are results are similar if we exclude these firms.

²⁶The Cortellis target tree is a hierarchical ontology used to classify drug targets. It is similar in format to the Kyoto Encyclopedia of Genes and Genomes (KEGG) target-based classification system that is commonly used in drug databases (for example, the National Library of Medicine’s PubChem database reports KEGG codes for compound entries).

²⁷The scoring system awards drugs higher target novelty scores if they are the first entrant into a target group, and assigns greater scores to drugs that are first to lower level branches (i.e., closer to the tree’s root). For example, a drug that is the first entrant to a fifth level branch is assigned a higher novelty score than a drug that is first in its sixth level branch group, but the ninth entrant in its relevant fifth level branch.

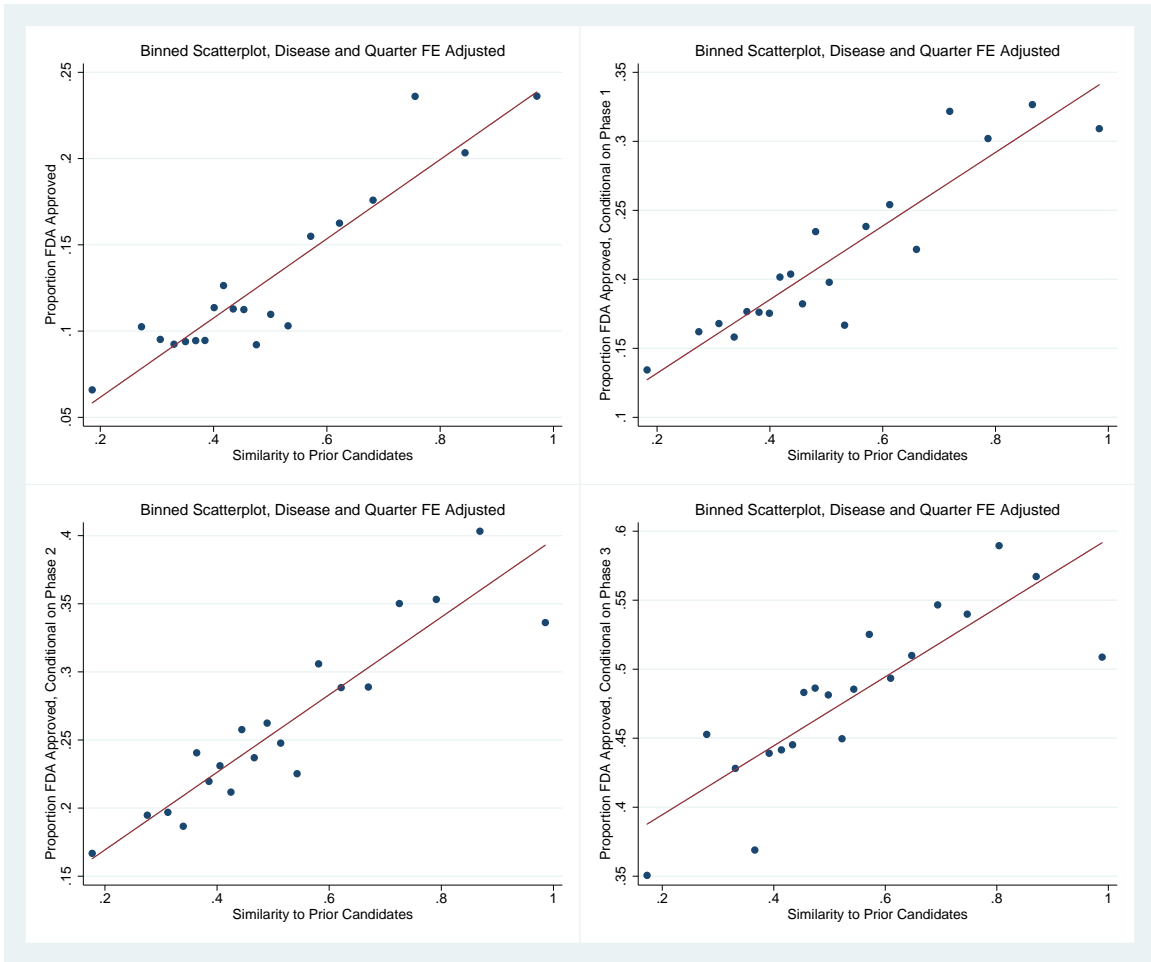
Appendix Tables and Figures

Figure A.1: # OF DRUG CANDIDATES OVER TIME



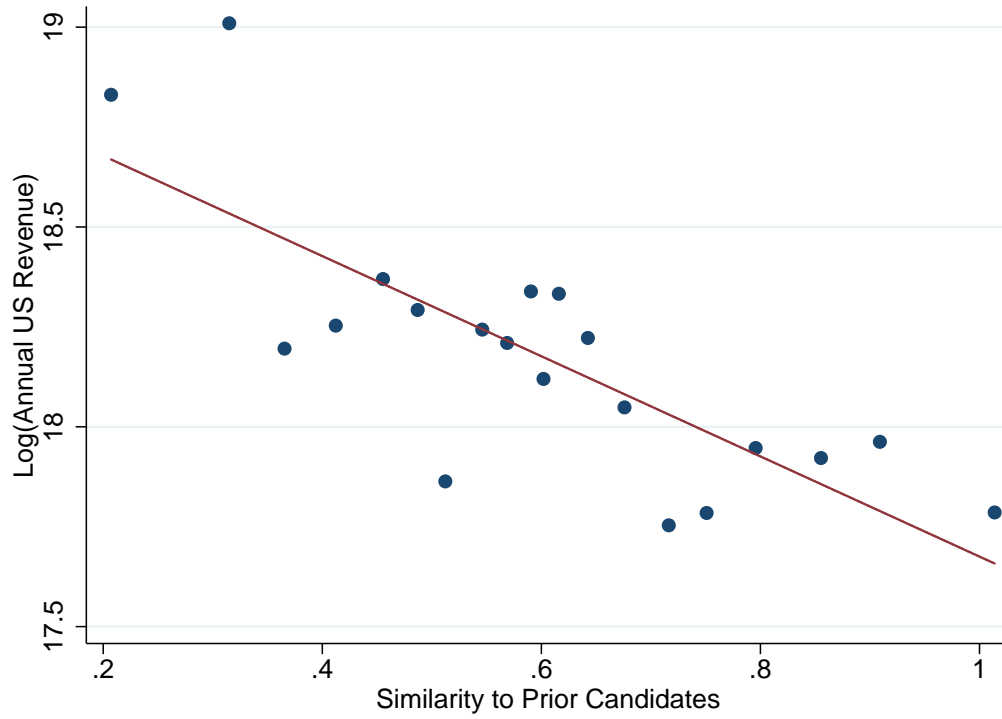
NOTES: This figure plots the number of new drug candidates for which we have data on molecular structure over time. The blue line all drug candidates. The red line represents drugs with similarity scores greater than 0.9, which indicates over 90% overlapping chemical structures. The green line plots 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.

Figure A.2: PROPORTION FDA APPROVED, BY DRUG SIMILARITY



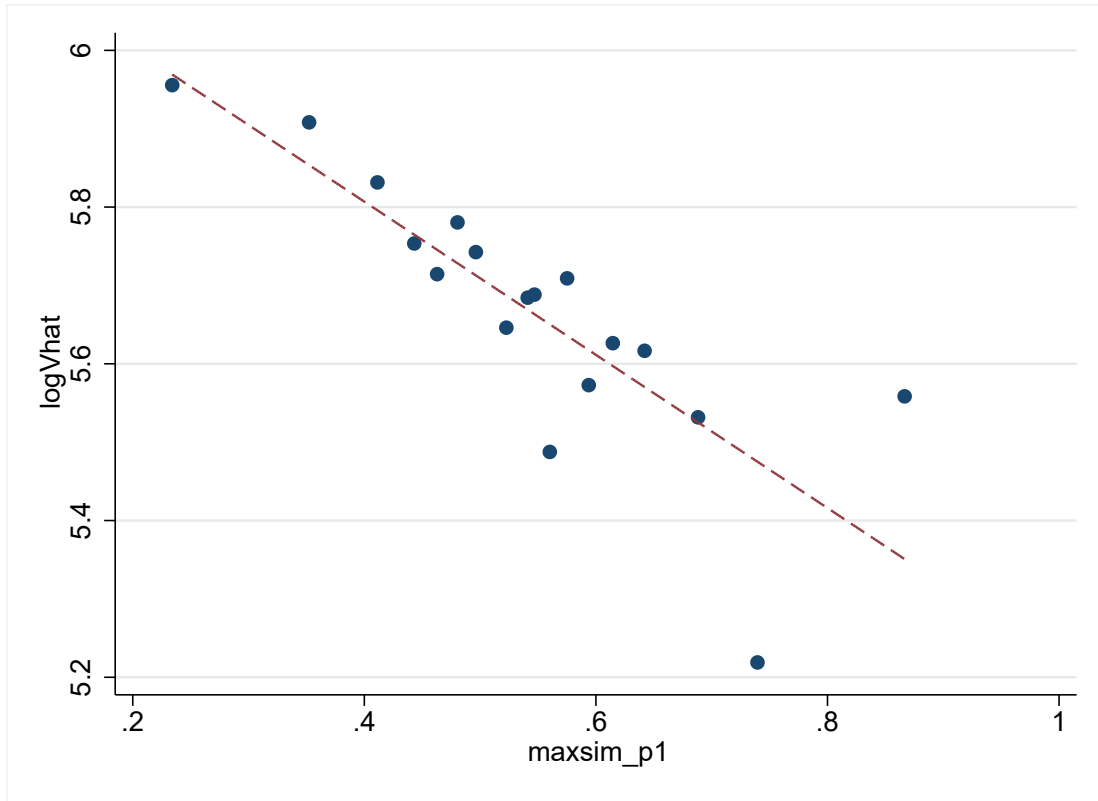
NOTES: Figure A.2 presents binned scatterplots of drug-level similarity against whether a drug is FDA approved. Each dot represents the proportion of candidates that FDA approved, among all candidates within a given similarity score bin, conditional on disease (ICD9) and quarter of development fixed effects. The top left panel examines all drug candidates; the top right represents only candidates that have made it into Phase 1 testing; the bottom left examines approval outcomes conditional on making it into Phase 2; the final figure examines outcomes conditional on Phase 3.

Figure A.3: REVENUE, BY DRUG SIMILARITY



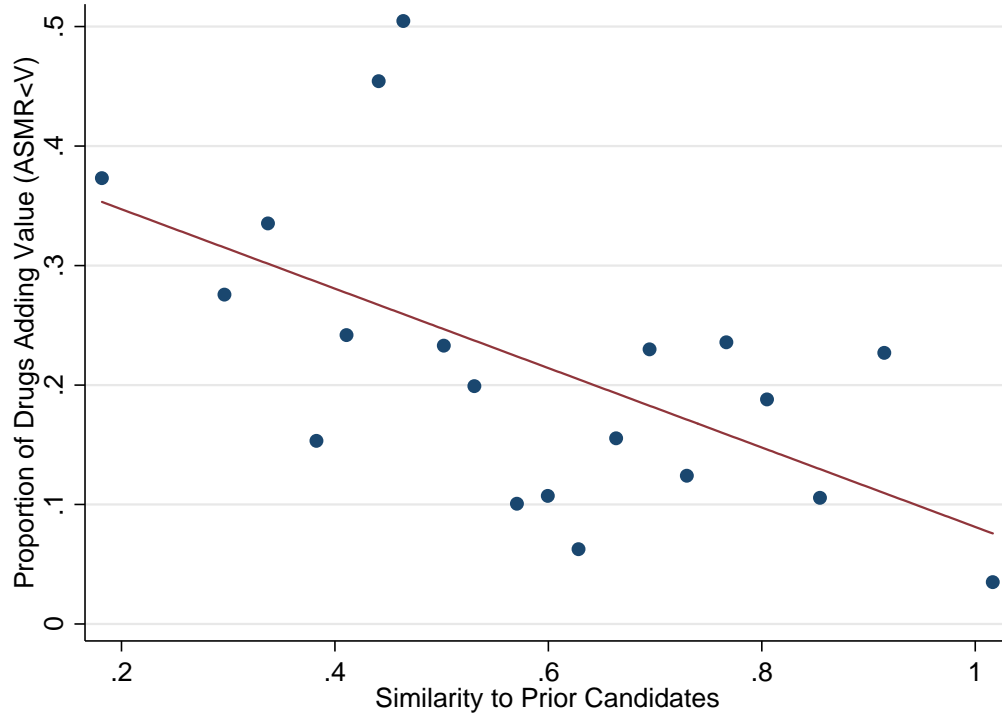
NOTES: Figure A.3 presents a binned scatterplot of drug-level similarity against revenue conditional on approval. The plot corresponds to the regression in Column (4) of Table A.5, which includes controls for drug indication, drug age, and firm dummies.

Figure A.4: DRUG SIMILARITY AND STOCK MARKET REACTION ON FDA APPROVAL



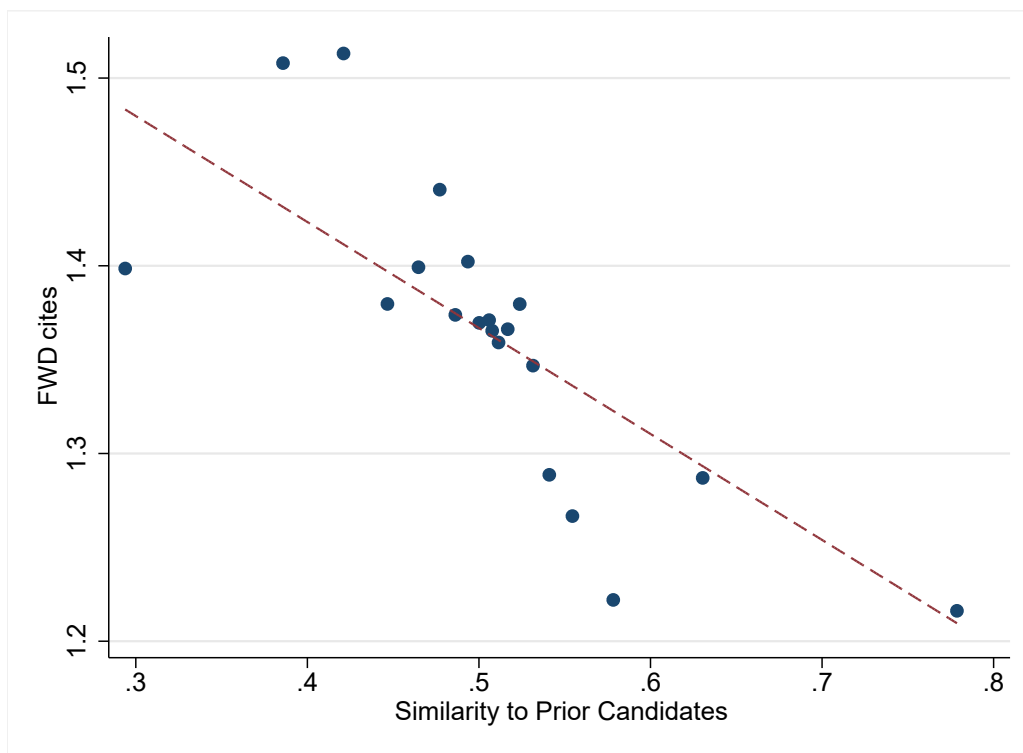
NOTES: Figure A.4 presents a binned scatterplot of drug-level similarity against the logarithm of the estimated dollar reaction on the (first) approval of the drug by the FDA. The dollar reaction to the FDA approval is estimated following the methodology of Kogan et al. (2017) and uses a 5-day window following the FDA approval. Each dot represents mean log value, among all candidates within a given similarity score bin, conditional on disease (ICD9); patent issue year; firm; and year of development fixed effects, which corresponds to Column (3) of Appendix Table A.6. We adjust our estimates for differences in the ex-ante probability of approval using the point estimates of Column (9) of Table A.4.

Figure A.5: DRUG SIMILARITY AND DRUG EFFECTIVENESS



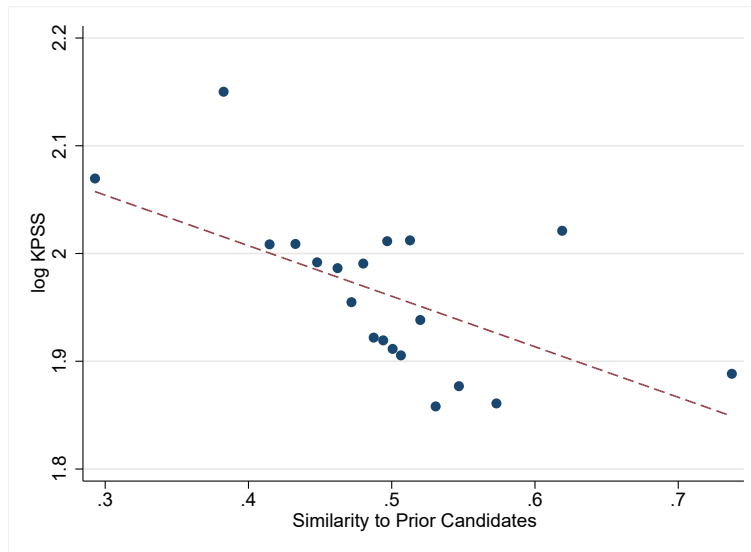
NOTES: Figure A.5 presents a binned scatterplot of drug-level similarity against drug added benefits. A drug's added benefit is derived from the French Haute Autorité de Santé (HAS) health system's clinical added benefits scores (Amélioration du Service Medical Rendu, or ASMR), which range from one to five (I to V), with V indicating no value added. In the plot above, the y-axis values represent the proportion of drugs in each similarity bin that had ASMR values less than V, after normalizing by disease area (ICD9) and the year of each drug's first regulatory approval year.

Figure A.6: DRUG SIMILARITY AND PATENT CITATIONS



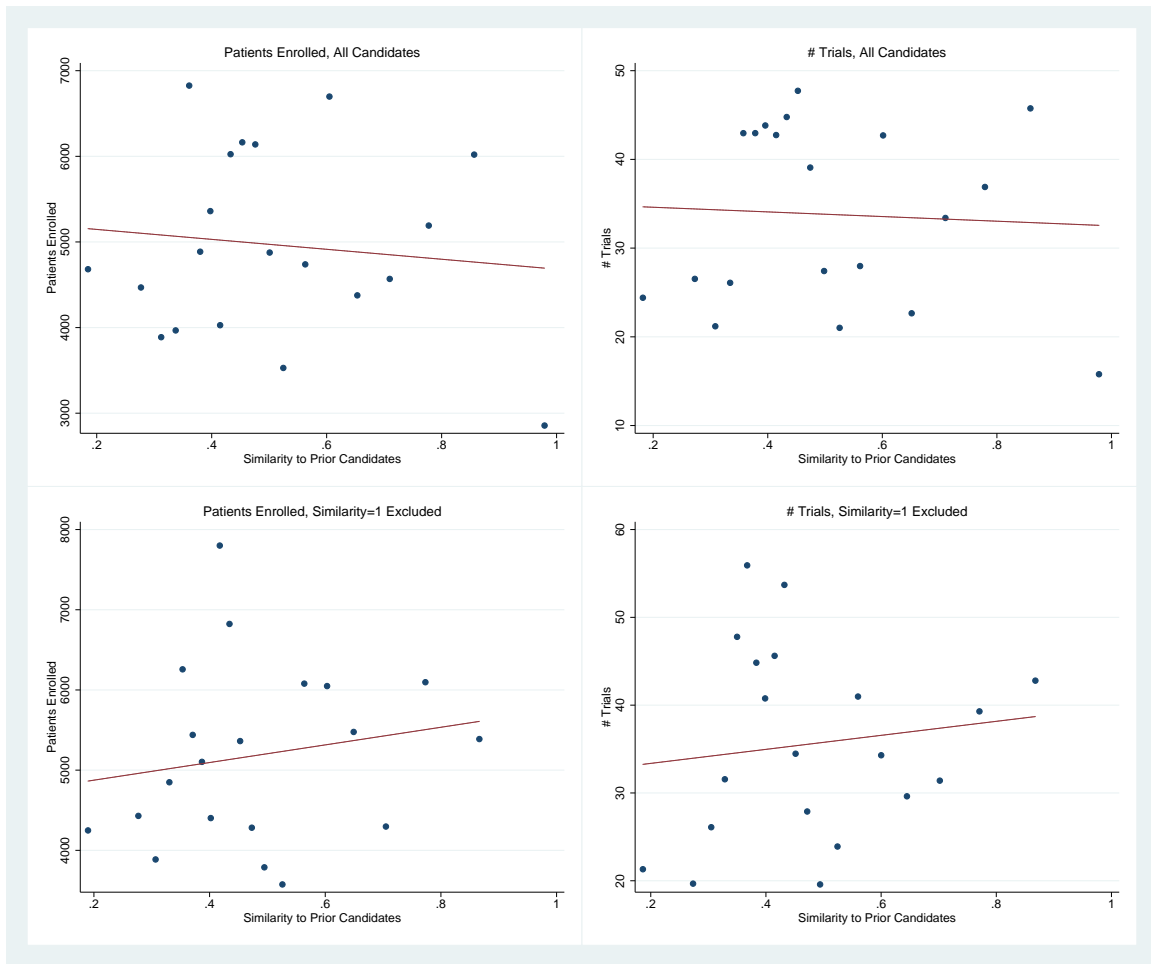
NOTES: Figure A.6 presents a binned scatterplot of drug-level similarity against the logarithm of one plus the number of forward citations the patent receives. Each dot represents mean log value, among all candidates within a given similarity score bin, conditional on disease (ICD9); patent issue year; company (assignee code), and year of development fixed effects. This specification corresponds to Column (4) of Table A.8. Please see Table A.8 for additional specifications.

Figure A.7: DRUG SIMILARITY AND MARKET VALUE OF PATENTS



NOTES: Figure A.7 presents a binned scatterplot of drug-level similarity against the logarithm of the [Kogan et al. \(2017\)](#) estimated patent values. Each dot represents mean log value, among all candidates within a given similarity score bin, conditional on disease (ICD9); patent issue year; firm and year of development fixed effects. This specification corresponds to Column (4) of Table A.9. Please see Table A.9 for additional specifications.

Figure A.8: PROXIES FOR DEVELOPMENT COSTS, BY DRUG SIMILARITY



NOTES: Figure A.8 presents a binned scatterplot of drug-level similarity against proxies for the direct cost of drug development. Each dot represents the mean number of patients enrolled (or number of trials conducted), among all candidates within a given similarity score bin, conditional on disease (ICD9) and quarter of development fixed effects. In the bottom two panels, we exclude drug candidates with a similarity score of 1 to restrict to candidates that likely did not rely on results of trials conducted for an identical past drug.

Figure A.9: Drug Similarity and Market Value of Patents: Placebo Experiments

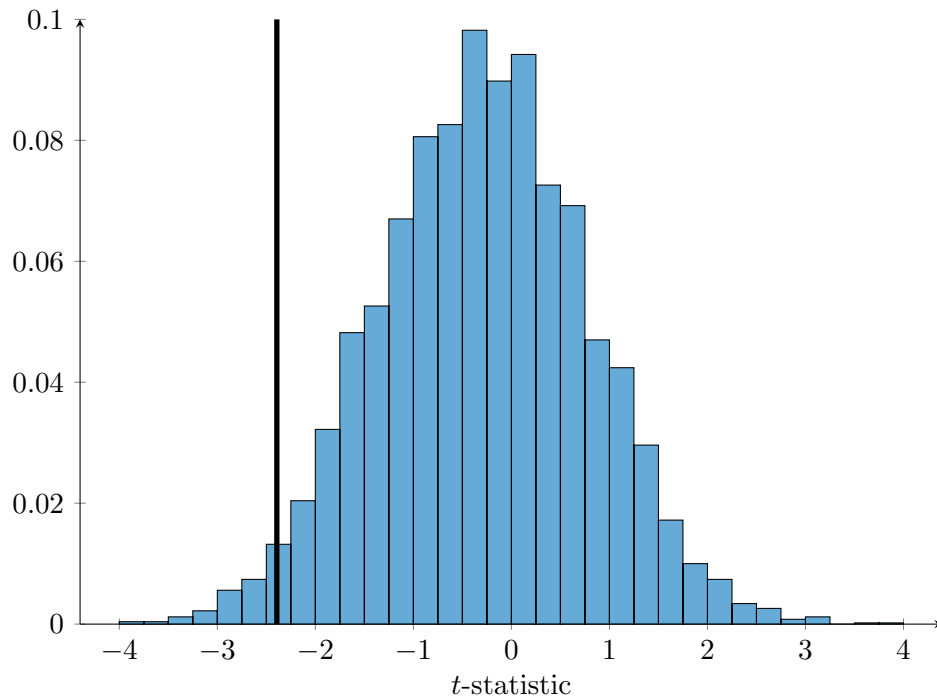
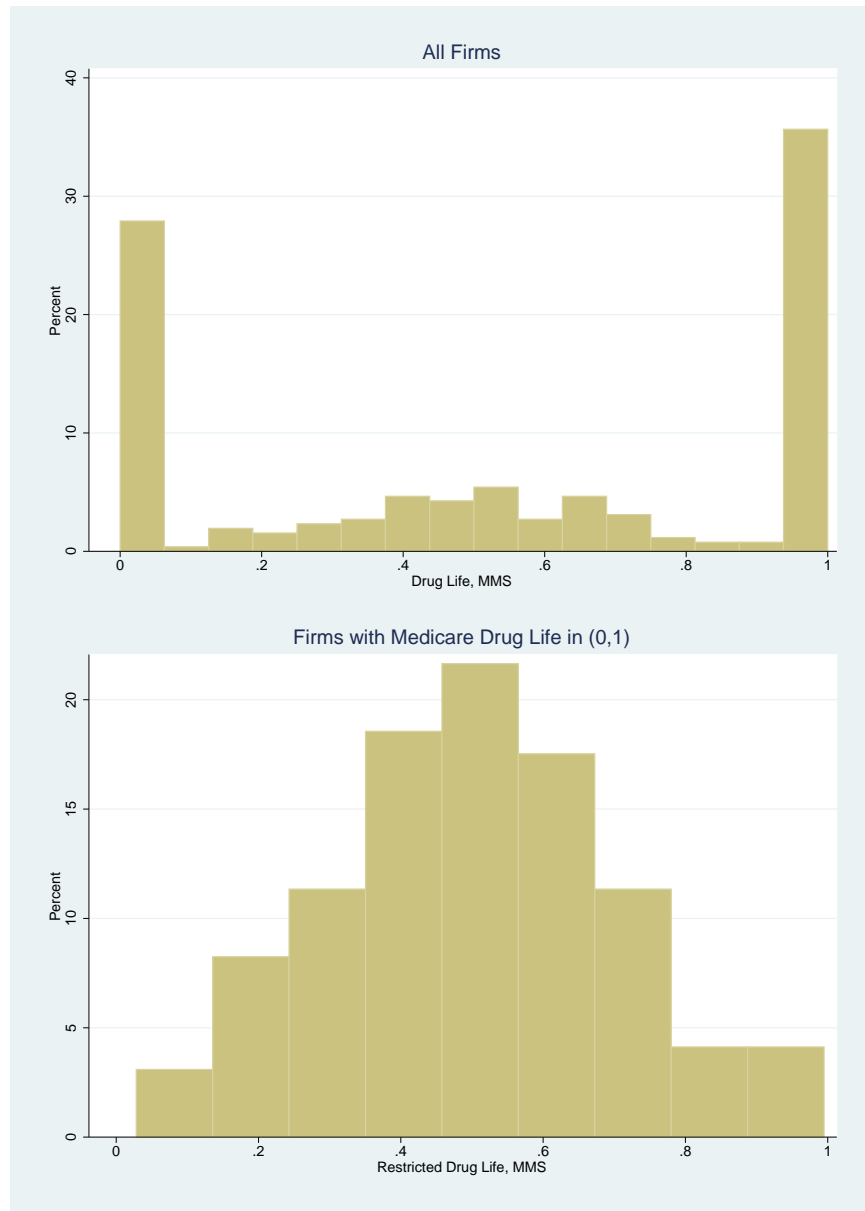


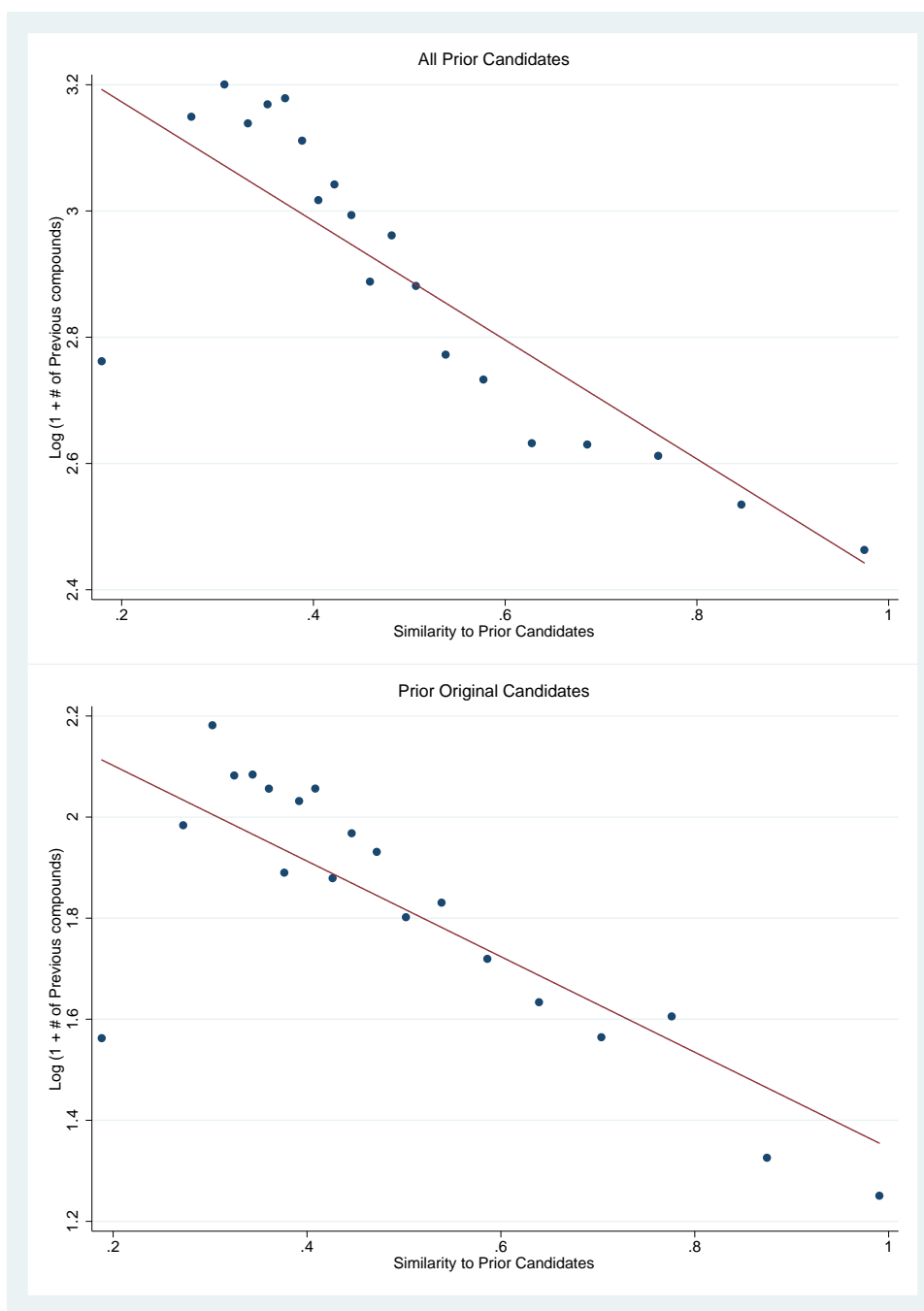
Figure plots the distribution of estimated coefficients t -statistics, from estimating equation (??) linking drug similarity and the [Kogan et al. \(2017\)](#) measure of patent value across 5,000 placebo experiments. In each placebo experiment, we randomly generate a different issue date for each patent within the same year the patent is granted to the firm. We then reconstruct the [Kogan et al. \(2017\)](#) using these placebo grant dates. The solid line on the right corresponds to the t statistic using the real data – column (6) in Table 2. Approximately 2.3% of the placebos generate estimates that are of the same sign—and more significant—than our empirical estimates.

Figure A.10: DISTRIBUTION OF MEDICARE DRUG LIFE IN 2003



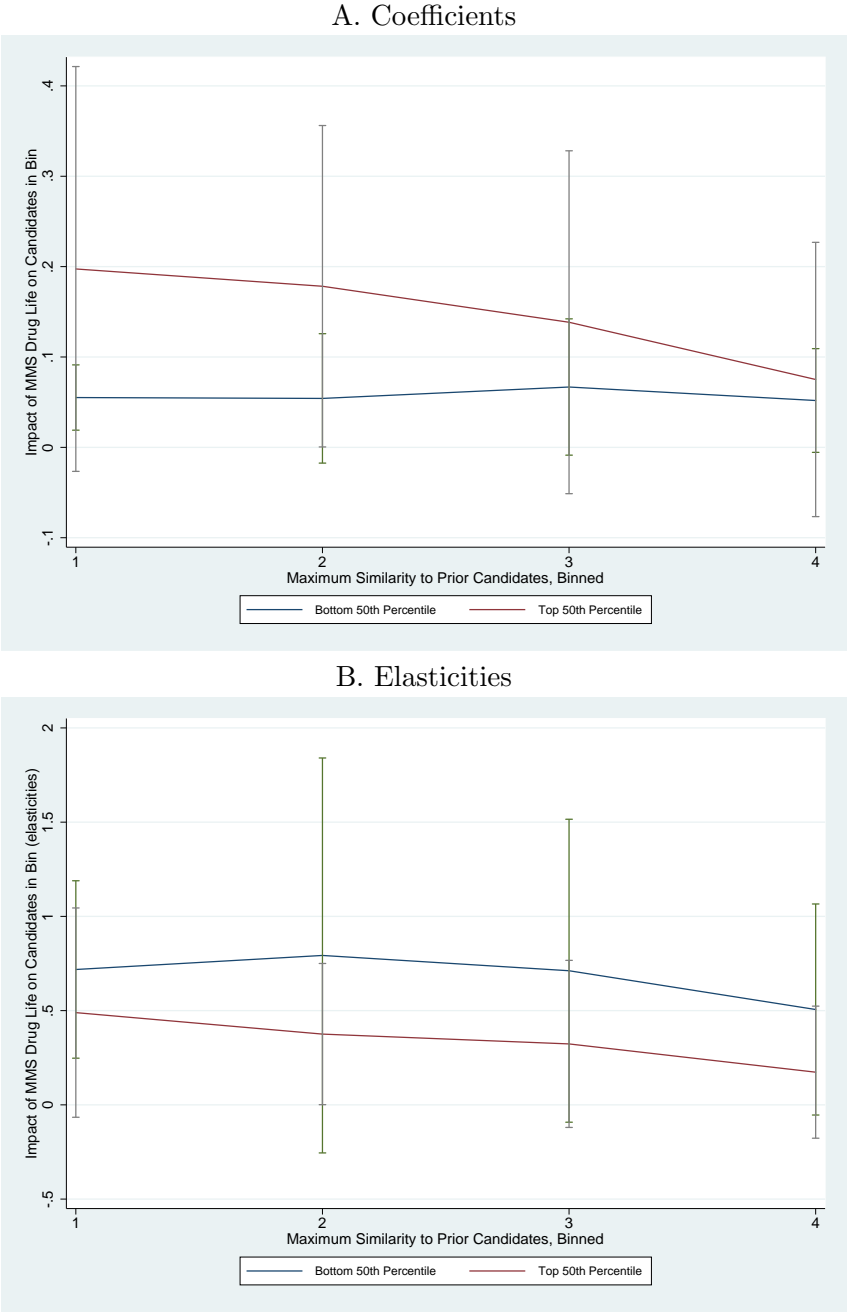
NOTES: Figure A.10 plots the distribution of Medicare Drug Life in 2003. Each observation is a firm in our main analysis sample.

Figure A.11: FIRM EXPERIENCE, BY DRUG SIMILARITY



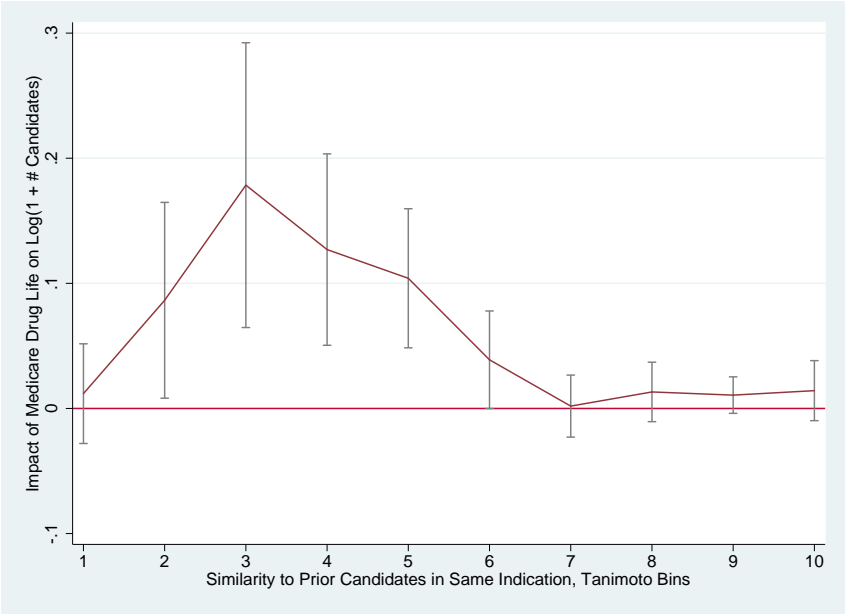
NOTES: Figure A.11 presents a binned scatterplot of drug-level similarity against measures of firm experience. Each dot represents the mean log of past firm experience, among all candidates within a given similarity score bin, conditional on disease (ICD9) and quarter of development fixed effects. In the top panel, past firm experience is defined as one plus the total number of compounds developed by this firm prior to a the drug candidate in question. In the bottom panel, we count experience using only past compounds for which the given firm had ownership at the time the compound first enters development.

Figure A.12: IMPACT OF ADDITIONAL RESOURCES ON NOVELTY, WITHIN INDICATION



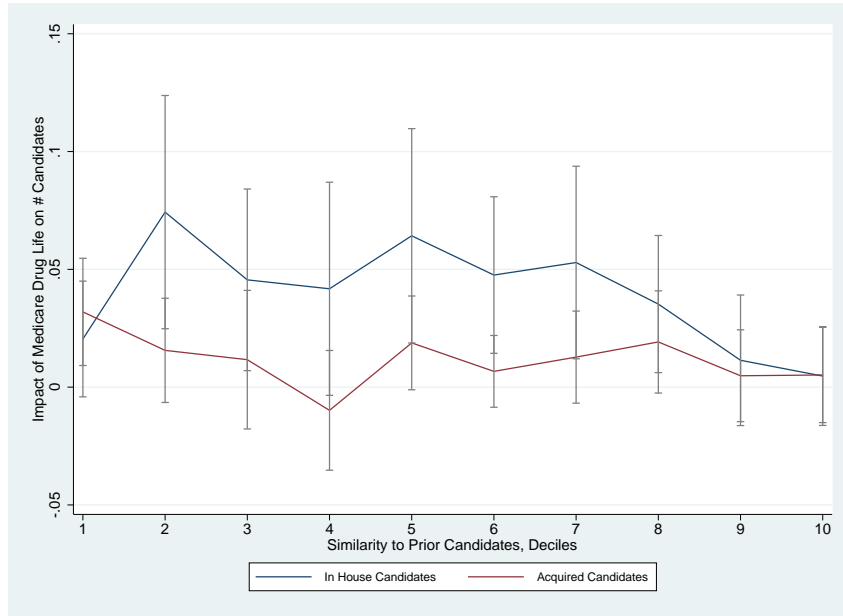
NOTES: Figure A.12 plots the estimated coefficients on $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$ from our main regression specification defined by Equation (3) across firm size groups (defined by total revenue generated by approved drugs prior to 2003). The outcome variable is number of drug candidates across novelty bins.

Figure A.13: IMPACT OF ADDITIONAL RESOURCES ON NOVELTY, WITHIN INDICATION



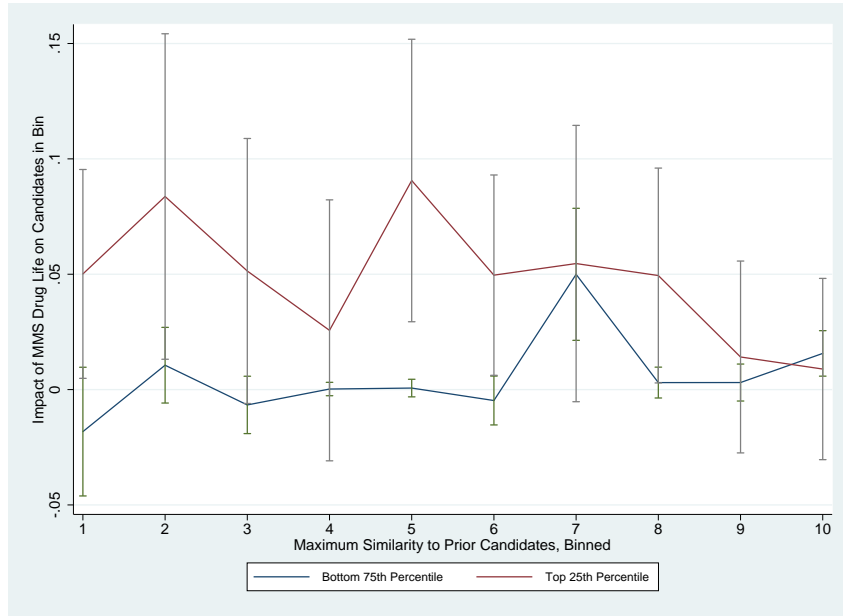
NOTES: Figure A.13 plots the estimated coefficients on $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$ from our main regression specification defined by Equation (3). This figure is analogous to the bottom panel of Figure 7 of the main text, except that similarity is measured with respect to other drugs in the same indication (disease).

Figure A.14: ORIGINAL VS. ACQUIRED



NOTES: Figure A.14 plots the estimated coefficients on $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$ from our main regression specification defined by Equation (3), with the sample split based on firm experience in drug development. Each point represents a different outcome variable: the number of new drug candidates in a given bin of similarity. The blue line (above) represents the coefficients corresponding firms. The red line (below) displays the coefficients for drugs that the developer acquired. Both sets of coefficients include 95% confidence intervals around the point estimates.

Figure A.15: EXPERIENCED VS. INEXPERIENCED FIRMS



NOTES: Figure A.15 plots the estimated coefficients on $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$ from our main regression specification defined by Equation (3), with the sample split based on experience. Each point represents a different outcome variable: the number of new drug candidates in a given bin of similarity. The red line (above) represents the coefficients corresponding to firms in the top 25th percentile of experience (as proxied by one plus the number of new drug candidates the firm had previously developed) while the blue line (below) displays the coefficients for firms in the bottom 75th percentile of firm experience. Both sets of coefficients include 95% confidence intervals around the point estimates.

Table A.1: PHARMACEUTICAL FIRMS AND DEBT FINANCE

	A. Compustat North America			B. Compustat Global		
	(1)	(2)	(3)	(1)	(2)	(3)
Pharmaceutical	-0.0330** (-2.60)	-0.0709*** (-4.75)	-0.0808*** (-5.24)	-0.00775 (-0.96)	-0.0287*** (-3.40)	-0.0324*** (-3.72)
Size, log		0.0188*** (32.09)	0.0239*** (40.39)		0.00650*** (37.41)	0.00658*** (35.70)
Profitability			-0.0384*** (-12.46)			-0.0270*** (-13.46)
Mean leverage ratio	0.174	0.174	0.174	0.118	0.118	0.118
N	261,158	261,158	249,845	533,580	533,577	493,448
R^2	0.008	0.058	0.086	0.003	0.024	0.022

NOTES: Table A.1 compares leverage ratios of the pharmaceutical firms in our sample and compares them to the broader Compustat universe. Standard errors are clustered by firm. Firm size is book assets (Compustat: at); profitability is income before extraordinary items (Compustat: ib) plus depreciation (Compustat: dp) over book assets. Panel A presents results for firms in Compustat North America; Panel B for Compustat Global. All specifications include time fixed effects. We report t -statistics in parentheses, with standard errors clustered by firm. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.2: DRIVERS OF PAIRWISE DRUG SIMILARITY

Drug Candidate Pairwise Similarity				
<i>Mean = 0.106</i>				
	(1)	(2)	(3)	(4)
Share Target-Action <i>Mean: 0.022</i>	0.167*** <i>(6.24e-05)</i>	0.122*** <i>(0.00838)</i>		
Share Indication <i>Mean: 0.149</i>			0.0102*** <i>(8.51e-06)</i>	0.0285*** <i>(0.00200)</i>
N	955,921,961	955,921,961	955,921,961	955,921,961
R ²	0.025	0.265	0.002	0.075
Target-Action FEs		X		
Indication FEs				X

NOTES: Table A.2 examines the relationship between indicator variables for sharing the same target-action or the same indication (ICD9) on the pairwise similarity of two drug candidates, call them drug A and drug B. Because single drug can be associated with multiple target-actions and indications, each observation is a drugA-actionA-indicationA-drugB-actionB-indicationB pair. We include such a pair for every pair of drugs in our data. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.3: PROPORTION FIRST IN TARGET, BY DRUG SIMILARITY

	First in Narrow Target		First in Broad Target	
	<i>Mean: 0.194</i>		<i>Mean: 0.068</i>	
	(1)	(2)	(3)	(4)
Similarity Measure	-0.210*** (0.0148)	-0.175*** (0.0153)	-0.144*** (0.00858)	-0.141*** (0.00921)
N	15,160	15,160	15,160	15,160
R ²	0.052	0.129	0.044	0.076
Quarter of Development FEs	X	X	X	X
Disease FEs		X		X

NOTES: Table A.3 examines the relationship between drug level similarity (maximum similarity to any prior developed drug candidate) and a drug's likelihood of being the first in its target, defined narrowly (target and action) and broadly (coarse target family). Observations are at the drug level and results are reported with robust standard errors. The accompanying binned scatterplot of results is shown in Figure 3. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.4: PROPORTION FDA APPROVED, BY DRUG SIMILARITY

		<u>All</u>		<u>Phase 1</u>		<u>Phase 2</u>		<u>Phase 3</u>	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Maximum Similarity	0.269*** (0.033)	0.227*** (0.031)	0.208*** (0.040)	0.300*** (0.045)	0.254*** (0.060)	0.312*** (0.051)	0.249*** (0.071)	0.271*** (0.073)	0.123 (0.088)
R^2	0.091	0.165	0.466	0.103	0.519	0.097	0.544	0.080	0.668
Development Year FEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ICD-9 FEs		Yes	Yes		Yes		Yes		Yes
Firm FEs			Yes		Yes		Yes		Yes
Observations	19191	19127	18488	11476	11036	9508	9152	5158	4873

NOTES: Table A.4 examines the relationship between drug level similarity (maximum similarity to any prior developed drug candidate that ever reached Phase 1 clinical trials) and a drug's likelihood of reaching FDA approval. Observations are at the drug-ICD9 level and results are reported with standard errors clustered at the firm level. The analysis sample changes by column, including all drugs (Columns 1 to 3), drugs that reach Phase 1 (Columns 4 and 5), drugs that reach Phase 2 (Columns 6 and 7), and drugs that reach Phase 3 (Columns 8 and 9). The accompanying binned scatterplot of results is shown in Figure A.2. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.5: REVENUE, BY DRUG SIMILARITY

	<u>Log(Annual US Revenue)</u>			
	(1)	(2)	(3)	(4)
Maximum Similarity	-1.449*** (0.280)	-1.307*** (0.286)	-1.253*** (0.297)	-0.641* (0.293)
R^2	0.092	0.272	0.293	0.574
Year FEs	Yes	Yes	Yes	Yes
ICD-9 FEs		Yes	Yes	Yes
Launch Year FEs			Yes	Yes
Firm FEs				Yes
Observations	11,256	11,243	11,243	11,230

NOTES: Table A.5 examines the relationship between drug level similarity (maximum similarity to any prior developed drug candidate that ever reached Phase 1 clinical trials) and a drug's revenue conditional on approval. Drug revenue data is derived by matching approved drugs to the Medicare Expenditure Panel Survey. We estimate a panel regression at the drug-ICD9-year level with year fixed effects throughout. To control for differences across drugs, we include fixed effects for indication (ICD-9); drug cohort (the year the drug is launched); and firm. We cluster the standard errors clustered at the calendar year and ICD-9 level. The accompanying binned scatterplot of results is shown in Figure A.3. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.6: MARKET REACTION TO FDA APPROVAL, BY DRUG SIMILARITY

	(1)	(2)	(3)
Maximum Similarity	-1.321*** (0.453)	-2.191*** (0.592)	-1.100*** (0.380)
R^2	0.065	0.373	0.858
Fixed Effects:			
Approval Year	Y	Y	Y
Indication (ICD-9)		Y	Y
Firm			Y
Observations	462	411	399

NOTES: Table A.6 examines the relationship between drug level similarity (maximum similarity to any prior developed drug candidate) and the logarithm of the estimated dollar reaction on the (first) approval of the drug by the FDA. The dollar reaction to the FDA approval is estimated following the methodology of [Kogan et al. \(2017\)](#) and uses a 5-day window following the FDA approval. Observations are at the drug level. We report standard errors in parentheses clustered by firm and indication. Controls include: 1) the year the drug is approved; 2) the ICD9 disease area treated by the drug; and 3) company fixed effects. The accompanying binned scatterplot of results is shown in [Figure A.4](#). * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.7: DRUG NOVELTY AND DRUG EFFECTIVENESS

	(1)	(2)	(3)	(4)	(5)	(6)
	Any Value Added	Any Value Added	High Importance	High Importance	ASMR Value	ASMR Value
	ASMR<V	ASMR<V	ASMR<IV	ASMR<IV		
Maximum Similarity	-0.343*** (0.058)	-0.263*** (0.053)	-0.100** (0.045)	-0.064 (0.041)	0.347*** (0.122)	0.208** (0.104)
R^2	0.650	0.760	0.529	0.687	0.596	0.739
Controls						
Development Year FEs	Yes	Yes	Yes	Yes	Yes	Yes
ICD-9 FEs	Yes	Yes	Yes	Yes	Yes	Yes
Firm FEs		Yes		Yes		Yes
N	1839	1778	1839	1778	1839	1778

NOTES: Table A.7 examines the relationship between drug level similarity (maximum similarity to any prior drug candidate that had reached phase 1 clinical trials) and the French Haute Autorité de Santé (HAS) health system's measure of clinical added benefits (Amélioration du Service Medical Rendu, or ASMR). The ASMR scores range from I (major value added) to V (no value added). The analysis sample includes approved small molecule drugs that received ASMR scores and that we were able to match to drugs in the Cortellis database. Controls include indication (ICD9 code), drug launch year and company identifiers. Standard errors are clustered by indication. The accompanying binned scatterplot of results is shown in Figure A.5. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.8: PATENT CITATIONS AND DRUG SIMILARITY

log(1 + citations)	A. All patents			
	(1)	(2)	(3)	(4)
Maximum Similarity	-0.022 (0.081)	-0.160* (0.084)	-0.130* (0.078)	-0.173** (0.078)
<i>N</i>	119080	119080	119069	118765
<i>R</i> ²	0.268	0.287	0.301	0.404
log(1 + citations)	B. US patents only			
	(1)	(2)	(3)	(4)
Maximum Similarity	0.213 (0.154)	0.011 (0.148)	-0.002 (0.136)	-0.565*** (0.196)
<i>N</i>	11,557	11,557	11,536	11,324
<i>R</i> ²	0.666	0.685	0.710	0.850
Fixed Effects:				
Country × Issue Year	Y	Y	Y	Y
Drug Development Year		Y	Y	Y
ICD-9			Y	Y
Firm				Y

NOTES: Table A.8 examines the relationship between drug level similarity (maximum similarity to any prior developed drug candidate) and the logarithm of one plus the number of forward citations. The matching between drugs and patents is from Cortellis. We restrict attention to patents issued prior to the FDA approval. Observations are at the drug-disease(ICD9)-patent level. We report standard errors in parentheses clustered by firm. Controls include: 1) the country and the year the patent is granted; 2) the ICD9 disease area treated by the drug; 3) the year the drug is developed; and 4) company fixed effects. The accompanying binned scatterplot of results is shown in Figure A.6. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.9: PATENT MARKET VALUE AND DRUG SIMILARITY

log(KPSS value)	US patents			
	(1)	(2)	(3)	(4)
Maximum Similarity	-1.428*** (0.447)	-1.662*** (0.386)	-1.618*** (0.361)	-0.469** (0.196)
<i>N</i>	5130	5130	5090	5031
<i>R</i> ²	0.104	0.206	0.346	0.862
Fixed Effects:				
Issue Year	Y	Y	Y	Y
Drug Development Year		Y	Y	Y
ICD-9			Y	Y
Firm				Y

NOTES: Table A.9 examines the relationship between drug level similarity (maximum similarity to any prior developed drug candidate) and the logarithm of the estimated patent value, where the latter is based on Kogan et al. (2017). The matching between drugs and patents is from Cortellis. We restrict attention to patents issued prior to the FDA approval. Observations are at the drug-disease(ICD9)-patent level. We report standard errors in parentheses clustered by firm. Controls include: 1) the year the patent is granted; 2) the ICD9 disease area treated by the drug; 3) the year the drug is developed 4) company fixed effects; 5) the interaction between company and year fixed effects. The accompanying binned scatterplot of results is shown in Figure A.7. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.10: DRUG NOVELTY AND DEVELOPMENT COSTS

(a) ALL CANDIDATES

	<u>Patients Enrolled</u>	<u># of Trials</u>
	(1)	(2)
Maximum Similarity	-580.394 (509.676)	-2.621 (3.550)
R^2	0.194	0.170
Qtr of Development FEs	Yes	Yes
ICD-9 FEs	Yes	Yes
Observations	8801	10546

(b) CANDIDATES WITH SIMILARITY SCORE < 1

	<u>Patients Enrolled</u>	<u># of Trials</u>
	(1)	(2)
Maximum Similarity	1099.570* (633.287)	7.982* (4.418)
R^2	0.201	0.175
Qtr of Development FEs	Yes	Yes
ICD-9 FEs	Yes	Yes
Observations	8280	9903

NOTES: Table A.10 examines the relationship between drug level similarity (maximum similarity to any prior developed drug candidate) and the the cost of drug development (as proxied for by the number of patients and number of clinical trials). Panel B excludes candidates with similarity scores of exactly 1, which may include extended release formulations that require fewer additional trials. Observations are at the drug level-ICD9 and results are reported with standard errors clustered by ICD9. The accompanying binned scatterplots of results are shown in Figure A.8. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.11: FIRM EXPERIENCE, BY DRUG SIMILARITY

	<u>Log(1 + All Prior Candidates)</u>		<u>Log(1 + Prior Original Candidates)</u>	
	(1)	(2)	(3)	(4)
Maximum Similarity	-0.764** (0.315)	-0.751*** (0.291)	-0.906*** (0.204)	-0.837*** (0.198)
R^2	0.030	0.078	0.069	0.124
Company FEs	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes
ICD-9 FEs		Yes		Yes
Observations	28521	28486	21220	21182

NOTES: Table A.11 examines the relationship between drug level similarity (maximum similarity to any prior developed drug candidate) and the experience of the firm (as measured by the log of past compounds). Observations are at the drug-icd9-firm level and results are reported with standard errors clustered by firm. The accompanying binned scatterplot of results is shown in Figure A.11. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.12: IN-HOUSE VS. ACQUIRED DRUG CANDIDATES

	(1)	(2)	(3)
	All	In House	Acquired
Post 2003 X Medicare Drug Life	0.263*** (0.096)	0.223** (0.086)	0.094* (0.049)
R^2	0.595	0.593	0.321
Company FEs	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes
Observations	16442	16442	16442

NOTES: Table A.12 reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. Model 1 repeats the result from our main regression specification (Column 6 of table 4). Model 2 limits the dependent variable to the number of new drug candidates that originated within the focal firm (in-house), while Model 3 includes only drug candidates that the focal firm acquired (originated at another firm) 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 A.13: IMPACT OF RESOURCES ON # ORIGINAL NEW CANDIDATES, BY SIMILARITY DECILE

(A) IN HOUSE CANDIDATES

	Log(1 + New In House Candidates), by Similarity Decile									
	1	2	3	4	5	6	7	8	9	10
Post 2003 X Medicare Drug Life	0.020 (0.015)	0.074** (0.030)	0.046* (0.023)	0.042 (0.027)	0.064** (0.028)	0.048** (0.020)	0.053** (0.025)	0.035** (0.018)	0.011 (0.017)	0.005 (0.013)
R^2	0.169	0.273	0.272	0.302	0.310	0.238	0.218	0.187	0.172	0.104
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

(A) ACQUIRED CANDIDATES

	Log(1 + New Acquired Candidates), by Similarity Decile									
	1	2	3	4	5	6	7	8	9	10
Post 2003 X Medicare Drug Life	0.032** (0.014)	0.016 (0.013)	0.012 (0.018)	-0.010 (0.015)	0.019 (0.012)	0.007 (0.009)	0.013 (0.012)	0.019 (0.013)	0.005 (0.012)	0.005 (0.012)
R^2	0.069	0.084	0.081	0.079	0.079	0.066	0.056	0.083	0.085	0.076
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 A.13 reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. In Panel A, the dependent variable is limited to new drug candidates that were originally developed in the focal firm, and varies by new drug candidates' deciles of maximum similarity compared to all prior drug candidates that reached phase I trials. In Panel B, dependent variable includes only newly acquired drug candidates that originated at other firms. 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. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.14: IMPACT OF RESOURCES ON # NEW CANDIDATES, BY NOVELTY

(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 A.14 reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. 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 $\text{Post} \times \text{Overall Drug Life}_{f,2003}$ and $\text{Post} \times \text{Firm MMS}_{f,2003}$ 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 A.15: FIRM EXPERIENCE

	Log(1 + New Candidates), by Experience		
	(1) All	(2) Top 25	(3) Bottom 75
Post 2003 X Medicare Drug Life	0.263*** (0.096)	0.260** (0.118)	0.053 (0.040)
R^2	0.595	0.578	0.049
Company FEs	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes
Observations	16442	11122	4040

NOTES: Table A.15 reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. Column (1) repeats the result from our main regression specification (Column (6) of Table 4). Column (2) limits the sample to firms in the top 25% of the experience distribution (as proxied by number of drug candidates previously developed), while Column (3) includes firms in the bottom 75th percentile in terms of experience. 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 A.16: IMPACT OF RESOURCES ON # NEW CANDIDATES, BY FIRM EXPERIENCE

(A) EXPERIENCED FIRMS (TOP 25TH PERCENTILE)										
	Log(1 + New Candidates), by Similarity Decile									
	1	2	3	4	5	6	7	8	9	10
Post 2003 X Medicare Drug Life	0.050* (0.027)	0.084* (0.043)	0.051 (0.035)	0.026 (0.034)	0.091** (0.037)	0.050* (0.026)	0.055 (0.036)	0.049* (0.028)	0.014 (0.025)	0.009 (0.024)
R^2	0.171	0.276	0.274	0.308	0.317	0.241	0.220	0.202	0.195	0.133
Company FEs										
Qtr of Development FEs										
Overall Drug Life/Firm MMS										
Observations	11122	11122	11122	11122	11122	11122	11122	11122	11122	11122
(A) LESS EXPERIENCED FIRMS (BOTTOM 75TH PERCENTILE)										
	Log(1 + New Candidates), by Similarity Decile									
	1	2	3	4	5	6	7	8	9	10
Post 2003 X Medicare Drug Life	-0.018 (0.017)	0.011 (0.010)	-0.007 (0.008)	0.000 (0.002)	0.001 (0.002)	-0.005 (0.006)	0.050*** (0.017)	0.003 (0.004)	0.003 (0.005)	0.016** (0.006)
R^2	0.045	0.039	0.032	0.030	0.028	0.043	0.034	0.039	0.033	0.054
Company FEs										
Qtr of Development FEs										
Overall Drug Life/Firm MMS										
Observations	4040	4040	4040	4040	4040	4040	4040	4040	4040	4040

NOTES: Table A.16 reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. In Panel A, the sample includes only firms in the top 25th percentile of experience (number of drugs developed by 2003). The sample Panel B includes only the remaining firms in the bottom three quartiles of firm experience. 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. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.17: IMPACT OF RESOURCES ON # NEW CANDIDATES, SIMILARITY WITHIN INDICATION

	Log(1 + New Candidates), by Similarity Decile									
	1	2	3	4	5	6	7	8	9	10
Post 2003 X Medicare Drug Life	0.050 (0.036)	0.089** (0.044)	0.072* (0.040)	0.094** (0.041)	0.080** (0.038)	0.092*** (0.030)	0.069** (0.033)	0.103*** (0.034)	0.056* (0.032)	0.030 (0.024)
R^2	0.186	0.234	0.293	0.317	0.348	0.365	0.333	0.300	0.251	0.209
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 A.17 shows that our results are robust to alternative definitions of novelty: we compute drug similarities relative to all prior drug candidates that reached phase I trials and were developed for the same disease area as the focal drug. We report the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.18: NEW BIOLOGICS

	<u>Log(1 + New Biologics)</u>		
	(1)	(2)	(3)
	All	Past Exp.	No Past Exp.
Post 2003 X Medicare Drug Life	0.045 (0.048)	0.352** (0.152)	0.007 (0.012)
R^2	0.366	0.306	0.083
Company FEs	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes
Observations	16442	825	15609

NOTES: Table A.18 reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$ but focuses on the development of biologics. The dependent variable is the log of one plus the number of new biologics introduced into development per company-quarter. New biologic drugs are identified through the Cortellis Investigational Drugs drug development histories. 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. Column 1 includes all firms, while Columns 2 and 3 separate firms by whether or not they had developed biologic drugs prior to 2004. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.19: NEW TARGETS

	Log(1 + New Target drugs)			
	(1)	(2)	(3)	(4)
	New Target- Actions	Coarse Target (6-levels)	Coarser Target (5-levels)	Novel Target Score
Post 2003 X Medicare Drug Life	0.039* (0.021)	0.021* (0.011)	0.016** (0.007)	0.024* (0.013)
R^2	0.237	0.123	0.097	0.156
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 A.19 reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. All new drugs, including both small molecules and biologic drugs are included in the dependent variable counts. The dependent variable in Column 1 is the log of one plus the number of drugs that the focal firm developed (in the given quarter) for new molecular target-actions. We define drugs with “new” target-actions as drugs that were the first drug candidate (chronologically across all firms) developed to treat any condition via the given target-action. The dependent variables in Columns 2 and 3 use coarser definitions of targets, based on the Cortellis target tree ontology. The “coarse” definition of targets in Column 2 counts the log of one plus the number of new drugs that were the first entrant to a target group six levels deep into the Cortellis target tree, while the “coarser” outcome in Column 3 is the same but for target groups five levels into the Cortellis ontology. Column 4 defines new target drugs as those in the top 10% of a “target novelty” score. This score is based off target tree position and entry order for targets associated with a given drug. 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.

Table A.20: IMPACT OF RESOURCES ON # NEW CANDIDATES, COMPANY TIME TRENDS

	Log(1 + New Candidates), by Similarity				
	All	Q 1	Q 2	Q 3	Q 4
Post 2003 X Medicare Drug Life	0.174* (0.099)	0.116** (0.057)	0.095* (0.049)	0.074 (0.050)	0.010 (0.042)
R^2	0.644	0.471	0.527	0.432	0.339
Company FEs	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes
Patent Life/Firm MMS X Post	Yes	Yes	Yes	Yes	Yes
Company-Qtr Trends	Yes	Yes	Yes	Yes	Yes
Observations	16442	16442	16442	16442	16442

NOTES: Table A.20 shows that our results are not driven by company-specific trends. The table reports the main specification coefficient for $\text{Post} \times \text{Medicare Drug Life}_{f,2003}$. The outcome variable in the first models includes all new drug candidates, while the other four models limit the dependent variable to the count of new drug candidates that fall into the given similarity quartile. 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. Additionally, these models include company-quarter indicator variables to capture any firm-specific time trends. Robust standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.21: IMPACT OF RESOURCES ON # NEW CANDIDATES, POISSON QUASI MAXIMUM LIKELIHOOD

	# New Candidates, by Similarity				
	All	Q 1	Q 2	Q 3	Q 4
Post 2003 X Medicare Drug Life	0.790** (0.389)	0.830 (0.593)	0.962** (0.445)	0.693 (0.514)	0.631 (0.577)
Post 2003 X Overall Drug Life	-0.397 (0.429)	-0.592 (0.614)	-0.312 (0.513)	0.208 (0.547)	-0.607 (0.659)
Post 2003 X Firm MMS	-0.495 (0.354)	-0.147 (0.477)	-0.592 (0.462)	-0.125 (0.428)	-0.622 (0.591)
<i>R</i> ²					
Company FEs	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes
Observations	15611	11136	10354	12319	12861

NOTES: Table A.21 reports the coefficients corresponding to those in our main specification, but obtained from a Poisson quasi-maximum likelihood estimation regression. The outcome variable in the first models includes all new drug candidates, while the other four models limit the dependent variable to the count of new drug candidates that fall into the given similarity quartile. 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. One can interpret the coefficient from the first column (0.790) as a one unit change in Medicare drug life leading to a 79% increase in all new drug candidates. This coefficient translates into an elasticity of 0.43. QML (robust) standard errors in parentheses, clustered around company identifiers. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.22: IMPACT OF RESOURCES ON # NEW CANDIDATES, BINARY TREATMENT

	Log(1 + New Candidates), by Similarity				
	All	Q 1	Q 2	Q 3	Q 4
Post 2003 X Above Median Medicare Drug Life	0.167*** (0.059)	0.111*** (0.040)	0.079** (0.035)	0.084** (0.035)	0.065** (0.028)
Post 2003 X Overall Drug Life	-0.138** (0.063)	-0.104** (0.041)	-0.060* (0.035)	-0.054 (0.036)	-0.062** (0.030)
Post 2003 X Firm MMS	-0.048 (0.042)	-0.014 (0.022)	-0.019 (0.018)	-0.014 (0.020)	-0.012 (0.020)
R^2	0.596	0.397	0.480	0.386	0.301
Company FEs	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes
Observations	16442	16442	16442	16442	16442

NOTES: Table A.22 shows our results are robust to a less parametric definition of the treatment variable, given that treatment might not be linear in medicare drug life because many of our firms have a Medicare exposure of 0 or 1. We define a binary treatment depending on whether our treatment variable is above or below the median. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.23:

Impact of Resources on # New Candidates, Alternative Definitions of Remaining Exclusivity

(A) 7 YEAR THRESHOLD FOR REMAINING DRUG LIFE

	Log(1 + New Candidates), by Similarity				
	All	Q 1	Q 2	Q 3	Q 4
Post 2003 X Medicare Drug Life	0.236** (0.098)	0.106** (0.054)	0.093** (0.046)	0.118** (0.052)	0.028* (0.037)
Post 2003 X Overall Drug Life	-0.214** (0.098)	-0.101* (0.053)	-0.075* (0.047)	-0.090* (0.052)	-0.030* (0.037)
Post 2003 X Firm MMS	-0.056* (0.042)	-0.020* (0.022)	-0.022* (0.017)	-0.015* (0.020)	-0.016* (0.019)
R^2	0.595	0.394	0.479	0.385	0.300
Company FEs	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes
Observations	16442	16442	16442	16442	16442

(A) 10 YEAR THRESHOLD FOR REMAINING DRUG LIFE

	Log(1 + New Candidates), by Similarity				
	All	Q 1	Q 2	Q 3	Q 4
Post 2003 X Medicare Drug Life	0.249** (0.103)	0.107* (0.056)	0.111** (0.048)	0.129** (0.059)	0.048 (0.040)
Post 2003 X Overall Drug Life	-0.218** (0.105)	-0.110** (0.055)	-0.092* (0.049)	-0.103* (0.061)	-0.039 (0.041)
Post 2003 X Firm MMS	-0.052 (0.043)	-0.021 (0.022)	-0.020 (0.016)	-0.013 (0.020)	-0.014 (0.020)
R^2	0.595	0.394	0.479	0.385	0.300
Company FEs	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes
Observations	16442	16442	16442	16442	16442

NOTES: Table A.23 shows that our results are robust to different definitions of the threshold for having long remaining patent life. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.24: IMPACT OF RESOURCES ON # NEW CANDIDATES, ANY DEVELOPMENT

	Any New Candidates, by Similarity				
	All	Q 1	Q 2	Q 3	Q 4
Post 2003 X Medicare Drug Life	0.187** (0.078)	0.130*** (0.048)	0.113** (0.048)	0.108** (0.053)	0.068* (0.037)
Post 2003 X Overall Drug Life	-0.166** (0.078)	-0.123** (0.049)	-0.091* (0.048)	-0.070* (0.055)	-0.063* (0.039)
Post 2003 X Firm MMS	-0.046* (0.040)	-0.015* (0.023)	-0.018* (0.018)	-0.010* (0.023)	-0.011* (0.023)
R^2	0.400	0.313	0.387	0.306	0.250
Company FEs	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes
Observations	16442	16442	16442	16442	16442

NOTES: Table A.24 shows that our results are robust to considering a binary dependent variable and are not driven purely by the intensive margin. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.25: IMPACT OF RESOURCES ON # NEW CANDIDATES, TOTAL PATENT LIFE CONTROLS

	Log(1 + New Candidates), by Similarity				
	All	Q 1	Q 2	Q 3	Q 4
Post 2003 X Medicare Drug Life	0.180*** (0.035)	0.119*** (0.021)	0.105*** (0.019)	0.111*** (0.019)	0.038** (0.019)
Post 2003 X Log(1 + Total Patent Life)	-0.085*** (0.014)	-0.066*** (0.010)	-0.051*** (0.010)	-0.048*** (0.009)	-0.021** (0.008)
Post 2003 X Firm MMS	-0.036 (0.039)	-0.004 (0.020)	-0.011 (0.016)	-0.006 (0.019)	-0.010 (0.020)
R^2	0.604	0.417	0.490	0.396	0.302
Company FEs	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes
Observations	16442	16442	16442	16442	16442

NOTES: Table A.25 shows that our results are robust to alternative specifications that control for the overall length of remaining patents. Specifically, we control for the total patent life instead of proportion of drugs on patent – this controls for the differential effect of part D by scale of firm more directly than controlling for the proportion of drugs with patent life remaining. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.

Table A.26: IMPACT OF RESOURCES ON # NEW CANDIDATES, EXTREME TREATMENT VALUES EXCLUDED

	Log(1 + New Candidates), by Similarity				
	All	Q 1	Q 2	Q 3	Q 4
Post 2003 X Medicare Drug Life	0.303** (0.141)	0.130* (0.077)	0.098* (0.063)	0.143** (0.068)	0.110* (0.056)
Post 2003 X Overall Drug Life	0.111* (0.166)	0.043* (0.085)	0.035* (0.084)	0.134* (0.080)	0.077* (0.067)
Post 2003 X Firm MMS	-0.179* (0.167)	-0.143* (0.088)	-0.061* (0.088)	-0.089* (0.082)	0.048* (0.076)
R^2	0.621	0.406	0.478	0.400	0.322
Company FEs	Yes	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes
Observations	6208	6208	6208	6208	6208

NOTES: Table A.26 shows that our results are robust to excluding firms with extreme values of Medicare exposure of 0 or 1. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.