Missing Novelty in Drug Development*

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July 6, 2020

Abstract

We provide evidence that risk aversion leads pharmaceutical firms to underinvest in radical and novel innovation. We do so by introducing a new measure of novelty: a drug candidate is 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. Consistent with a simple model of costly external finance, a plausibly exogenous positive shock to firms' net worth leads the development of novel (and riskier) drug candidates. This pattern suggests that even large public firms behave as though they are risk averse, reducing their willingness to invest in potentially valuable radical innovation.

JEL Codes: G11, G31, G32, O31, O32.

*We are grateful to Jason Abaluck, Leila Agha, Pierre Azoulay, Amitabh Chandra, 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, Kelly Shue, Ariel Stern, Michael Serrano-Wu, Motohiro Yogo, Joshua Graff Zivin, and numerous seminar participants and discussants for helpful comments and suggestions. We also thank Descartes Holland, Jiaheng Yu, and Shumiao Ouyang for outstanding research assistance; and 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.

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Technological innovation is a key engine for growth; hence, understanding the frictions that impede the development of new ideas is critical. Unlike investments in physical capital, investments in research and development are characterized by considerable uncertainty. As a result, forces that limit firms' willingness to take risks may lead them to forego innovative investments and focus instead on safer but more marginal projects.[1] Our goal in this paper is to understand the extent to which firm risk aversion limits investment in innovative projects. To do so, we focus on the pharmaceutical industry, a setting that is both important but also where these frictions are likely to be particularly salient.

Using detailed data on firms' drug development decisions, we provide evidence suggesting that risk aversion leads even large firms to invest in too few innovative projects. 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 investments ex-ante. Specifically, early patents associated with novel drug molecules are more valuable than patents associated with more derivative molecules. Having established that novel drugs appear to be superior investments than me-too drugs raises the issue of why firms do not develop more novel drugs. 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—that are also more valuable on average. This result—which holds even for profitable, publicly-traded firms—stands in contrast to the complete markets benchmark in which a firm's willingness to take (diversifiable) risks is independent of its net worth. By contrast, our findings are consistent with a dynamic model of investment with costly external finance, in which firms favor conservative drug development strategies in order to manage the risk of their cashflows. A positive cashflow shock leads to more novel R&D not because the firm is literally cash constrained, but because the increase in firm's net worth reduces its effective risk aversion.

We begin by developing a methodology for assessing the novelty of drug candidates.[2] To construct our measure of novelty, we first compute a drug's pair-wise chemical similarity to prior

[1] This intuition goes back at least to Arrow (1962), who writes: "any unwillingness or inability (by firms) to bear risks will give rise to a non optimal allocation of resources, in that there will be discrimination against risky enterprises as compared with the optimum." There are several reasons why agency frictions may lead firms to discriminate against risky projects, even if these risks are diversifiable. For instance, modern finance theory implies that agency frictions may lead firms to exhibit risk averse behavior. In the classic model of Froot, Scharfstein, and Stein (1993), firms invest conservatively in order to avoid states of the world in which they need to raise costly external funds—external finance is costly due to agency frictions between investors and managers (Myers and Majluf, 1984). More recently, dynamic agency models make a similar prediction: managers invest conservatively in order to avoid dismissal if their investments perform poorly (DeMarzo, Fishman, He, and Wang, 2012). All these models predict that firms indeed underinvest in projects with high (idiosyncratic) uncertainty.

[2] Identifying the novelty of drug candidates is important given existing concerns regarding the innovativeness of the pharmaceutical industry: Marcia Angell, a former editor of the *New England Journal of Medicine* argues that pharmaceutical output is a poor measure of innovation because firms often concentrate their research on

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 then define a drug candidate to be novel if it is molecularly distinct from all prior drug candidates—that is, we define novel drugs as those that have low maximum Tanimoto similarity to prior candidates. Our novelty measure reveals 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. For example, Mevacor and Zocor, two very similar statins, share an 82 percent overlap in their chemical structure. Importantly, ours is an ex-ante measure of novelty that is available independently of whether the drug is successful. Since it is observable when a drug candidate enters development, our metric can be used to study firms' willingness to invest in innovative drugs at the time of invention.

Using our measure of novelty, we first show that, contrary to the popular view, large firms are more likely to develop novel drug candidates than smaller firms: novel drugs constitute 56% of large firms' development pipelines, compared to 47% for smaller firms. This result stands in contrast with leading models of endogenous innovation and firm size (Akcigit and Kerr, 2018), in which small firms are more likely to engage in radical innovation. We argue that standard models of endogenous growth typically ignore the significant uncertainty inherent in pursuing radical innovations, which combined with costs of external finance may lead firms to behave as if they are risk averse, even though the underlying risks may be diversifiable from the perspective of firm shareholders. In this world, drug development decisions become sensitive to firms' net worth: larger firms are willing to take more risks and develop novel drugs because they are better able to weather setbacks in the drug development process. The rest of the paper examines this idea in more detail.

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 higher expected rewards. To arrive at this conclusion, we compare early-stage chemical patents associated with more versus less novel drug candidates. In the pharmaceutical industry, firms have a strong incentive to patent potential drug candidates at discovery: patents protect against intellectual property theft during a long and expensive development process that, due to federal reporting requirements, is impossible

variations of top-selling drugs already on the market, sometimes called "me-too" drugs. http://bostonreview.net/angell-big-pharma-bad-medicine

to conduct in secret. Unlike most other industries, patenting in pharma occurs at the beginning of the R&D process rather than at the end. As a result, the value of a patent at approval is a useful indicator of a drug candidate's NPV at the time the drug development decision is made: this value reflects development costs going forward: its likelihood of approval, expectations of a drug's profitability conditional on approval, as well the value a firm may derive from a failed candidate due to learning-by-doing.

Our findings suggest that novel drugs are higher net present value (NPV) investments than derivative drugs. We use two proxies for the value of a drug patent: 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 significantly greater contributions to stock market value and receive more citations: 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 underinvest in novelty. Indeed, the fact that large firms are significantly more likely to develop novel drugs than small firms suggests that financial frictions may play a role. These frictions, which can arise as the result of agency problems between investors and managers, are particularly salient in the pharmaceutical industry: not only is developing drugs a highly uncertain and expensive process, but the long development times with fewer milestones are likely to lead to significant asymmetries of information between insiders and outsides; further, pharmaceutical firms have few tangible assets which makes debt financing scarce.[3] A relatively standard model of financing frictions would imply that the need to manage cashflow risk leads firms to favor more conservative development strategies—underinvest in riskier projects, even if the underlying cashflows can be diversified away by investors. In the model, a positive shock to net worth (either current or expected cashflows) lowers the likelihood the firm will need to raise costly external finance and is therefore more willing to invest in risky projects.[4]

[3]Approximately one in ten drug candidates are approved by the FDA, while the average lag between discovery and market approval is approximately 10 years. A 2014 report published by the Tufts Center for the Study of Drug Development (CSDD) pegs the cost of developing a prescription drug that gains market approval at $2.6 billion, a 145 percent increase, correcting for inflation, over the estimate the center made in 2003. Pharmaceutical firms have significantly lower leverage, and are less likely to pay out to investors, than the average firm in Compustat (see Online Appendix for details).

[4]In this class of models, firms internalize the possibility that novel candidates are more likely to fail and can leave them with financing shortfalls in the future. As a result, firms engage in risk management: they hold excess cash and tilt their development to safer but more derivative drug candidates—even when novel drug candidates are ex-ante

The second part of this paper explores this idea by examining how cashflow shocks impact firms' development decisions.[5] 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.[6] By contrast, we find no evidence that firms increase the development of very derivative, "me-too," drugs. In terms of magnitudes, our estimates 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. In addition, we find evidence that these drugs being developed as a result of the cashflow shock are on average more valuable. These findings are consistent with a

more valuable. In the Online Appendix (Section D), we provide an example of such a model in which novel drugs are "missing" because concerns about managing cashflow risk discourage firms from investing in novel candidates.

[5] Anecdotal evidence indeed suggests pharmaceutical firms fund innovation from internal cash. One notable example is AbbVie, a large publicly traded firm which produced the world's top selling drug (Humira) from 2012 to 2017. Using 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

[6] Our primary analysis focuses on small molecule drugs. That said, we find similar results using alternative novelty measures that also include large molecule (biologic) drugs. For instance, Table A.21 reports that treated firms develop more drugs (of any type) for use on novel diseases pathways and targets (i.e, enzymes, receptors and ion channels). This pattern holds when we define novel targets narrowly as new "target-actions" (i.e., phosphoinositide 3-kinase inhibitor), or at coarser levels of granularity based on an ontology tree of drug targets (i.e, cytokine receptors).

model in which risk management considerations lead firms to under-invest in riskier (novel) drug candidates—relative to the frictionless benchmark.

A key assumption in our identification strategy is that we are able to isolate a cashflow shock from a shock to new investment opportunities. The fact that we document "missing novelty" even in situations in which the underlying project returns are unaffected from Medicare Part D implies that our identification strategy is at least partially successful. In particular, if we were simply identifying the impact of an increase in demand generated by the expansion in Medicare coverage, then we would expect the increased novelty we see to be concentrated in markets serving elderly consumers. This is not the case; even though 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. 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.

Last, we also examine heterogeneity in firm responses to an increase in their cashflows. Our model predicts that there will be more 'missing novelty' at firms with lower cash-holdings (relative to their scale), because those firms will exhibit more risk aversion in their R&D investments. The data are consistent with this prediction: we see strong increases in drug development (particularly novel drug development) among public firms that had low cash reserves prior to the passage of Medicare Part D. By contrast, we see no marginal response among firms who already had substantial cash reserves. That said, we observe increases in novel drug development in response to our cashflow shock even among publicly traded firms, which suggests that the prospect of facing R&D failure and uncertain cashflows in the future leads even these relatively large firms to invest conservatively today. These concerns are likely to be particularly salient in the pharmaceutical industry, where long development times with fewer milestones exacerbates problems of asymmetric information between insiders and outside investors.

By focusing on the ex-ante risk characteristics of individual projects, our work sheds light on a particular economic mechanism (risk aversion) through which financial frictions affect corporate investment. Specifically, there is a voluminous literature studying the impact of financing frictions on the level of physical investment (for instance, Lin and Paravisini, 2013; Almeida, Campello, Laranjeira, and Weisbenner, 2011; Frydman, Hilt, and Zhou, 2015); hiring decisions (Chodorow-Reich, 2014; Duygan-Bump, Levkov, and Montoriol-Garriga, 2015); and investments in R&D (see e.g. 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; Howell, 2017; Acharya and Xu, 2017). The most closely related papers in this literature establish a causal link between a shock to firm cashflows and firm decisions. Howell (2017), for instance, shows that government grants can spur innovation among early stage startups. This result provides strong evidence that financial constraints are important barriers to innovation for small firms, which use these marginal resources to generate proofs of concept that allow them to secure additional funds from venture capitalists. Our setting, however, is quite different; we study R&D investments among pharmaceutical firms, many of which are large and hold significant amounts of cash.

In contrast to most of the literature, our data allows for a deeper analysis of the underlying mechanism. That is, our novelty measure allows us to characterize the risk and return of the marginal projects being undertaken as a result of a positive shock to firm net worth—rather than aggregated outcomes at the level of individual firms or geographic locations. This granular analysis is valuable along two dimensions. First, the fact that novel drugs are based on more valuable patents allows us to rule out 'empire-building,' whereby managers deploy additional resources to pursue inferior projects as in Blanchard, de Silanes, and Shleifer (1994). Second, and more importantly, it sheds light on the 'black box' of firm investment decisions and therefore *why* such a cashflow-investment relation exists in our setting. Our view is that a positive cashflow shock leads to more novel R&D not because the firm is literally cash constrained (which would be realistic for the startups studied in Howell (2017), but not for more established firms) but because the increase in firm's net worth reduces the its effective risk aversion. As such, our findings suggest that what limits innovation in established firms is risk aversion—that is, concerns about future cash shortfalls rather than the lack of financial resources at the present.

This distinction between static and dynamic considerations is not merely academic—it has policy implications. Specifically, finding a positive link between firm cashflow and innovation decisions can focus attention on policies that stimulate R&D through subsidies. These policies are likely to be effective in some cases (for instance, as in Howell, 2017). Yet, the same policy may be too costly to implement for more established firms, many of which have significant cash reserves. By identifying firm risk aversion as a limiting factor, our results also lend support to an alternate set of policies that can also incentivize radical innovation without a significant transfer of liquidity—for instance, by improving the relative risk/return tradeoff of investing in novel versus me-too drug candidates. Examples of such policies include: expedited regulatory approvals for novel drugs; tax credits or extended market exclusivity for more novel therapies; creating diversified portfolios of drugs, as proposed in Fernandez, Stein, and Lo (2012); or by providing convex incentive schemes to managers and entrepreneurs, as done, for example, by venture capital firms.

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, Garthwaite, and Hermosilla, 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.

Finally, our work also contributes to the literature on the measurement of innovation. A key advantage of our measure is that it is an ex-ante indicator of the novelty of an innovation. By contrast, existing measures of innovation typically confound ex-ante novelty with ex-post success. For example, focusing on highly cited patents conflates novelty with ex-post impact. Similarly, focusing on pharmaceutical innovation, counting the number of particularly promising candidates credits firms for novel innovations only when they succeed (see, for instance Dranove et al., 2014). Similarly, crediting drugs as novel if they are the first to treat a particular indication ignores innovation in common disease categories for which there already exist treatments (see e.g., DiMasi and Paquette, 2004; Dranove et al., 2014; DiMasi and Faden, 2010; Lanthier, Miller, Nardinelli, and Woodcock, 2013). By contrast, in order to study R&D decisions, one needs a measure of ex-ante novelty; our work makes substantive progress toward this direction.

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 on 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).[7] 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 Application, Cortellis employees will work to ex-post determine the dates of its earlier clinical development.

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.[8] 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).

[7] In 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.

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

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),

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

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).[9] 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:

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

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).

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).

[9] For example, consider a classic example of a me-too drug, Nexium, and its antecedent, Prilosec. Prilosec is a "racemic mixture," meaning that it is a mixture of two 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.

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. Appendix Table A.1 provides more details on the underlying distribution of novelty across phases of development.

1.3 Which firms develop more novel drugs?

We next examine the types of firms that are more likely to engage in novel drug development. A common view is that small firms are much more likely to engage in radical innovation than large firms (see, for instance, Akcigit and Kerr, 2018). The rationale is that larger firms are more likely to be incumbents and thus have less of an incentive to invest in radical innovation than new entrants.

By contrast, we find that larger firms are more likely to develop novel drugs than smaller firms. We consider three proxies for firm size. First, we examine whether the firm is publicly listed (can be matched to Compustat) or not. Second, within the sample of Compustat firms, we can measure firm size by the firm's total revenue. Last, we also consider the number of approved drugs that firm has at a given point in time—the advantage of this measure is that, unlike sales revenue, is available for the full sample of firms.

Panel B of Figure 2 summarizes our key finding: larger and more established firms (those with more than 20 approved drugs in their portfolio) are more likely to develop novel drugs than younger and smaller firms (firms with no approved drugs in their portfolio). Specifically, focusing on small firms, 47 percent of new drug candidates being developed are novel. By contrast, over 55 percent of the drug candidates developed by larger firms can be classified as novel.

Table 1 presents a more detailed analysis between measures of firm size and the novelty of developed drugs. Focusing on all drug candidates (Panel A), Columns (1) and (2) show that a given drug candidate's maximum similarity is approximately 0.12 standard deviations lower—that is, the drug is more novel—when it is developed by a firm that is publicly listed. Columns (3) and (4) shows that the novelty-firm size relation also holds within public firms: a one standard deviation increase in (log) firm revenue is associated with a 0.1–0.12 standard deviation decline in the maximum similarity of a drug candidate subsequently developed by the firm. Within the entire sample of firms, Columns (5) and (6) show that a one standard deviation increase in the

number of approved candidates leads to a 0.09–0.10 standard deviation decline in a drug's maximum similarity. These magnitudes are economically relevant. Panel B shows that these findings are driven by in-house development rather than acquisitions of drug candidates from other firms. When we restrict the sample to drug candidates that are developed in-house, the statistical relation between drug novelty and firm size is still statistically significant, but the economic magnitudes are stronger: the point estimates increase by a factor of 1.5 to 2.

In sum, we find that larger firms are more likely to develop novel drug candidates than smaller firms. One way to reconcile our findings with a relatively standard model of endogenous innovation and firm size—such as Akcigit and Kerr (2018)—is to recognize two key aspects of the decision to innovate. First, innovation outcomes are highly uncertain investments; radical innovations even more so. Second, financial markets are imperfect, and innovative firms are more likely to face frictions in raising capital than the average firm—see Appendix Section A.4 for a discussion. A direct consequence is that firms behave as if they are risk averse, even though the underlying risks may be diversifiable from the perspective of firm shareholders. That is, the need to manage cashflow risk leads all firms to favor more conservative development strategies relative to a frictionless benchmark. In this world, drug development decisions become sensitive to firms' net worth: larger firms are willing to take more risks and develop novel drugs than small firms because they are better able to weather setbacks in the drug development process. Indeed, this is one of the reasons given in Arrow (1962) as to why large firms may be more innovative than smaller firms.

The rest of our paper pursues this idea in more detail. In Section 2 we argue that developing a novel drug is a riskier—though higher expected returns—development decision than developing a me-too drug. Section 3 shows how firm size (net worth) influences drug development decisions. We first outline a model in which financing frictions lead firms to underinvest in radical innovation out of a need to manage the risk of their cashflows. Larger firms have higher net worth and are therefore better able to weather adverse development outcomes than small firms—which leads them to take more chances than smaller firms. The model implies that an exogenous increase in firms' net worth leads firms to tilt their development towards developing more novel drugs. The rest of the section tests this prediction using an exogenous shock to firm cashflows exploiting the passage of Medicare Part D in 2003.

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.3 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.[10]

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 (e.g., proteins, cells, tissues, etc.) that cannot be compared with Tanimoto scores. Although biologics make up for only 20 percent of drug development, their share is increasing and they 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 ex-ante expected return of investing in novel drugs is

[10] Appendix Table A.4 shows that these results are robust to other specifications and controls.

somewhat more challenging, since one does not observe outcomes for drugs that are not approved. To address this issue of missing data, we 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. Here, we should emphasize that the outcome of the FDA approval process is an outcome of decisions undertaken by both the FDA and the firm. The FDA cares about consumer safety, so it will not approve drugs with significant side effects. Drug development is costly, hence firms will abandon drugs that they think are unlikely to be approved by the FDA based on the outcome of clinical trials. The outcome of these clinical trials is information that the firm does not have when it decides to start developing a drug candidate. The possibility that (future) clinical trials show low efficacy, or unfortunate side effects, and the firm will find it optimal to suspend development is a risk the firm is facing when deciding to invest in developing a drug candidate.

We estimate a linear probability model that relates a candidate's approval status (Outcome_i) to its ex-ante novelty, given by its maximum similarity score:

$$\text{Outcome}_i = a + b\,\text{Maximum Similarity}_i + c\,Z_i + \varepsilon_i. \tag{3}$$

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 target 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 -0.21×0.208=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.1 and Table A.5 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 Are Novel Drug Candidates Higher NPV Investments?

So far, we have established that novel drugs are riskier investments than me-too drugs—but also that they are more valuable conditional on FDA approval. When making development decisions, however, firms are concerned with the expected (or ex-ante) benefits of developing a drug candidate.

The ideal measure of a drug candidate's value should capture the net present value of expected revenue and costs going forward. This value should include the firm's expectation of future revenue conditional on approval; the development and manufacturing costs; the likelihood of FDA approval; as well as the value to the firm if the candidate is not approved by the FDA.[11]

Measuring the economic value of the key patents associated with a drug molecule is as close as one can get to observing the NPV of the drug development decision. In particular, a key feature of our setting is that firms apply for patent protection relatively early on in the development process: drug companies aim to patent all molecules that they suspect may have any pharmacological value. These patents, which cover the active ingredients in a drug, rather than auxiliary characteristics such as its coating, are typically taken out at the end of the discovery phase and long before serious development begins on a drug.[12] Indeed, 94 percent of drugs entering pre-clinical development in our data have a patent application. The costs of discovery—in addition to being relatively small, see Appendix A.3—are also already sunk at the time the development decision is made. As a result, the value of a patent incorporates most expected benefits and costs of developing a drug candidate, and is therefore a valid proxy for the expected benefit of developing the drug candidate.

We focus on patents filed early on in the development process, and examine two patent-level outcomes: the Kogan et al. (2017) estimate of the economic value of the patent (KPSS) and the

[11] In Appendix C.2 we show that, across a variety of metrics, *approved* novel drugs are privately and socially more valuable: they 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). However, these metrics are not necessarily informative about the ex-ante value of these investments, which depend on outcomes that are difficult to observe. For example, it is probable 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.

[12] Section A.2 in the Online Appendix discusses the patenting process in detail.

number of forward citations received by the patent.[13] We restrict our attention to key patents—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 B.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. We scrape priority dates and the citation data for these 31,915 patents from Google Patents. Since a drug may be associated with multiple main patents, our analysis in this section is at the drug-indication-patent level.

2.2.1 Stock market reactions to patent grants

We begin by examining the correlation between novelty and the KPSS measure of patent values. Because patent approval occurs very early in the drug development process, market reactions to patent approval incorporate the net present value of all costs and benefits, including likelihood that the drug candidate does not ultimately make it to market.[14] 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 (2) 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.6 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 C.2.2 which condition on drug approval (20 percent). Given that it is

[13] Kogan et al. (2017) provide a direct estimate of the market value of a patent based on the firm's stock market reaction around a patent grant. We extend the analysis of Kogan et al. (2017) to all the US patents in our sample, which ends in September 2016.

[14] One potential worry is that patents of novel and derivative drug molecules may differ in their ex-ante likelihood of being granted. Indeed, one could argue that patents associated with novel molecules are more likely to be successful ex-ante—see the discussion in Appendix A.2. If this is the case, then it will bias our results against finding a positive link between novelty and value. In particular, the reaction to stock prices in the news of a successful patent application of a novel drug molecule is likely to be smaller than the reaction to a derivative molecule, even if the underlying patent values are similar—the KPSS estimate of patent value *underestimates* the value of novel relative to derivative drug patents.

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.

2.2.2 Patent citations

As further evidence that novel drugs generate higher economic benefits in expectation, we next examine citations received by patents associate with more or less novel drug candidates. Hall et al. (2005) argue that the number of forward citations a patent receives are significantly related to economic value. Harhoff, Narin, Scherer, and Vopel (1999) and Moser, Ohmstedt, and Rhode (2011) provide complementary evidence regarding the positive relation between patent citations and economic value, and Abrams and Sampat (2017) specifically document a relation between citations to drug patents and various measures of private and social value.

We estimate Equation (3) where now the dependent variable is equal to the logarithm of (one plus) the number of citations a patent receives. In contrast to the previous section, our sample now is not restricted to public firms in the United States. Column (3) 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-year where the patent is issued (to control for the fact that the frequency of citations varies across patent offices); 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.7 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 a increase of 0.12 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.7 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).

2.3 Discussion and Caveats

Our results so far strongly suggest that novel drug candidates are riskier but higher expected return investments. However, one of the difficulties in measuring value is that we do not directly observe development or production costs. For instance, it is possible that novel drugs are more expensive to develop. Assessing the costs of development for a particular candidate is challenging

because 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 account for a substantial proportion of a drug's development cost. In Appendix Table A.8 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.

Comparing estimates of the value of *patents* associated with novel versus me-too drugs overcomes these limitations of the data. That is, 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 validate 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.2, 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 (2) 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 than ours. We conclude that it is unlikely that our results are spurious.

In sum, our estimates suggest that novel drug candidates are on average more valuable investments than me-too candidates. 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 potential explanation is excessive risk aversion—potentially arising due to financial frictions. Specifically, 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, in the presence of costly external

finance, firms are less willing to take risks and therefore invest in less novel 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 standard neoclassical model of investment, all drug candidates that are deemed (ex-ante) profitable should be undertaken. In addition, the discount rate used to evaluate a potential investment should be independent of the idiosyncratic risk of the project. Last, cashflows that are orthogonal to the firm's investment opportunities should have no effect on the firm's drug development decisions. In brief, firms' investment decisions should not be sensitive to idiosyncratic risk, and the firm's net worth or current cash reserves are irrelevant.

To guide our empirical work, we develop a simple, yet tractable, model of investment in (potentially) innovative drugs. The key assumption in the model is that external finance is costly. Theoretical foundations for this 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). Consistent with this view, Table A.9 in the Online Appendix shows that pharmaceutical firms are significantly less likely to be financed by debt, pay dividends or engage in share buybacks compared to firms in other industries with similar levels of profitability and size.

The goals of the model are twofold. First, it provides intuition about how the presence of financial frictions can lead to firm risk averse behavior: firms may 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 shock to net worth—a shock to current and future cashflow shock. Our model builds on Bolton, Chen, and Wang (2011), who provide a tractable framework to study dynamic investment, financing, and risk management decisions in continuous time. To simplify exposition, we outline the main ingredients of the model and then discuss its key predictors. To conserve space, we briefly summarize the main intuition of the model here; all details are relegated to Appendix D.

The key model mechanism that generates firm aversion to idiosyncratic risk is that decision makers wish to avoid future states of the world in which project cashflows are low. In our model, this aversion to risk arises due to the presence of costly external finance: if the firm runs out of cash, it pays a cost to access new finance. In the presence of this friction, firms engage in risk management: they hold cash inside the firm and avoid investing in risky drugs—even if these risks are diversifiable from shareholders' perspective—out of fear that these projects might fail, leaving them with reduced cashflows in the future.[15] A positive shock to expected cashflows makes these costly states of the world less likely. Hence, affected firms are more willing to undertake risky investments. In what follows, we explore this prediction in more detail.

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 cashfows 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 their 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

[15] Alternative interpretations of our modeling setup are possible. We view the underlying friction as an agency problem which leads to costly external finance: investors do not trust managers with their capital, and hence impose a cost whenever the managers' access financial markets. This friction leads to a wedge between the cost of financing a project with internal cashflows and the cost of raising outside funds (Myers and Majluf, 1984). Alternatively, investors may terminate the manager the firm's economic performance is sufficiently low (Smith and Stulz, 1985; DeMarzo et al., 2012); our model nests this case by re-interpreting the fixed cost of raising external capital as the manager facing the possibility of costly termination when cashflows are low, as in DeMarzo et al. (2012). More broadly, the same model 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 the firm's headquarters; if she pursues a risky project that fails, she will have to seek additional funds from the 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.

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 B.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 $\text{MMS}_{f,2003}$, 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.[16] 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, $\text{Overall Drug Life}_{f,2003}$, 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 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.10.

[16]The 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 B.6

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

$$\text{Medicare Drug Life}_{f,2003} = \sum_{i \in A_f} \left[\frac{\text{Drug MMS}_{i,2003}}{\sum_{j \in A} \text{Drug MMS}_{j,2003}} \mathbb{I}(\text{on patent in } X \text{ yrs})_{i,2003} \right] \quad (4)$$

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:

$$\begin{aligned} \text{New Drug Candidates}_{ft} = {} & a_0 + a_1 \text{Post} \times \text{Medicare Drug Life}_{f,2003} \\ & + a_2 \text{Post} \times \text{Overall Drug Life}_{f,2003} \\ & + a_3 \text{Post} \times \text{Firm MMS}_{f,2003} + \delta_f + \delta_t + e_{ft} \end{aligned} \quad (5)$$

Our main coefficient of interest is a_1, which captures the *cashflow* impact of our main treatment variable defined in Equation (4). We allow for an interaction with the post Part D period for both Overall Drug Life and Firm $\text{MMS}_{f,2003}$. 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.11 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 (5), 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 (5) 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 $\frac{75}{75+50} \times 0 + \frac{50}{75+50} \times 1 = 0.4$.[17]

Before continuing, we note a few aspects of the data that merit discussion. First our 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. The type of selection can be seen in Appendix Table A.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. In brief, our empirical strategy selects for larger, more established firms.[18]

Second, the outcome variable is highly skewed; Table A.2 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 primarily outcome measures. In the Appendix, we show that our findings are robust to using alternative specifications, including count models (see A.12).

[17] Table A.2 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.3 shows a smoother distribution of Medicare Drug Life for firms with non extremal values and we show in Appendix Tables A.13 and A.14 that our results are robust to restricting to this subsample, or to using a binary treatment measure.

[18] That said, the descriptives that we report in Section 2 and in Section C.2 of the Online Appendix 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 over 90 percent of these drugs are associated with firms in our natural experiment sample.

3.3 Results

3.3.1 New Candidates

Table 3 examines the causal impact of a financial shock, as described in Equation (6), 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 Post $\times$ 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 Post $\times$ 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.[19] 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.[20] In Section 3.5, we translate these magnitudes in terms of dollars for a subset of our firms.

3.3.2 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 5 reports estimates of Equation (6) 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 A.1).

[19] This 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.

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

Since the number of drugs in each bin does vary, we also report the estimates across novelty deciles in Panel B of Figure 5. 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 firm risk aversion—even though the underlying risks are diversifiable from the shareholders' perspective. We see that a positive shock to firm net worth 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 that margin 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 A.4. 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.

3.3.3 Event Studies

One potential source of concern is that the differences in responses among the treatment and control group reflect pre-existing trends. To address this concern, Figures 6 and 7 show how the estimated effect of the cashflow shock on the number of new and novel drugs, respectively, vary over time. Focusing on Figure 6, we see that firms with different values of Medicare Drug $\text{Life}_{f,2003}$ 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 7 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.11 also shows that our main results are robust to including company-year-quarter linear trends.

In Figure 7, 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 form higher expectations of future cashflows.[21] The fact that firms can quickly alter their development pipeline is

[21] The model in Section 3 has i.i.d. cashflow shocks. However, the same intuition would apply if firms were to anticipate 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).

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. As drugs progress through the development stage, uncertainty about their eventual likelihood of approval is resolved. If a cashflow shock reduces firms' effective risk aversion, we expect that the magnitude of these responses would be smaller for later phase drugs. Indeed, Figure A.6 and Table A.15 in the Online Appendix show that firms respond to cashflow shocks primarily by increasing their investments in early stage novel drugs. 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.

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.

3.4.1 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 their existing portfolio of drugs.

Our empirical results support this prediction. Table 4 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.

3.4.2 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 were 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 5, 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.[22] 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 6 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

[22] We assign a Medicare Market Share for drug candidates based on their indication (ICD9). We estimate MMS at the ICD9 level by computing the share of payments from Medicare that go to all approved drugs prescribed within a given ICD9 indication.

least partially successful in isolating a shock to the profitability of current assets from a shock to firms' investment opportunities.

3.4.3 Are these marginal drugs more valuable?

So far, our results show that, consistent with our model, firms that receive a positive shock to their net worth tilt their development towards more novel (that is, riskier) drugs. Here, we examine whether these marginal novel drugs being developed in response to the cashflow shock are also more valuable on average (as is the case in our model). To do so, we re-estimate. Equation (5), but now the main outcome variable is the average value of drugs being developed in a given quarter,

$$\begin{aligned} \text{NPV of New Drug Candidates}_{ft} &= a_0 + a_1 \text{Post} \times \text{Medicare Drug Life}_{f,2003} \\ &\quad + a_2 \text{Post} \times \text{Overall Drug Life}_{f,2003} \\ &\quad + a_3 \text{Post} \times \text{Firm MMS}_{f,2003} + \delta_f + \delta_t + e_{ft} \end{aligned} \tag{6}$$

For each drug candidate, we first identify the market value of its primary patents based on Kogan et al. (2017) following our analysis in Section 2.2. Then, we compute the average over all drug candidates a company invests in, in a given quarter. As before, our main coefficient of interest is a_1, which captures the *cashflow* impact of our main treatment variable.

Table 7 presents our results. In Columns (1) and (2), we see that the average value of drugs developed by treated firms increases as a result of the cashflow shock we identify. In terms of magnitudes, a one-standard deviation increase in the treatment intensity is associated with a 0.8 log point increase in the market value of the primary patents associated with the new drugs being developed. These magnitudes are large, but also imprecisely estimated due to the small sample: the 90 percent confidence interval ranges from 0.3 to 1.4 log points. This increase in average value for developed drugs, combined with our earlier result that treated firms develop more novel drugs (but not more me-too drugs), is consistent with the idea that firms switch from low-value me-too to high-value novel drugs. However, there is also an alternative possibility: perhaps firms are switching from low-value to high-value me-too candidates instead. We find no evidence that this is the case: when we restrict the sample to me-too drugs (those with a maximum similarity score higher than 0.8) in Columns (3) and (4), we see that there is no increase in average value among the set of me-too candidates in response to treatment.

In sum, we see that treated firms respond to an increase in net worth by developing both riskier (novel) and more valuable drugs. We interpret these results as evidence of under-investment in novel drugs, consistent with our model.

3.5 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 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 (6), but with the log of firm profits and R&D spending as dependent variables. These results are reported in Table 8. Columns (1) and (2) show that firms with higher Medicare Drug Life in 2003 experienced higher growth in R&D and operating cashflows in the years following treatment. We find no evidence in Columns (3) and (4) that treated firms respond by increasing their borrowing—an alternative explanation for why firms appeared to increase their drug development before Part D cashflows were realized.[23]

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.[24]

[23]This is not particularly surprising given that pharmaceutical firms are significantly less likely than other firms to use debt financing (see, e.g. Table A.9 in Appendix) given the relative difficulty of collateralizing their IP.

[24]There are several caveats to this analysis. Because some of our firms include large conglomerates (for instance, firms such as Dow Chemical), our R&D figures include spending on sectors that may not be related to pharmaceuticals. More generally, we caution that while we estimate a causal impact of Medicare exposure on drug output, we cannot say that we estimate the associated productivity of R&D spending because lags between R&D expenditure and final commercial output are difficult to predict when it comes to drug innovation. 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 (2015) use variation in demographic trends, and find 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

3.6 Firm Heterogeneity

We next examine how the impact of cashflows on drug development decisions varies across firms. The simple model described in Section 3.1 predicts that firms with low level of cash holdings (relative to their scale) will exhibit greater risk aversion than firms with high levels of cash holdings—since the value function of the latter firms is close to linear, as Figure A.5 in the Appendix illustrates. As a result, we expect firms with lower levels of cash holdings to be more responsive to treatment. Figure 8 presents the results of this analysis (see Appendix Table A.16 for more details).

We find some evidence that the response to treatment varies with the pre-treatment level of cash holdings. Specifically, within the sub-sample of firms that we match to Compustat (see Section 3.5), we estimate our main Equation (5) separately for firms above, versus below, the median in terms of their ratio of cash holdings to assets in fiscal year 2002—that is, right before the passage of Medicare Part D. We see that firms with low cash holdings were significantly responsive to treatment; these firms develop more drug candidates, and the point estimates are higher for novel candidates than me-too candidates. By contrast, firms that are above the median in terms of cash holdings show no statistically significant response to treatment.

Our results indicate that firms with low past cash holdings are more sensitive to the treatment than other firms—though the difference is not always statistically significant. Naturally, there are caveats: cash holdings are endogenous, so we may expect that firms that face higher costs of external finance to hold more cash. This force would tend to produce the opposite pattern than what we find in the data.

3.7 Additional Results and Robustness Checks

Here, we provide a brief description of some additional results. We refer the reader to Appendix C.4 for an extensive list of robustness and specification checks.

In Section 3.3 we showed that firms that experienced an increase in cashflows developed more novel drugs. One potential concern is that we observe the value of the patent when it is issued; it is possible that firms incur substantial (and differentially higher for novel drugs) costs between the time the patent is applied for and the time it is issued. This is unlikely: as we discuss in Appendix A.2, novel molecules are easier to patent than derivative ones. Nevertheless, to dispel any remaining doubts, we restrict our primary analysis to those drug candidates which already have a US patent issued prior to their earliest development date—approximately 41 percent of the sample. For this set of drugs, it is clearly the case that both discovery and patenting costs are sunk and

that we document may reflect the development of pre-existing research ideas—which were unexplored by choice (for instance, due to risk aversion).

should not be factored into their decision to pursue development. Appendix Figure A.7 shows that our findings are qualitatively similar when we restrict in this sub-sample.

Another 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.19 and Figure A.8 in the Appendix).

Next, we consider the role of biologic drugs. Our measures focus on chemical similarity as measured by Tanimoto scores. A limitation of this approach is that it can only be applied to small molecule drugs, and not to more complex biological entities, known as biologics, which 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.20 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.

Finally, in Table A.21, we also look at alternative measures of novelty based on a hierarchical classification used to classify drugs' molecular targets. Though less precise in their measurement of drug similarity, these alternative definitions of novelty allow us to include biologic drugs alongside small molecules, and are consistent with how prior papers have categorized drug novelty (Shih, Zhang, and Aronov, 2018; Krieger, 2020). These analyses also yield qualitatively similar results: more treated firms disproportionately increase their investments in novel drugs. This relationship holds for both the combined set of biologics and small molecules, and separately for the two types of drugs.

4 Conclusion

We introduce a new measure of drug novelty based on molecular structure and investigate firms' decisions to develop novel versus 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 that 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. In addition, treated firms develop more valuable drugs in response to the cashflow shock we identify. Our results suggest that increased cashflows lead to more innovation by reducing firms' effective risk aversion, and therefore inducing 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 favoring policies that increase pharmaceutical profits, our paper lends support for policies that alter the relative risk/reward tradeoff associated with investing in novel versus 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, which 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.

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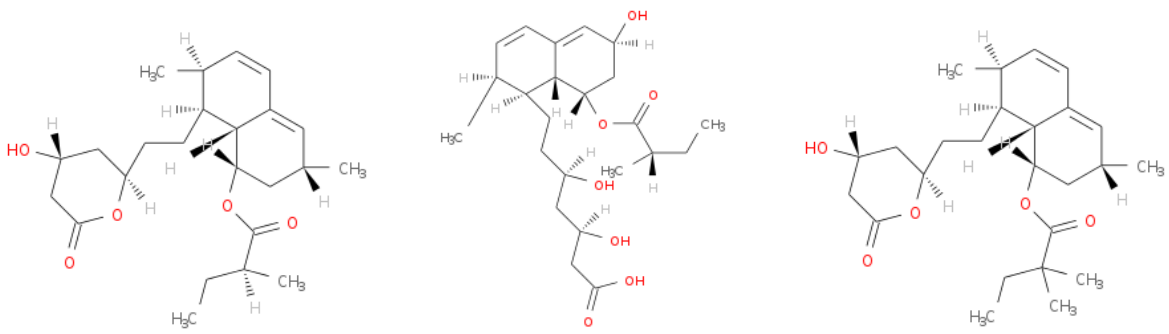
Tables and Figures

Figure 1: Similarity for Statins



Mevacor
(Similarity Score=0.25)

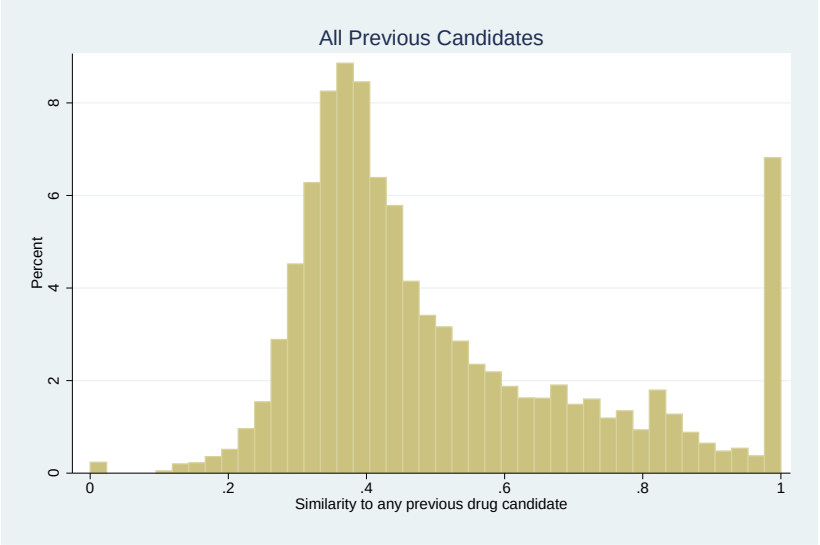
Pravachol
(Similarity Score =0.61)

Zocor
(Similarity Score =0.82)

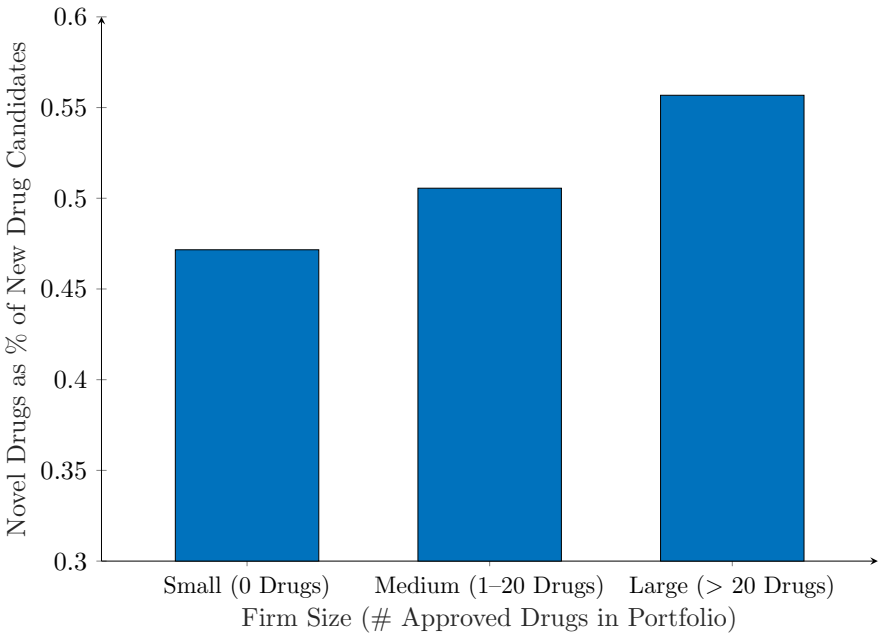
Notes: Figure 1 provides the molecular structure and maximum similarity score of three early statins. Mevacor (Lovostatin) was the first FDA approved statin (approved in September 1987) and its Tanimoto similarity to prior molecules is 0.25. Pravachol (Pravastatin) is was the second such statin, approved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

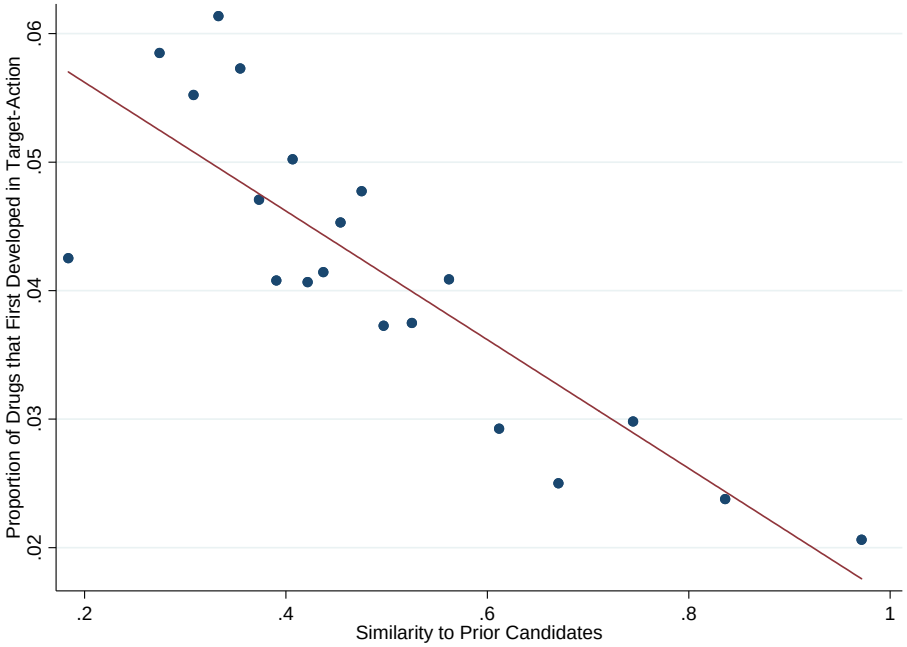


B. Novelty and Firm Size



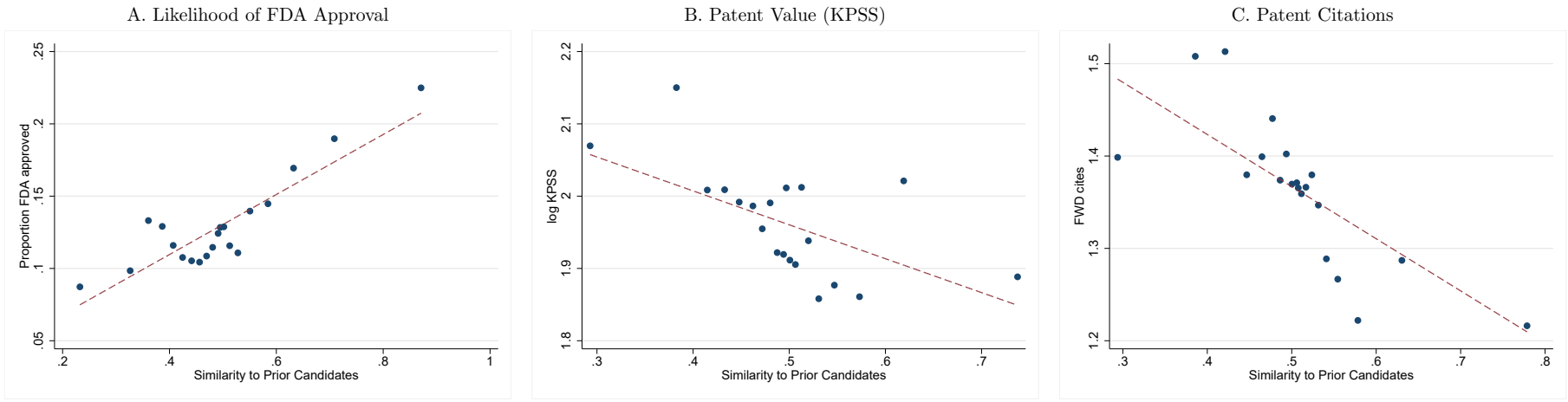
Notes: Figure 2 displays descriptive statistics of our novelty measure. Panel A displays the distribution of our drug similarity measure. A drug's similarity is measured as its similarity to the most similar drug candidate that had previously entered Phase 1 clinical trials. For more details on this similarity measure, see Section 1.2. Panel B shows the relation between novelty and firm size. Specifically, each bar plots the ratio of novel to me-too drug candidates (based on above and below median values of maximum similarity) for small, medium, and large firms (classified based on the size of their portfolio of approved drugs).

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.

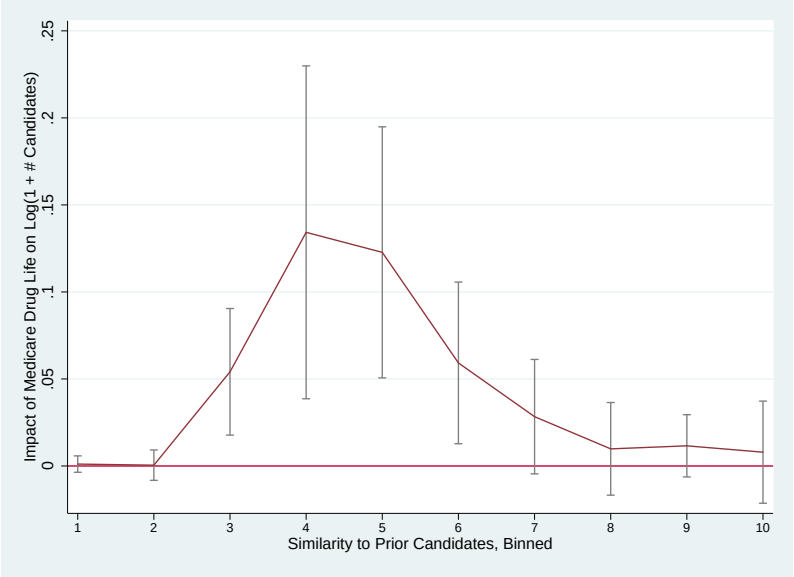
Figure 4: Drug Novelty: Risk and Expected Return



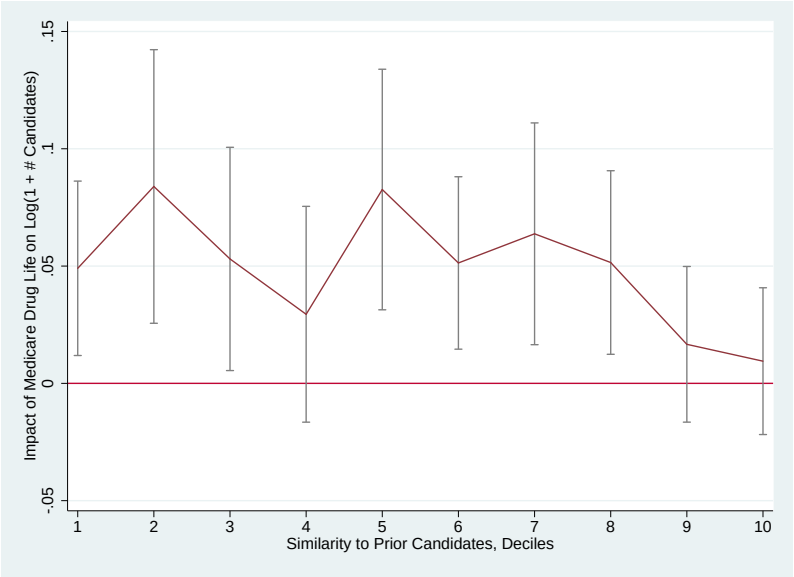
Notes: Figure 4 presents binned scatterplots of drug-level similarity against several drug characteristics. Panel A examines whether a drug is FDA approved. Panel B examines the logarithm of the Kogan et al. (2017) estimated patent values. Panel C examines the logarithm of one plus the number of forward citations the patent receives. 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.1–A.18 for more details.

Figure 5: Impact of Additional Resources on Novelty of Drug Investments

(a) Coefficients

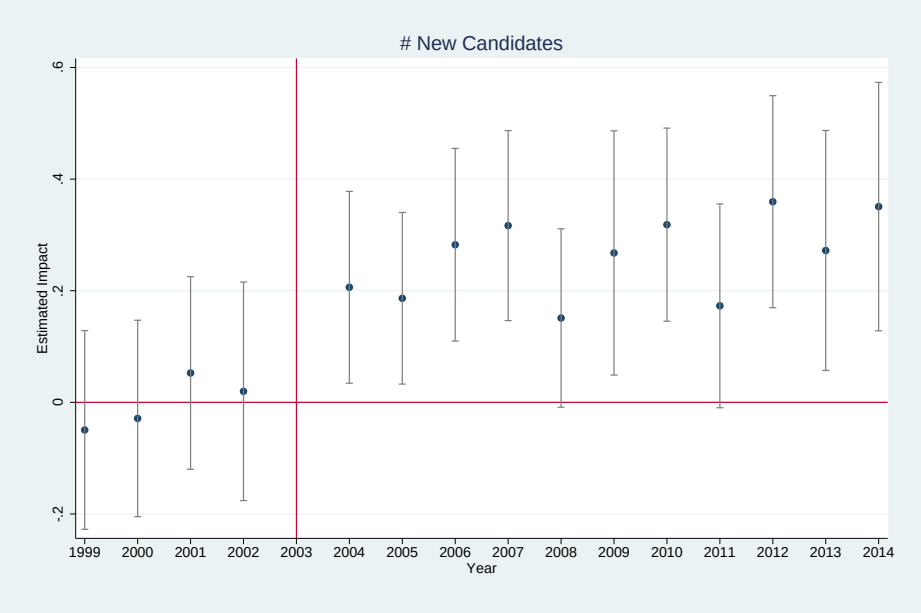


(b) Deciles



Notes: Figure 5 plots the estimated coefficients on Post × Medicare Drug Life$_{f,2003}$ from our main regression specification defined by (6). 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.

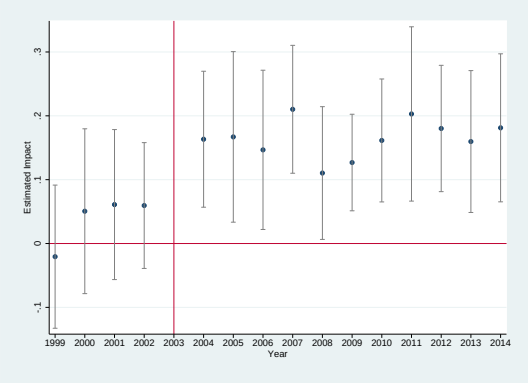
Figure 6: Event Studies: # of New Candidates



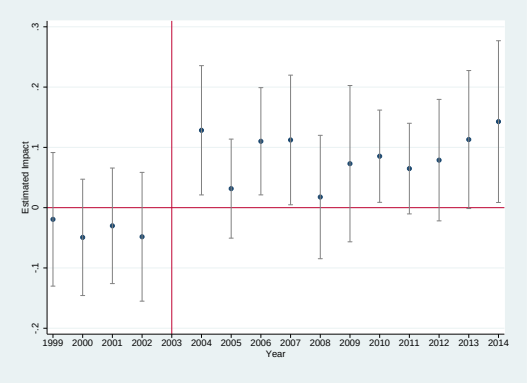
Notes: Figure 6 reports the accompanying event study associated with Column 6 of Table 3. Each dot represents the coefficient on Medicare Drug Life$_{f,2003}$ interacted with an indicator variable for that given year. 2003 is the omitted year, and 90th percentile confidence intervals are reported.

Figure 7: Event Studies: # of New Candidates, by Similarity Quartile

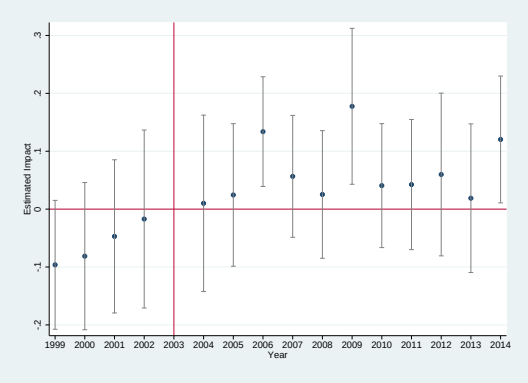
(a) Similarity Quartile 1



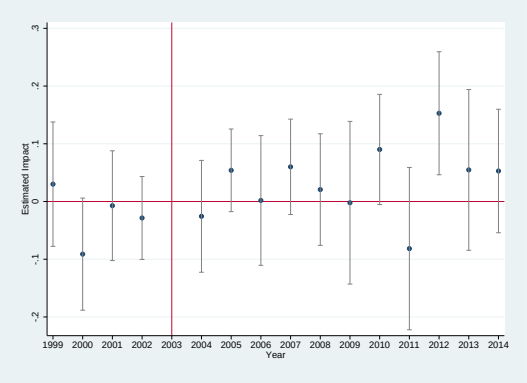
(b) Similarity Quartile 2



(c) Similarity Quartile 3

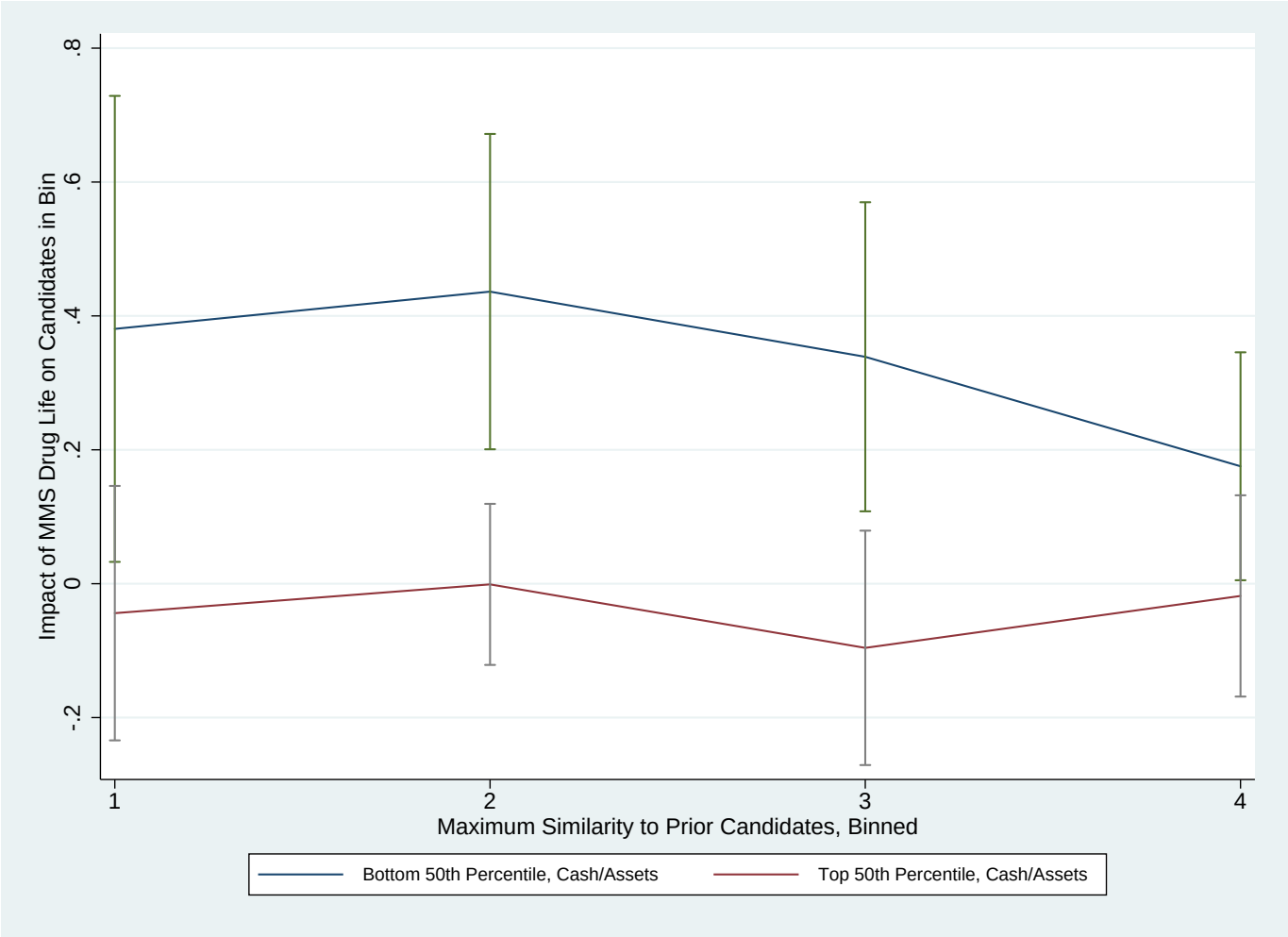


(d) Similarity Quartile 4



Notes: Figure 7 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 8: Response to treatment, as a function of level of cash holdings



Notes: Figure 8 reports the coefficient on our main treatment variable (Medicare Drug Life in equation (5) in the main text) estimated across two different subsamples: firms in Compustat that are above (red line), or below (blue line) the median in terms of their cash holdings (Compustat: ch) to book assets (Compustat: at) in fiscal year 2002. We estimate equation (5) separately in each sub sample. The points on the horizontal axis correspond to groups of drugs of different levels of novelty—quartile 1 is the drugs that are most novel (lowest maximum similarity, whereas quartile 4 is the drugs that are least novel (highest maximum similarity). Error bars denote 95% confidence intervals.

Table 1: Drug Novelty and Firm Size

Maximum Similarity	A. All drug candidates						B. In-house drug candidates only					
	Private / Public Firm		Revenue (Public Only)		# of Approved Drugs		Private / Public Firm		Revenue (Public Only)		# of Approved Drugs	
	(1)	(2)	(3)	(4)	(5)	(6)	(1)	(2)	(3)	(4)	(5)	(6)
Public Firm	-0.022**	-0.024***					-0.048***	-0.049***				
	(0.009)	(0.007)					(0.009)	(0.009)				
Log(Revenue)			-0.006**	-0.005**					-0.008***	-0.009***		
			(0.003)	(0.002)					(0.003)	(0.005)		
Log(1+# Appr. Drugs)					-0.010***	-0.009***					-0.015***	-0.015***
					(0.002)	(0.002)					(0.002)	(0.002)
R^2	0.061	0.143	0.043	0.135	0.065	0.146	0.084	0.159	0.071	0.149	0.091	0.166
Observations	41055	41027	18691	18642	41055	41027	16264	16197	5701	5628	16264	16197
Fixed Effects:												
Dev. Qtr.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ICD-9		Yes		Yes		Yes		Yes		Yes		Yes

Notes: Table 1 shows the correlation between the novelty of a drug candidate (decreasing in its maximum similarity to previous candidates) and three proxies for the size of the developing firm: whether the firm is in Compustat (columns 1 and 2); within the set of firms in Compustat, the logarithm of the firm's total revenue in the fiscal year each drug first enters development (columns 3 and 4); and the number of approved drugs the firm has up to the point the drug entered development (columns 5 and 6). Panel A considers all drug candidates as outcome variables, whereas Panel B restricts to in-house development only. Depending on the specification, we include development quarter and indication (ICD-9) fixed effects. Robust standard errors are in parentheses, clustered around company identifiers. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table 2: Drug Novelty, Risk and Expected Return—Summary Table

	Risk	Measures of Expected Value	
	Likelihood of FDA Approval	Patent Value	Patent Citations
	(1)	(2)	(3)
Maximum Similarity	0.208***	-0.469**	-0.173***
	(0.025)	(0.196)	(0.078)
Observations	19,127	5,031	116,611
Appendix Table/Column	A.5.(3)	A.6.(4)	A.7.(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); and company. Please see the notes to the relevant Appendix Tables for more details. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table 3: 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**	0.860**	0.847**	0.057**	0.268***	0.263***
	(0.084)	(0.363)	(0.365)	(0.027)	(0.096)	(0.096)
Post 2003 X Overall Drug Life		-0.707*	-0.694*		-0.229**	-0.225**
		(0.366)	(0.368)		(0.098)	(0.098)
Post 2003 X Firm MMS			-0.153			-0.049
			(0.140)			(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 3 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 (6), with Post $\times$ Overall Drug Life$_{f,2003}$ and Post $\times$ Firm MMS$_{f,2003}$ both included as independent variables. Robust standard errors are in parentheses, clustered around company identifiers. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table 4: Portfolio Expansion (Candidates New to Firm)

	New Indications		New Targets	
	(1)	(2)	(3)	(4)
	Log(1+ #)	Δ HHI	Log(1+ #)	Δ HHI
Post 2003 X Medicare Drug Life	0.160**	-0.013*	0.101*	-0.020***
	(0.069)	(0.008)	(0.060)	(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 4 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 Post × Medicare Drug Life$_{f,2003}$. All models include a full set of company and quarter indicator variables, with Post × Overall Drug Life$_{f,2003}$ and Post × 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 5: 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**	0.084**	0.110**	0.115**
	(0.041)	(0.042)	(0.043)	(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**	0.090**	0.192**	0.138**
	(0.038)	(0.041)	(0.080)	(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 5 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 adolescants 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 6: 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**	0.060**	0.060**	0.016
	(0.029)	(0.030)	(0.028)	(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**	0.084**	0.084**	0.040
	(0.043)	(0.039)	(0.035)	(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**	0.058*	0.062*	0.026
	(0.037)	(0.030)	(0.033)	(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 6 reports the main specification coefficient for Post × 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 Post × Overall Drug Life$_{f,2003}$ and Post × 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: Average Value of New Drug Investments

	Patent Value			
	All Drugs		Me-too Drugs	
	(1)	(2)	(3)	(4)
Post 2003 X Medicare Drug Life	2.130**	126.431***	0.016	-10.238
	(0.819)	(34.085)	(0.375)	(11.814)
R^2	0.650	0.576	0.370	0.251
Company FEs	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes
Observations	584	584	584	584
Specification	Logs	Levels	Logs	Levels

Notes: Table 7 examines the average value of the drugs developed 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 × Medicare Drug Life$_{f,2003}$. The dependent variable is the average KPSS value of patents associated with the new drug candidates developed by the firm in a given quarter. In Columns (1) and (2) evaluate the value of all new drugs, while Columns (3) and (4) limit the dependent variable to the set of me-too drugs (those with a maximum similarity score higher than 0.8). All specifications include a full set of company and quarter indicator variables, with Post × Overall Drug Life$_{f,2003}$ and Post × 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: Impact on R&D and Profits

	(1) Log(RD)	(2) Log(Profits)	(3) Log(Debt)	(4) 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 8 examines the response of firm-level research spending, operating cashflow, and debt to our main treatment variable, Post $\times$ Medicare Drug Life$_{f,2003}$. The dependent variable is either the logarithm of R&D spending; the logarithm of operating cashflows (Compustat: ib + 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 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. 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"

A Drug Development and the Pharmaceutical Industry

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.[25]

Having identified a set of promising compounds, researchers focus next on testing its pharmacokinectic and pharmacodynamic properties: how the body impacts the drug (that is, its absorption or bioavailability) and how the drug impacts the body (e.g., drug actions or toxicity), 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.

[25] Firms 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).

The following table summarizes the timing of the drug development process (see e.g., Matthews, Hanison, and Nirmalan, 2016)

1. Discovery
    - Target identification (e.g., what protein should we try to inhibit to treat this condition?)
    - Hit identification (e.g., high-throughput screening to identify molecules that may interact with this protein)
    - Patenting happens after a promising "lead" compound is identified
2. Pre-clinical development
    - In vitro and animal (in vivo) studies (e.g., to study toxicity and efficacy in non-human models)
    - Pharmacokinetics and pharmacodynamics (e.g., to study how the compound is metabolized in the body)
    - Firms apply for permission to begin human trials
3. Clinical Trials
    - Phase 1 trials (to check safety in humans)
    - Phase 2 trials (initial tests of efficacy)

- Phase 3 trials (large scale, double blinded studies usually carried out across multiple research sites and with thousands of patients).

4. Regulatory Approval

As further supporting evidence, Table A.22 shows that most drugs that enter our sample already have patents. In particular, we compare the timing of firms' patents priority and issue dates, relative to the date they enter pre-clinical development (Step 2 in the timeline above). We find that 93.9% of drug candidates in our sample have a patent application by the time they enter pre-clinical development. On average, firms receive priority on patents 34 months prior to their first date of recorded pre-clinical development.

A.2 The Patenting Process

Unlike most innovative industries, patenting happens at the beginning of the drug development process. In particular, firms incur the greatest R&D costs during clinical trials, and these costs are extremely high. Federal laws mandate the disclosure of drug development programs (through investigational new drug applications) prior to permission for human trials, making it impossible to develop drugs in secret. As such, firms will not invest in developing a drug candidate unless they have property rights over their investments. In addition, chemical patents protect against intellectual property theft in pre-clinical development, allowing drug developers to publish early studies on new chemicals, disclose to investors, and negotiate potential alliances and partnerships–all of which are important for participating in the modern drug development market. Patenting is therefore one of the first steps in developing a drug—not the culmination of the process. Indeed, the fact that patents are taken out before clinical trials underlies the main point in Budish et al. (2015), who argue that long clinical trial times eat into a drug's period of patent protection, creating much smaller "effective" patent lives that reduce incentives to development treatments for some types of drugs.

As with other patents, pharmaceutical patent applications are evaluated on the basis of their novelty and utility. However, in drug development, novelty generally creates a greater barrier than utility. In particular, since drug compounds are in general *patented before they are tested and developed*, the notion of "utility" differs for drugs, relative to inventions that already exist as products at the time of patenting. For products that already exist, one can simply make a determination as to whether that product has utility. Because drugs are not developed products at the time of patenting, an examiner cannot require a drug to actually "work." Rather, utility claims are assessed based on evidence of its *potential* therapeutic value. Because this is vague, practitioners

generally believe that novelty is the more stringent barrier.[26] A typical way to assess novelty is to search the prior art for examples of similar molecules that are described in other patents, which can be especially challenging if the firm is operating in a more "crowded" chemical space where other patents have claimed similar compounds or overlapping "Markush" structures.[27] This process is increasingly aided by automatic patent searching software comparing the molecular similarity of the to-be-patented compound against previous compounds. Such algorithms use the same or similar measure of molecular similarity that we use to define novelty. As such, the molecules we describe as novel are also—by definition—novel in the eyes of the patent examiner, clearing an important hurdle for patenting.

We therefore expect that, if anything, novel molecular compounds are generally *easier* to patent than derivative drug molecules—since the patent application for a molecularly novel candidate is more likely to pass the novelty criterion for patentability. This pattern mitigates our concern about selection into the patenting sample: if it were the case that the hurdle for novel drugs is higher, we would be worried that a higher NPV for patented novel compounds may not be representative of the overall relationship between NPV and novelty. Further, the KPSS measure may then also be differentially biased upward for novel compounds: the market may be more surprised when a novel drug is patented than a me-too drug, in which case the stock market would update more sharply on approval of a novel drug than a me-too drug even if the underlying values were similar.

However, this is not the case: Figure A.9 shows that patent applications associated with novel drug candidates are approved more quickly that patents associated with me too drugs. This comports with the view that the patenting of me-too molecules requires many more exchanges between the firm and the patent office—for instance, Harhoff and Wagner (2009) find that more controversial claims lead to slower grants. This makes it highly unlikely that novel compounds are more positively selected by the patenting process than me-too compounds. If anything, me-too compounds are more likely to be held to a higher bar. Here, we note that the speed of approvals is potentially endogenous: firms may choose to prioritize their most valuable patents, e.g. by means of preparing their applications more carefully and following the work of the patent office more closely, resulting in a negative relation between approval times and the value of a patent (Harhoff and Wagner, 2009; Regibeau and Rockett, 2010). Viewed from this perspective, our results in Figure A.9 imply that novel drugs are more valuable.

[26] See, for instance,
https://blogs.sciencemag.org/pipeline/archives/2015/12/10/how-do-you-find-a-new-compound-to-patent

[27] See https://en.wikipedia.org/wiki/Markush_structure

A.3 Development Costs

Drug development is expensive. DiMasi, Grabowski, and Hansen (2016) estimate that the direct cost to firms of developing a single approved drug is over $1.4 billion and has been increasing over time. This total cost of development is spread unevenly across the stages of drug development. In particular, one aspect of the pharmaceutical industry that is unique relative to other industries in which innovation is important is that discovery and patenting costs are small. DiMasi et al. (2016) show that discovery costs account for about 2% of total development costs. The costs of drug discovery are relatively low for two reasons. First, the bulk of what is truly uncertain in discovery is "target identification" – the process of understanding what biological targets (proteins, genes, and RNA) play a role in inhibiting or stimulating a disease. Much of this work is actually carried out in academia: for instance, Sampat and Lichtenberg (2011) show that 60% to 70% of approved drugs are based on NIH funded research. Galkina Cleary, Beierlein, Khanuja, McNamee, and Ledley (2018) show that NIH funding contributed to published research associated with every one of the 210 new drugs approved by the Food and Drug Administration from 2010 to 2016. Thus, much of the costs of discovery are actually publicly funded and not borne by firms. Second, once the targets are identified and verified, the remaining discovery work consists of identifying compounds that might interact productively with the target. Small molecules (the focus of our paper) are generally low cost to synthesize in small batches and testing them usually does not involve expensive, long-horizon lab work. Indeed, in recent years, these processes have become increasingly automated and sometimes use computer modeling ('virtual screening') to further reduce costs (Hughes, Rees, Kalindjian, and Philpott, 2011; Walters, 2019).

The bulk of a drug's development cost occur post-discovery. DiMasi et al. (2016) argue that clinical costs accounting for over two thirds of the total cost. Phase 3 trials, in particular, can be extremely 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. As a result, a useful proxy for development costs are the number of patients enrolled in clinical trials and the number of trials associated with drugs. Since trials are so expensive, recruiting patients and running trials constitutes a substantial proportion of a drug's development cost. Table A.8 shows that there is no relation between either the size or the length of a clinical trial and the novelty (maximum similarity) of the molecule being tested.

A.4 Financing Drug Development

Pharmaceutical firms face some unique challenges that make external finance particularly costly. In particular, most pharmaceutical firms have a highly concentrated portfolio of drugs. As we see in Panel A of Appendix Figure A.10, approximately 60% of the firms in the entire sample have a single approved drug in their portfolio. This pattern is only partly skewed by smaller firms: even when focusing on the sample of firms in our main analysis in Section 3 (which is skewed towards larger firms) approximately 75% of the firms in this subsample have fewer than 10 approved drugs in their portfolio. Consequently, as we see in Panel B, their sales is highly concentrated in very few drugs.

A direct consequence of such high asset concentration is that the success or failure of a single drug candidate matters considerably for firm value. As a result, information asymmetries between insiders and outsiders become much more important than other firms with a diversified asset portfolio. Further, asymmetries of information are not only more important, but also likely more severe: the existence of long development times with fewer milestones—the average lag between discovery and market approval is around 10 years—implies that outside investors likely know less than insiders. .

Given the presence of these informational asymmetries, pharmaceutical firms primarily rely on internal funds for drug development—consistent with the pecking order theory (Myers and Majluf, 1984). When internal funds become scarce, the main source of external finance is equity. Financing drug development with debt is challenging because most pharmaceutical firms few have assets that can be reliably used as collateral. Unlike firms in other sectors, for instance software, patents for drug candidates are taken out early in the development process, before the efficiency and utility of the drug candidate is known. As a result, accepting drug patents as collateral is 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.[28] Consistent with this view, firms in the pharmaceutical industry have indeed lower leverage ratios than comparable firms in other industries (see Appendix Table A.9 for more details).

In addition to having lower debt, Panels B and C of Appendix Table A.9 show that pharmaceutical firms are significantly less likely to pay dividends or engage in share repurchases. Focusing on Columns (6) and (9), we see that, compared to firms of similar size and profitability in other industries, pharmaceutical firms are 11 to 13 percentage points less likely to pay cash dividends or buy back shares. These magnitudes are quite large given that approximately half of the firms in Compustat either pay dividends or buy back shares in a given year. This lower propensity to pay

[28] 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 (Mann, 2016). Further, most of these pharmaceutical patents concern medical devices: 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.

out to investors suggests that these firms attach a high value to holding cash inside the firm—a consequence of facing financial frictions.

Overall, academics and policymakers agree that pharmaceutical firms face some unique financing challenges (Fagnan, Fernandez, Lo, and Stein, 2013; Thakor and Lo, 2017; Adam Jørring and Thakor, 2017). On October 9, Representatives Juan Vargas and Thomas Rooney introduced a bill that would allow the NIH to create a "megafund" to diversify the risk of drug development, saying: "The simple truth is that in biotech and life sciences, traditional financing vehicles of private and public equity are becoming less effective. The life sciences industry needs novel approaches to early-stage development."[29] Indeed, while much of startup investing has moved towards a "spray-and-pray" strategy with a larger number of smaller investments celebrating "fast failure," biotech investors have moved in the opposite direction. Top biotech venture capital firms now routinely incubate their own companies (seeding the concept and founding team) and prefer larger and fewer investment rounds.[30] Such a model in which VCs essentially mimic internal capital markets underscores the difficulty that external investors face when making large investments at an arms length: this wedge between is precisely what we mean when we say that pharma firms face costly external finance.

B Data Construction

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

B.1 Drug Development Histories

Our drug development data primarily comes from the Cortellis Investigational Drugs and Clinical Trials databases.[31] 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, therapuetic 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.

[29] See [source]https://www.institutionalinvestor.com/article/b14z9ypfg10q6q/mits-andrew-lo-touts-megafund-to-tackle-cancer-rare-diseases

[30] For a summary of this trend, see 'The Creation of Biotech Startups: Evolution Not Revolution" (*Forbes*, August 15, 2019; https://www.forbes.com/sites/brucebooth/2019/08/15/the-creation-of-biotech-startups-evolution-not-revolution.

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

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 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.

B.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 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.

B.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 C.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 correllations between our drug novelty measure and annual drug revenue, controlling for sales year, the drug's approval year, and therapeutic area (see Section C.2.1).

B.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

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

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 to 36 percent 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

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

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

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

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 B.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.5 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

$$\widehat{\log \xi_j} = \log \hat{\Delta} V_j - 0.123\, \text{maxsim}_j. \tag{B.4}$$

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

B.5 Drug Effectiveness (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.

B.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.[32] When we could not match an approved drug to the Federal Register data, we used the patent expiration dates of the drugs' affliated "Orange Book" patents listed by the FDA.[33]

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.

B.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 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 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.

[32] We thank Duncan Gilchrist for sharing this Federal Registrar data.

[33] The 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.

B.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.

C Additional Results

C.1 Descriptive facts in measured novelty

Panel A of Appendix Figure A.11 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 Appendix Table A.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 A.11 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, Jones, van Reenen, and Webb, 2017).

C.2 Novelty and Measures of Value for Approved Drugs

Here, we examine the correlation between several proxies of private and social value and drug novelty within the sample of approved drugs. 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.

C.2.1 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 to 2012. To match drugs to Cortellis, we employ a name-matching procedure. Appendix B.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. That is, blockbuster drugs are more likely to be novel. 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.23 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.[34] 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.

C.2.2 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 B.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.24 reports estimates using different combination of controls. In terms of magnitudes, a one standard deviation increase in novelty is associated with approximately

[34] Further, 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.

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.

C.2.3 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 a 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 B.5.

We find that novel drugs contribute greater clinical benefits than me-too drugs. 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.25 reports results using additional specifications.

C.3 Firm Heterogeneity

One limitation of this analysis in Section 3.6 is that it is restricted to public firms in Compustat, which account for approximately one-half of our sample. We next turn to the entire sample and 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. That is, in the model, cash holdings are partly driven by retained earnings. 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 (6) separately across the firms that are below or above the median prior firm revenue in 2003.

Appendix Table A.17 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 versus 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 versus me-too drugs—see Appendix Figure A.12.

Here, we note one caveat: our measure of prior revenue may conflate past profitability with prior experience. More experienced firms likely have more opportunities to develop novel drugs than less experienced firms. Thus, the lack of differential response across the two sets of firms with different levels of past revenue is not particularly surprising; there is simply not enough variation in the data to separate past cashflows from investment opportunities.

C.4 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.21 in the Appendix, shows the results of this analysis for two 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).[35] These results show that treated firms differentially develop more drug candidates aimed at new biological targets. This pattern holds for the full set of drugs and for each separate group (small molecules and biologics).

In addition, we find that our results are not driven by pre-existing firm-specific trends (Appendix Table A.11), and are robust to alternative definitions of novelty with respect to prior candidates for the same indication (Appendix Table A.29). Further, our results are robust to different empirical specifications: Table A.12 in the Appendix considers Poisson count models, Table A.30 considers a binary outcome variable (based on whether the firm have any new drugs), and Table A.13 considers a binary treatment. Our results are also robust to different definitions of treatment: Table A.10 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.31 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

[35]The 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).

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.3; Table A.14 shows that are results are similar if we exclude these firms.

D Model

Here we present a baseline model that guides our empirical work.

D.1 Model Setup

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 $\lambda\, dt$ 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 new drug at time t costs $f\, K$. 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

$$\frac{dK_t}{K_t} = \chi\, I_t\, \tilde{S}\, dN_t - \delta\, dt. \tag{D.1}$$

Here, dN_t is a Poisson variable with intensity $\lambda\, dt$ 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. Over time, 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,

$$dA_t = \mu\, dt + \sigma\, dZ_t. \tag{D.2}$$

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 on its scale of operations or customer base, K_t.

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

$$dY_t = K_t\, dA_t - I_t f K_t dN_t. \tag{D.3}$$

Firms can fund drug development through accumulated cash or external financing. External financing has a fixed and a 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

$$dW_t = dY_t + (r - c)W_t\, dt + dH_t - dU_t, \tag{D.4}$$

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,

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

subject to (D.1)–(D.2). 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

$$V(W_t, K_t) = v(w_t)\, K_t, \qquad w_t \equiv \frac{W_t}{K_t}, \tag{D.5}$$

where the function $v(w)$ solves the Hamilton-Jacobi-Bellman equation (D.16) in Appendix D.4.

D.2 Model Predictions

Given the form of the firm's value function (D.5), the key variable that determines firm policies is its cash holdings to scale ratio w. Figure A.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 marginal value of cash is equal to one, and therefore $v(w) = \bar{v} + w$. In that case, the firm will develop all drugs i whose expected payoff exceeds their development cost,

$$\bar{v}\, p_i\, \chi_i \geq f. \tag{D.6}$$

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

$$p_i\,(1+\chi_i)\,v\left(\frac{w-f}{1+\chi_i}\right) + (1-p_i)\,v\,(w-f) - v(w) \geq 0. \tag{D.7}$$

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 (D.7) to the frictionless case (D.6), 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 (D.7) 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 varies 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 A.4 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 being 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 illustrates how these frictions may impact the novelty of drugs that are developed. The black line corresponds to the supply of development opportunities; we assume the slope of that line is similar for novel and me-too drugs. 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 the me-too 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.

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}. Hence, our model makes two unambiguous predictions about how a firm will respond to a positive cashflow shock. First, firms will develop more drugs overall, but more importantly, they will develop relatively more novel than me-too drugs.

D.3 Discussion of Modeling Assumptions

The key assumption in the model is the presence of 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 therefore induces firms to take on more risk, just as a shock to current cashflows would.

D.4 Details of the 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.

D.4.1 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

$$p_i \Big(V(K_t + \chi_i K_t) - V(K_t) \Big) - f K_t > 0. \tag{D.8}$$

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

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

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

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

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

$$v_0\, p_i\, \chi_i \geq f. \tag{D.9}$$

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

D.4.2 Financing Frictions

Profits minus investment equals

$$dY_t = K_s\, dA_s - f\, I_{i,s}\, K_s\, dN_t \tag{D.10}$$

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

$$dW_t = dY_t + (r-c) W_t\, dt + dH_t - dU_t \tag{D.11}$$

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

The objective of the firm equals

$$V(W_t, K_t) = E_t \int_t^\infty e^{-r(s-t)} \Big(dU_t - dH_t - dX_t \Big) \tag{D.12}$$

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

$$dU_t - dH_t = K_s\, dA_s - f\, I_{i,s}\, K_s\, dN_s \tag{D.13}$$

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:

$$r\,V(W,K) = V_W\left[K\,\mu + (r-c)W\right] + \frac{1}{2}\,V_{WW}\sigma^2\,K^2 - \delta V_K\,K + \\ + \lambda \max_I \Big\{ \int_p \int_\chi \Big(p\,V(W - f\,K\,I, K + \chi\,I\,K) + (1-p)\,V(W - f\,K\,I, K) - V(W,K) \Big) G(p,\chi) d\chi dp \Big\}$$

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

$$p_i V(W - f\,K, K + \chi_i\,K) + (1-p_i)V(W - f\,K, K) - V(W,K) \geq 0 \tag{D.14}$$

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

$$V(W_t, K_t) = K_t\,p(w_t), \qquad w_t \equiv \frac{W_t}{K_t}. \tag{D.15}$$

The HJB equation thus becomes

$$0 = v'(w)\big(\mu + (r-c)\,w\big) + \frac{1}{2}\,v''(w)\sigma^2 - \delta\left(v(w) - wv'(w)\right) - r\,v(w) + \\ + \lambda \max_{I(p,\chi)} \int\int \Big[p\Big((1+\chi I)v\left(\frac{w - f\,I}{1+\chi I}\right) - v(w)\Big) + (1-p)\Big(v\left(w - f\,I\right) - v(w)\Big)\Big] G(p,\chi)\,dp\,d\chi. \tag{D.16}$$

and the firm will invest in drug i iff

$$p_i(1+\chi_i)v\left(\frac{w-f}{1+\chi_i}\right) + (1-p_i)v\left(w-f\right) - v(w) \geq 0 \tag{D.17}$$

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:

$$v'(\bar{w}) = 1. \tag{D.18}$$

The above can be seen as the limiting case of

$$v(w) = v(\bar{w}) + (w - \bar{w}), \qquad w > \bar{w}. \tag{D.19}$$

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

$$v''(\bar{w}) = 0. \tag{D.20}$$

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

$$V(0, K) = V(mK, K) - \phi K - (1 + \gamma)\, m, K \tag{D.21}$$

or after re-normalization,

$$v(0) = v(m) - \phi - (1 + \gamma)\, m. \tag{D.22}$$

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

$$v(z) = v(m) - \phi - (1 + \gamma)\,(m - z). \tag{D.23}$$

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

$$v'(m) = 1 + \gamma. \tag{D.24}$$

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 $n = 1 \ldots k$, set

$$v_n^1 = v^0(m(n)) - \phi - (1 + \gamma)\,(m(n) - w_n). \tag{D.25}$$

given the $m(n)$ above.

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

$$v_n^1 = \hat{v}_n \tag{D.26}$$

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

$$\hat{v}_n \leq \hat{v}_{n-1} + (w_n - w_{n-1}) \tag{D.27}$$

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

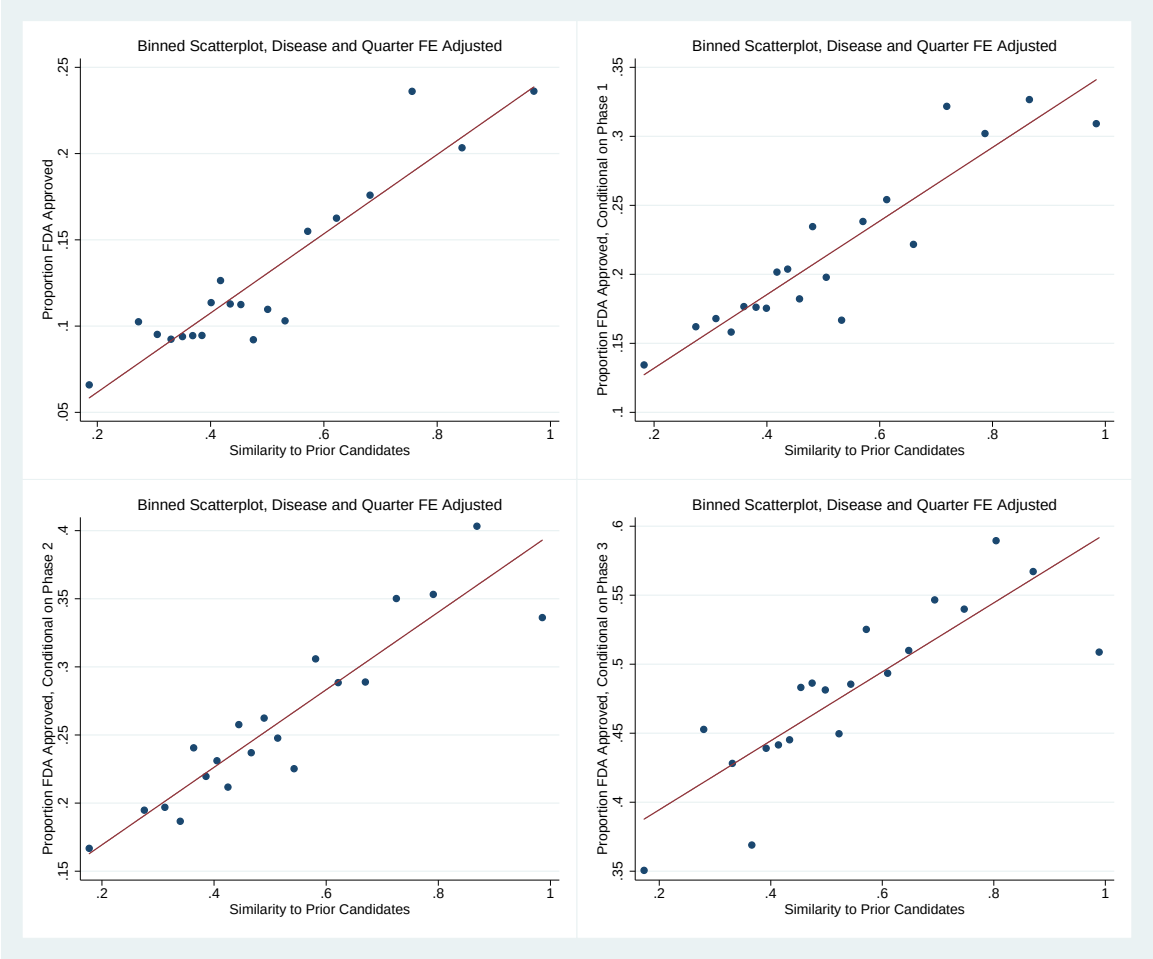
$$v_m^1 = \hat{v}_{n^*-1} + (w_m - w_{n^*-1}) \tag{D.28}$$

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.

Appendix Tables and Figures

Figure A.1: Proportion FDA Approved, by Drug Similarity



Notes: Figure A.1 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.2: Drug Similarity and Market Value of Patents: Placebo Experiments

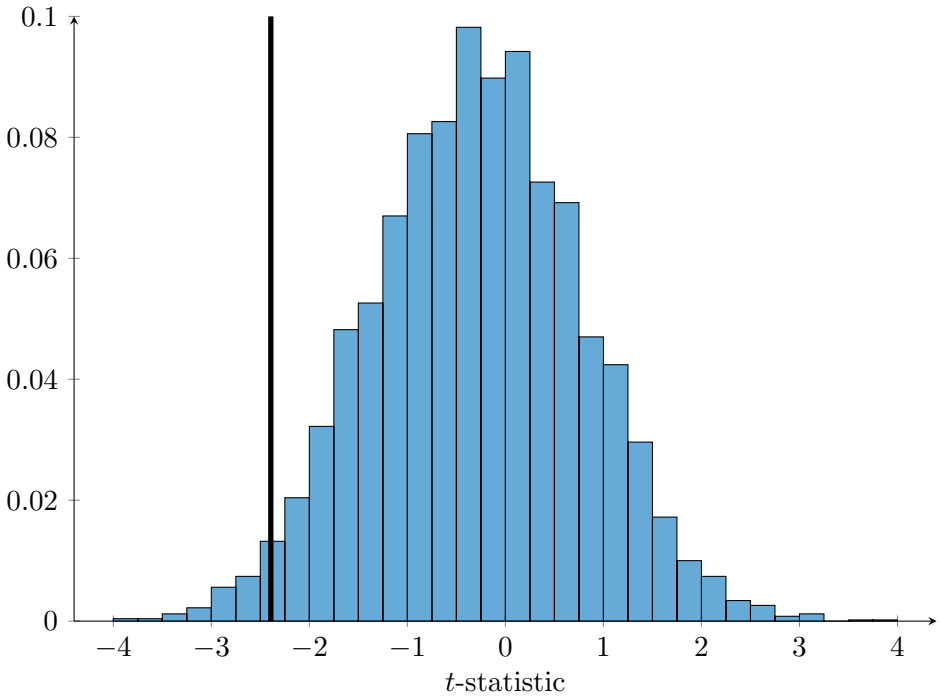
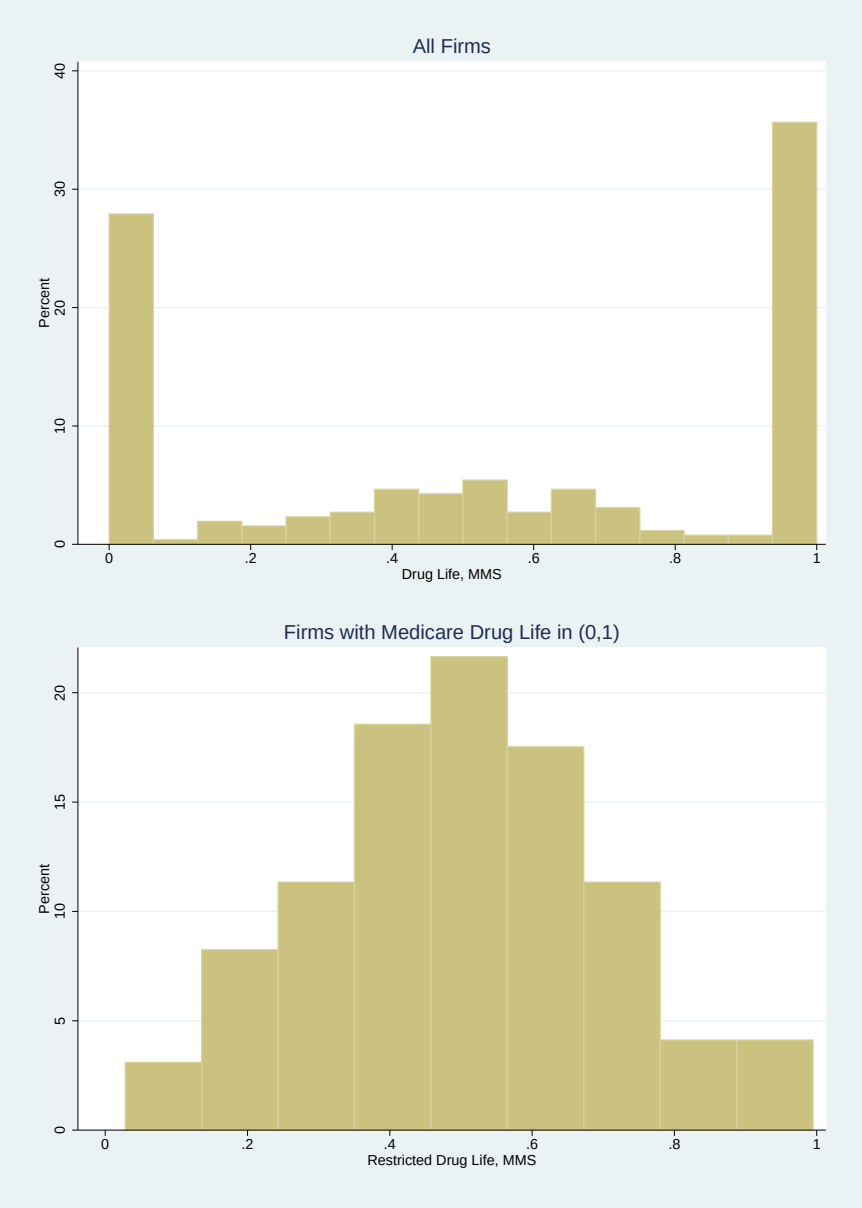


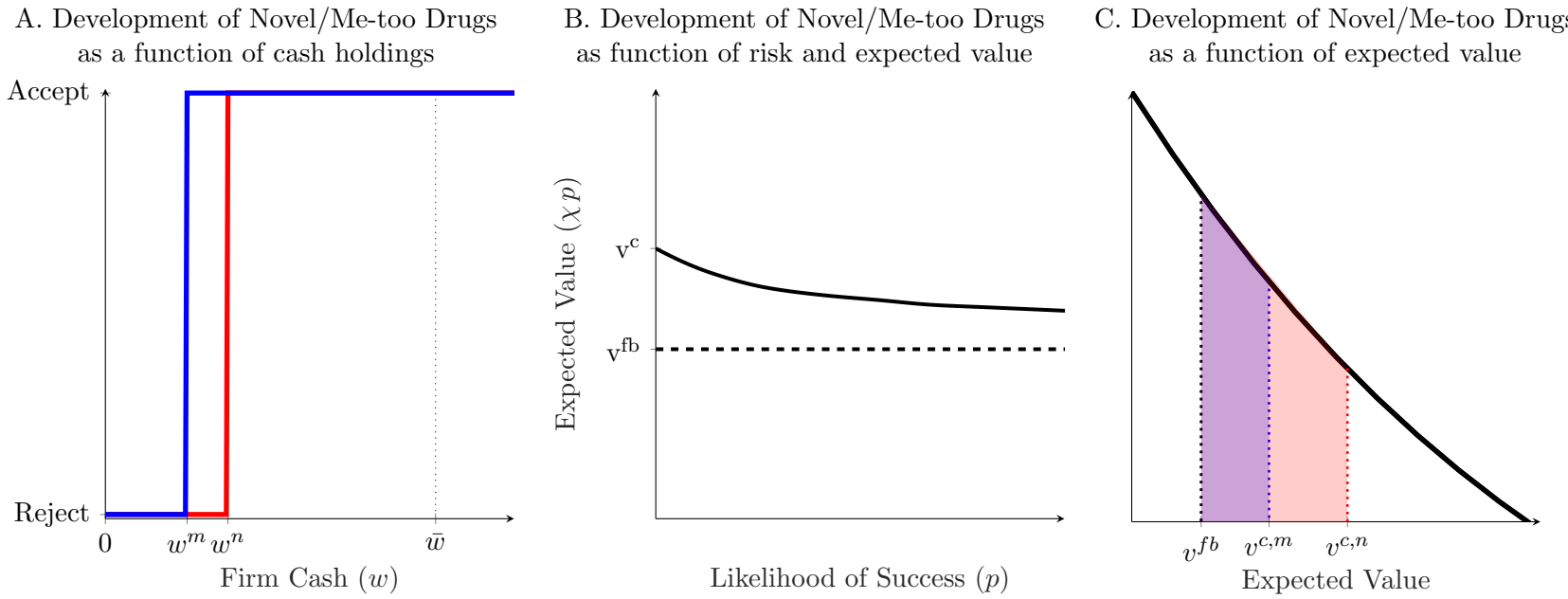
Figure plots the distribution of estimated coefficients t-statistics, from estimating equation (3) linking drug similarity and the Kogan et al. (2017) measure of patent value across 5,000 placebo experiments. In each placebo experiment, we randomly generate a different issue date for each patent within 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.3: Distribution of Medicare Drug Life in 2003



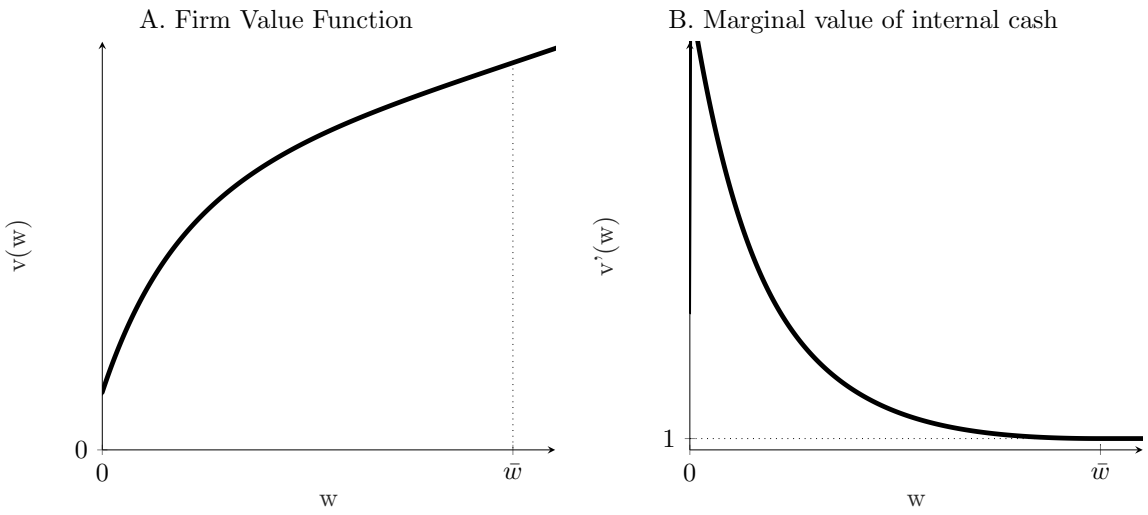
Notes: Figure A.3 plots the distribution of Medicare Drug Life in 2003. Each observation is a firm in our main analysis sample.

Figure A.4: Model and Drug Development Decisions



Notes: Figure A.4 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 illustrates an example in which relaxing financing frictions (to the first-best level) affects the development threshold for drugs of different levels of riskiness. The black line denotes the supply of drug opportunities, which is assumed to be the same for novel (high-risk) and me-too (low-risk) drugs. The red and blue shaded areas correspond to the increase in the development of novel and me-too drugs if the firm were to transition to the frictionless benchmark. Here, 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.

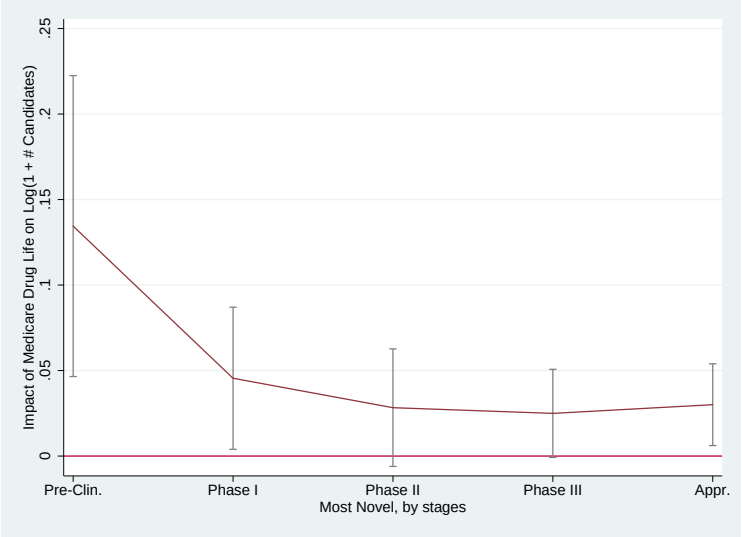
Figure A.5: Model Solution



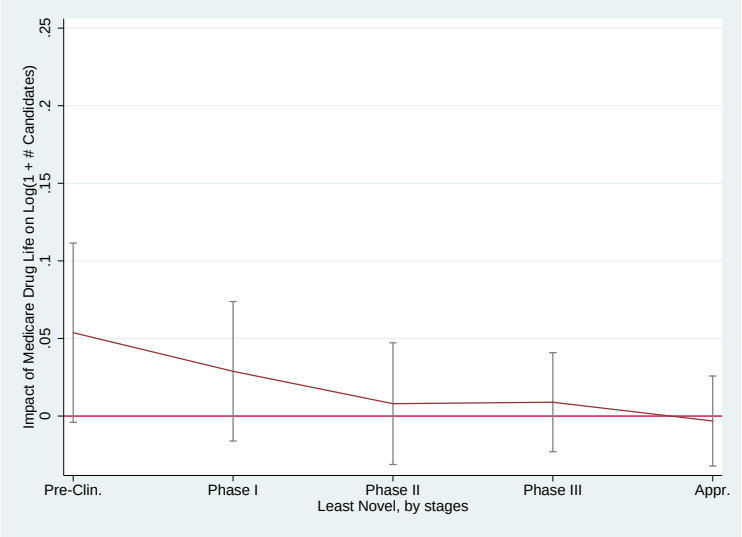
Notes: Figure A.5 plots the solution to the model in Section 3.1, specifically the properties of the firm's value function $V(K, W) = v(w)\, K$, where $w \equiv W/K$. See Appendix D.4 for details.

Figure A.6: Impact of Medicare Drug Life on # of New Candidates, by Stages of Development – Novel Drugs

(a) Most Novel



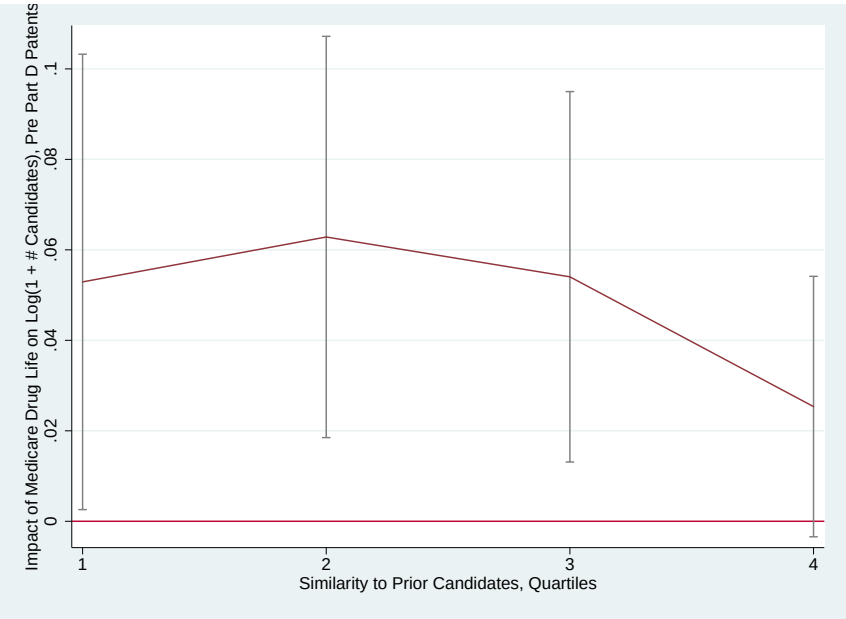
(b) Least Novel



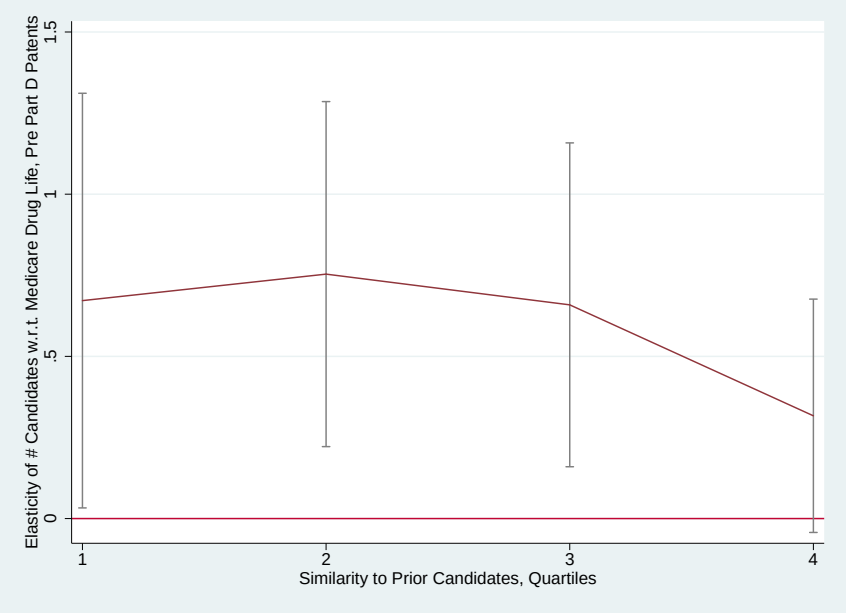
Notes: Figure A.6 reports the event study regression coefficients for impact of medicare drug life on the number of new drug candidates, by stage of development. Our outcome variables are the number of new candidates in different stages of development for each quarter. Each dot represents the coefficient on Medicare Drug Life$_{f,2003}$ for each stage of development. Panel A reports results for the most novel (top quartile) drugs, while Panel B shows the coefficients for the least novel (bottom quartile) drugs. 90th percentile confidence intervals are reported.

Figure A.7: Development of novel vs me too drugs in response to treatment—restricting to drugs that have a granted patent prior to pre-clinical entry

(A) Coefficient Estimates

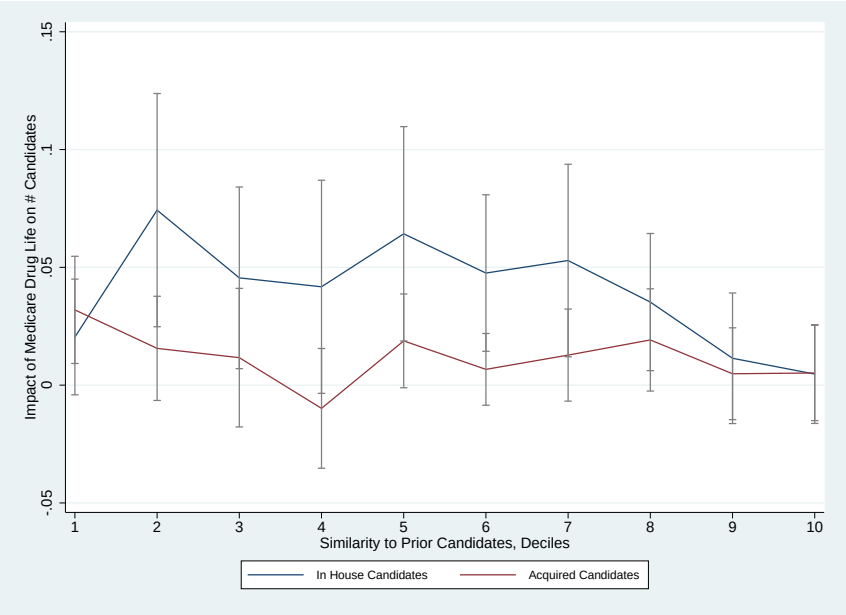


(B) Implied Elasticities



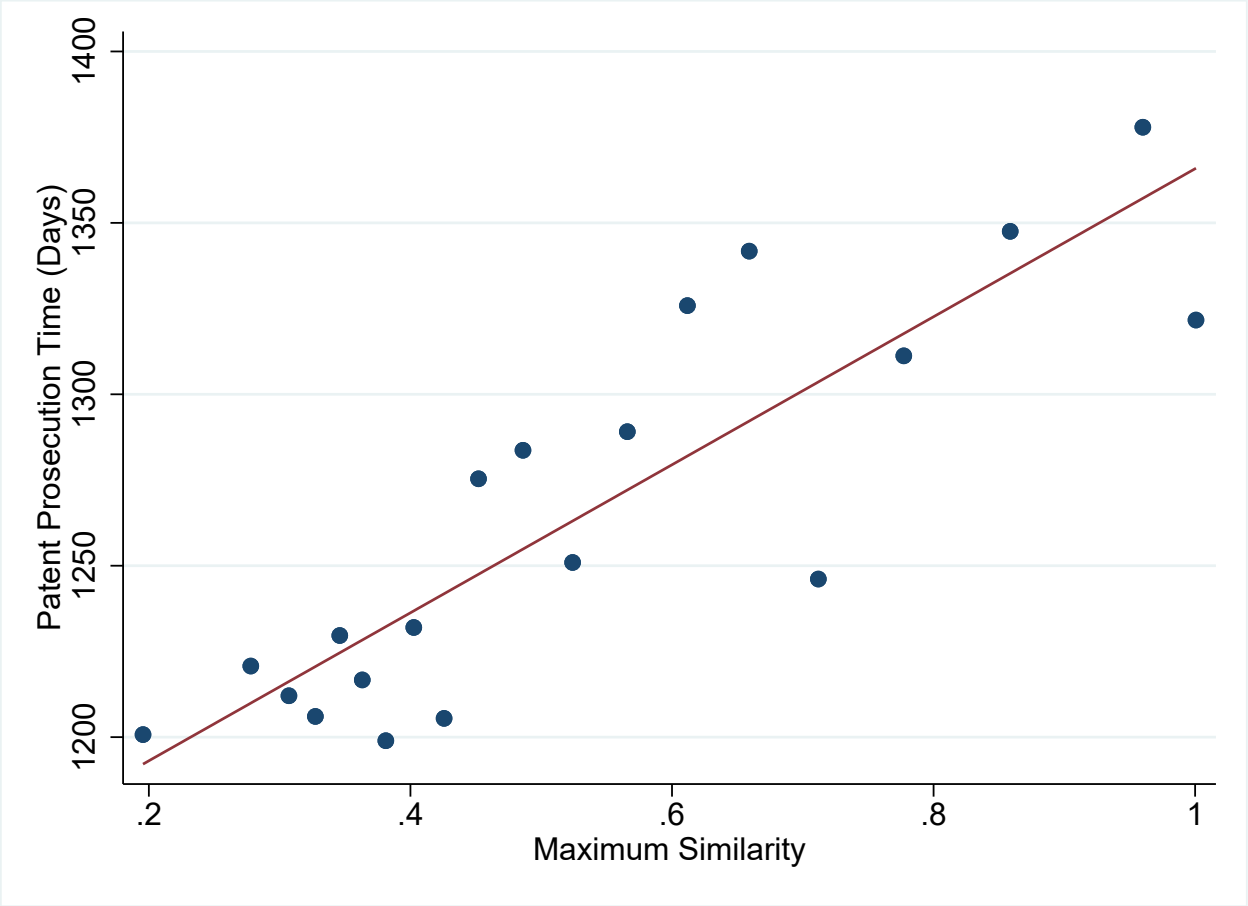
Notes: These figures reports the coefficient on our main treatment variable (Medicare Drug Life in equation (12) of the main text. Each point represents a different outcome variable: the number of new drug candidates in a given quartile of similarity (with 1 being the most novel). In this analysis, we restrict to drugs that have patents that are granted prior to the drug entering pre-clinical development. Error bars denote 95% confidence intervals.

Figure A.8: Original vs. Acquired



Notes: Figure A.8 plots the estimated coefficients on Post × 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.9: Time-to-Patent: Novel vs Me-Too Drugs



Notes: This figure presents a binned scatterplot of drug-level similarity against length of patent prosecution—that is, the difference between the patent issue and application date. Each dot represents the average prosecution time, among all candidates within a given similarity score bin, conditional on disease (ICD9) and quarter of development fixed effects.

Figure A.10: Drug Companies have undiversified drug porfolios

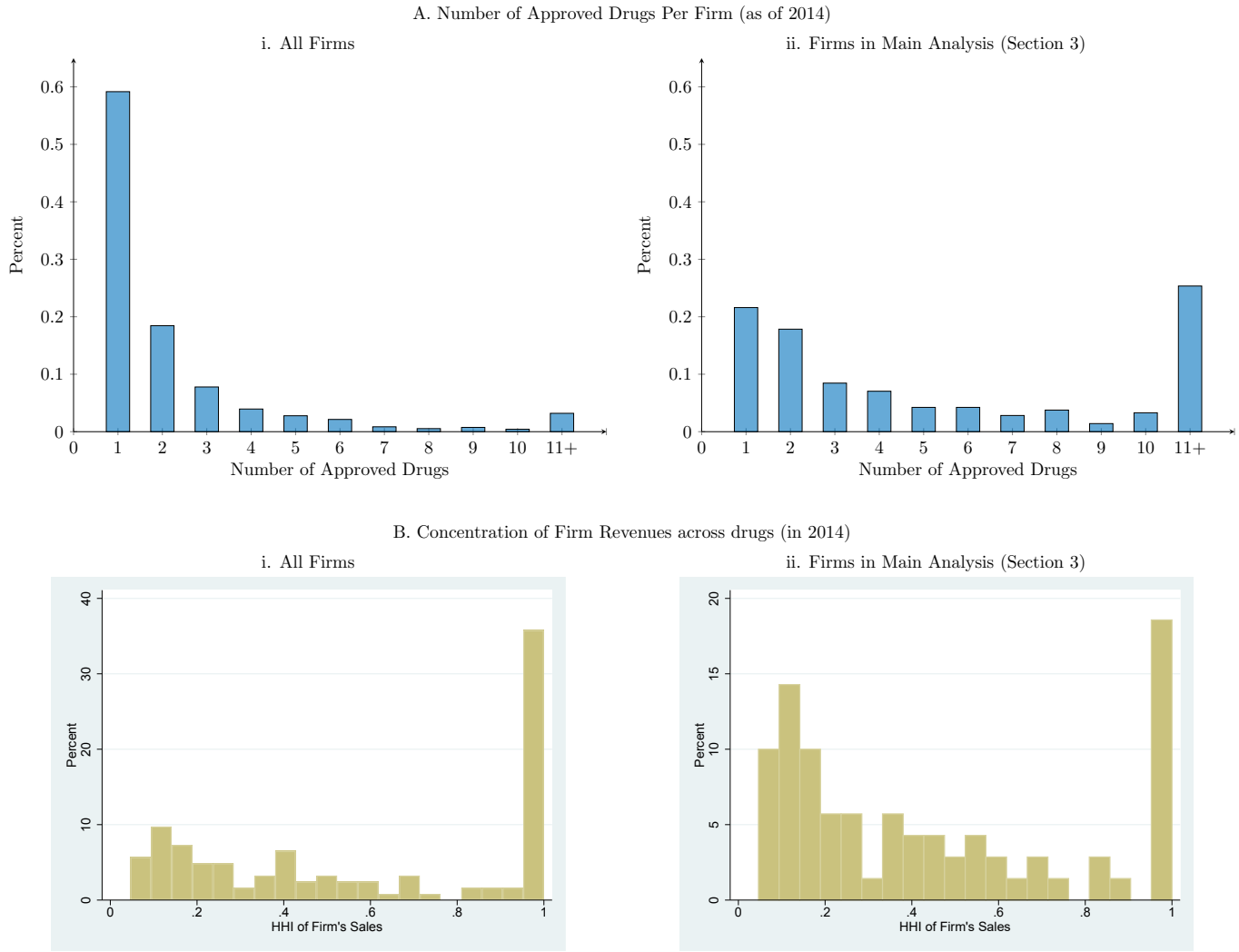
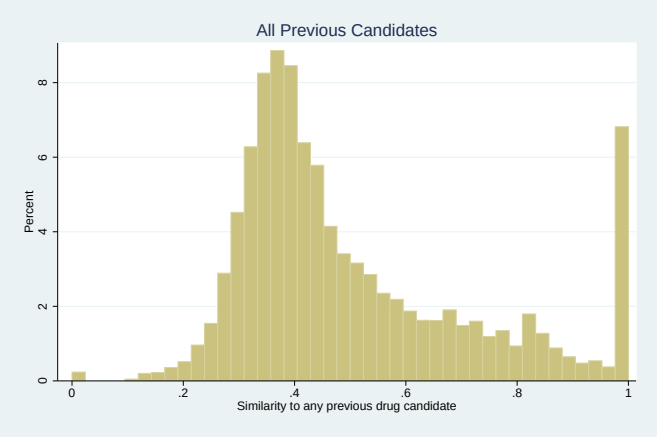


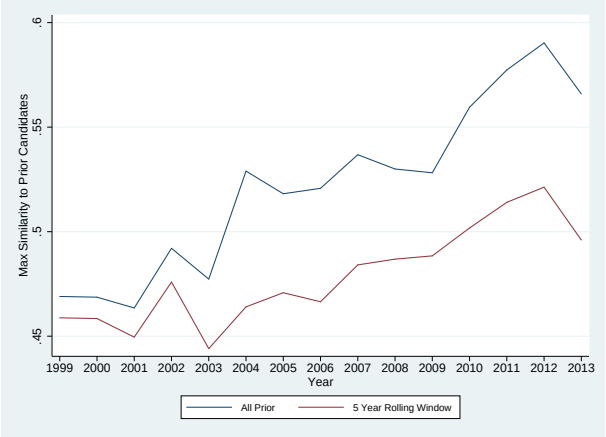
Figure the distribution of the number of approved drugs (Panel A) and the concentration of sales (HHI, Panel B) across drugs for firms in the entire sample that have at least one approved drug (left panel) and firms in our main analysis (right panel).

Figure A.11: Drug Novelty, Descriptive Statistics

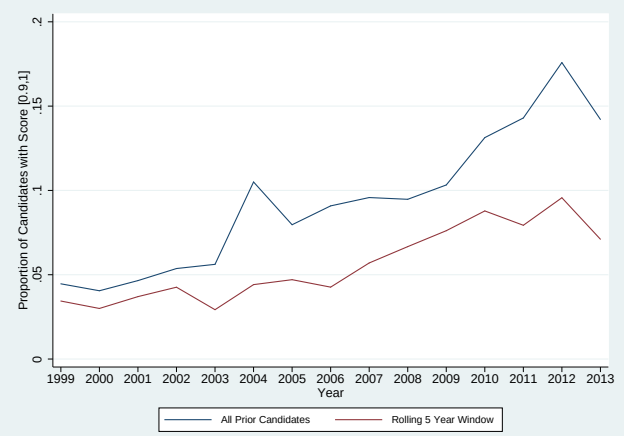
A. Distribution of Similarity



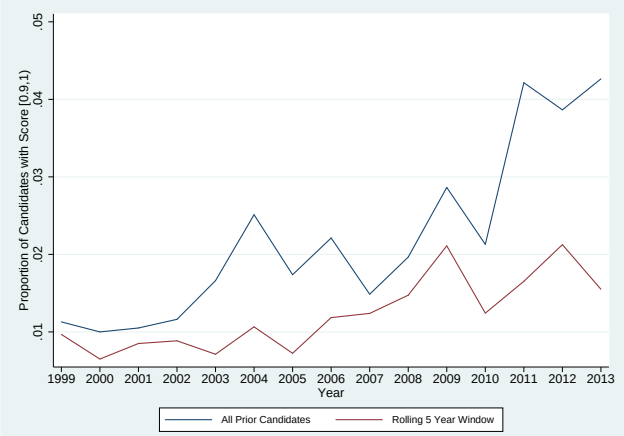
B. Average Similarity Over Time



C. Proportion > 0.9



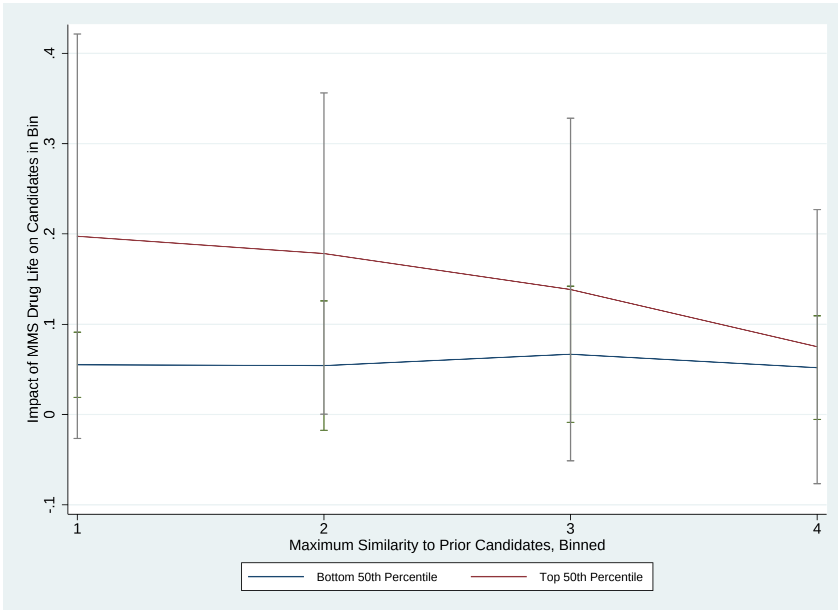
D. Proportion > 0.9, excl. Combination



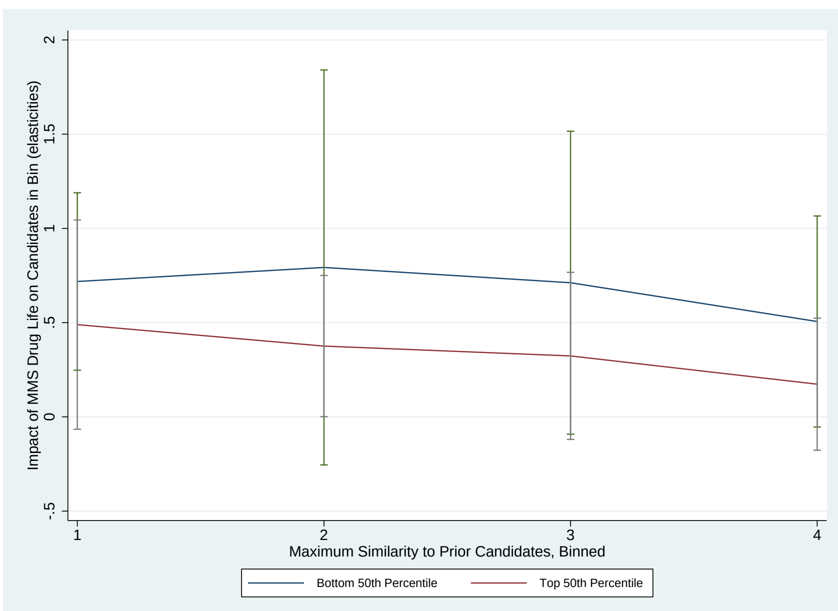
Notes: Figure A.11 displays descriptive statistics of our novelty measure. Panel A displays the distribution of our drug similarity measure. A drug's similarity is measured as its similarity to the most similar drug candidate that had previously entered Phase 1 clinical trials. For more details on this 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 A.12: Impact of Additional Resources on Novelty, within Indication

A. Coefficients



B. Elasticities



Notes: Figure A.12 plots the estimated coefficients on Post × Medicare Drug Life$_{j,2003}$ 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.

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.13: # of Drug Candidates over Time

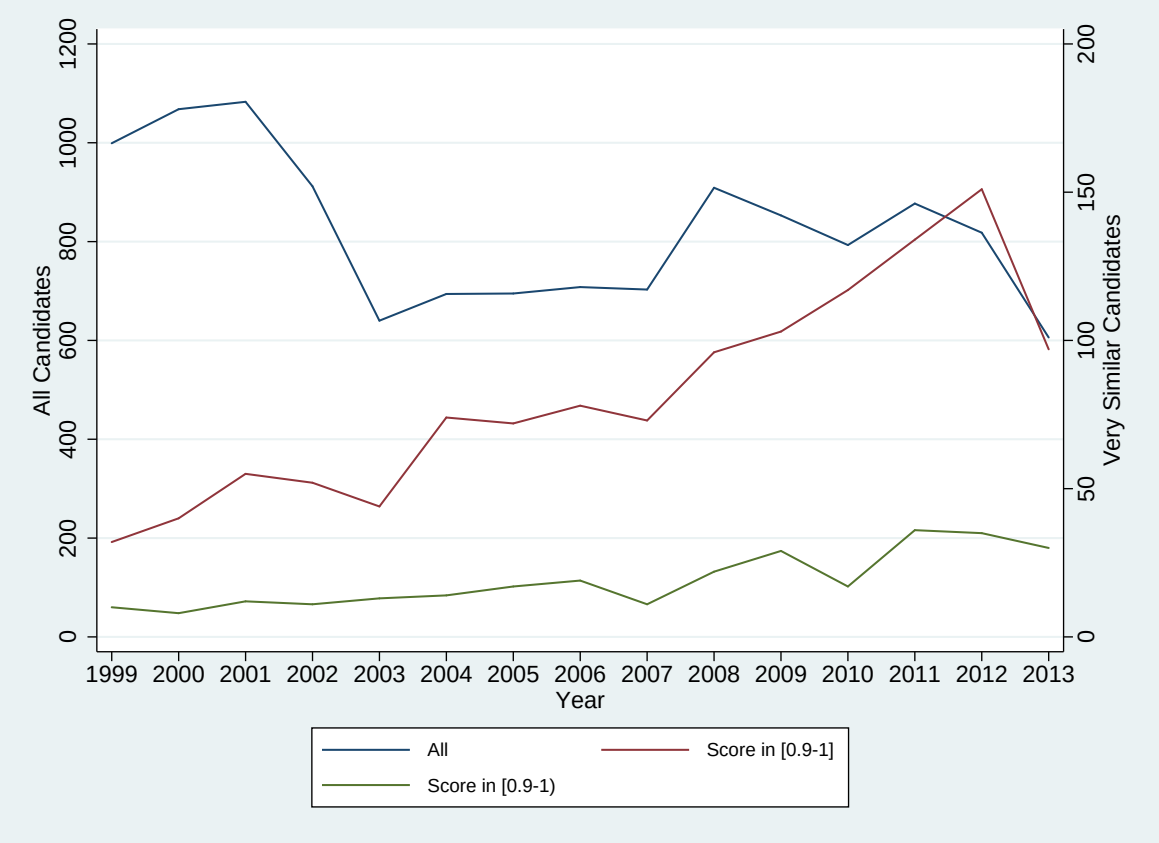
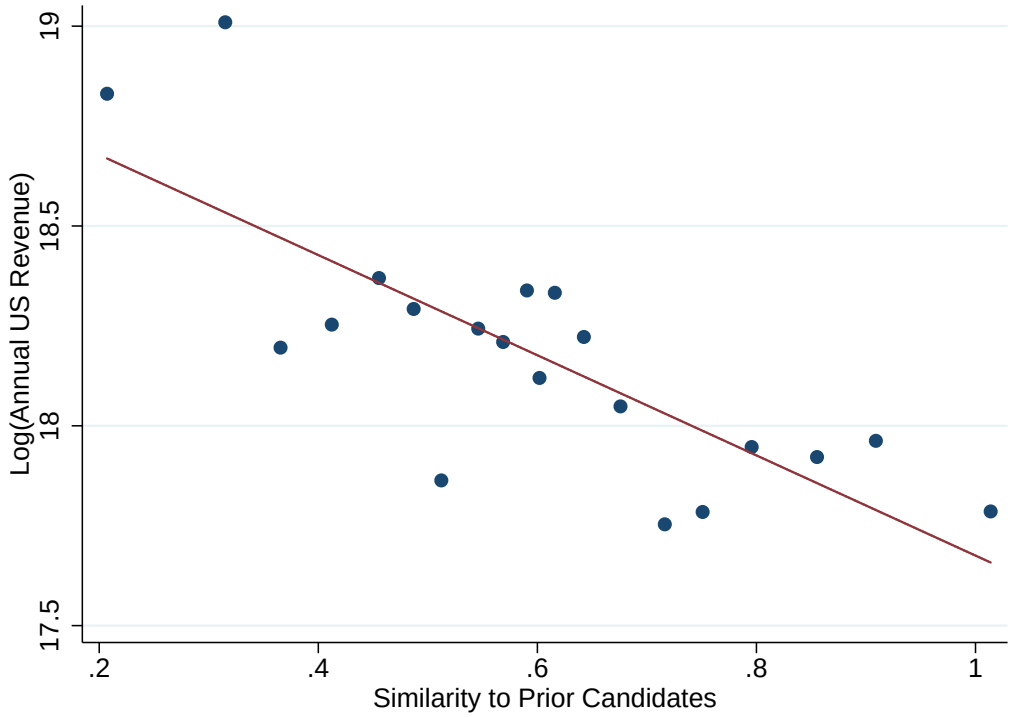
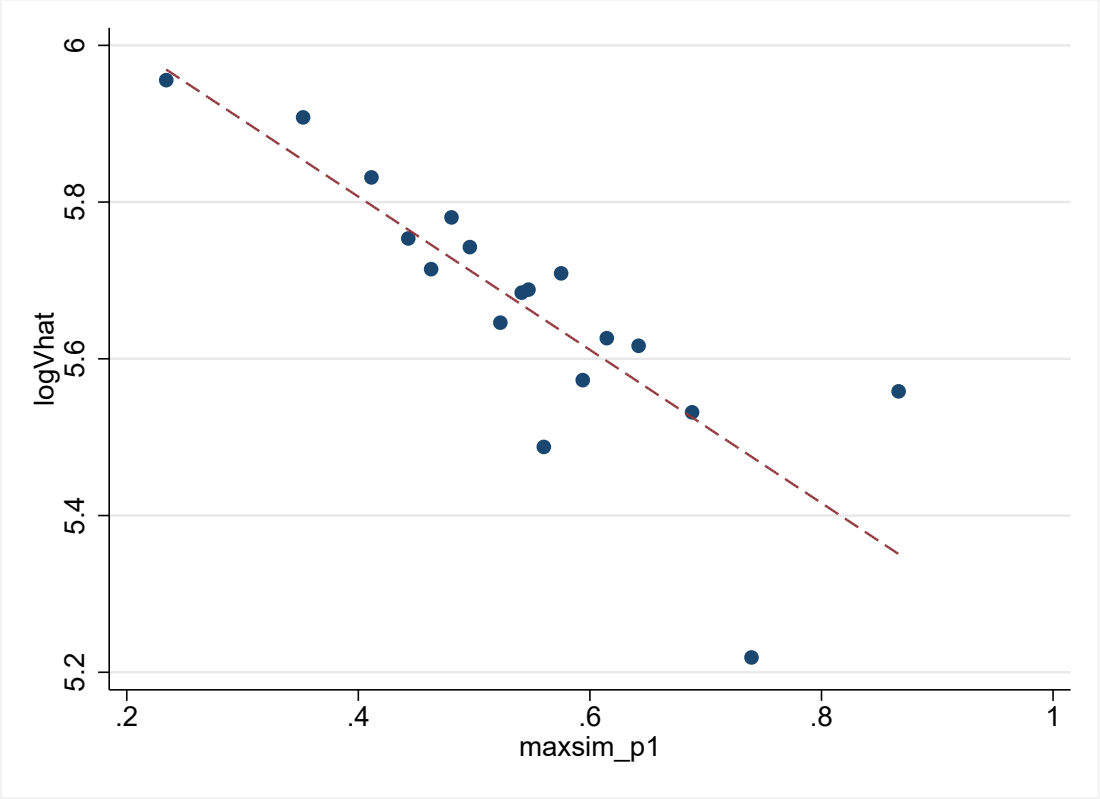


Figure A.14: Revenue, by Drug Similarity



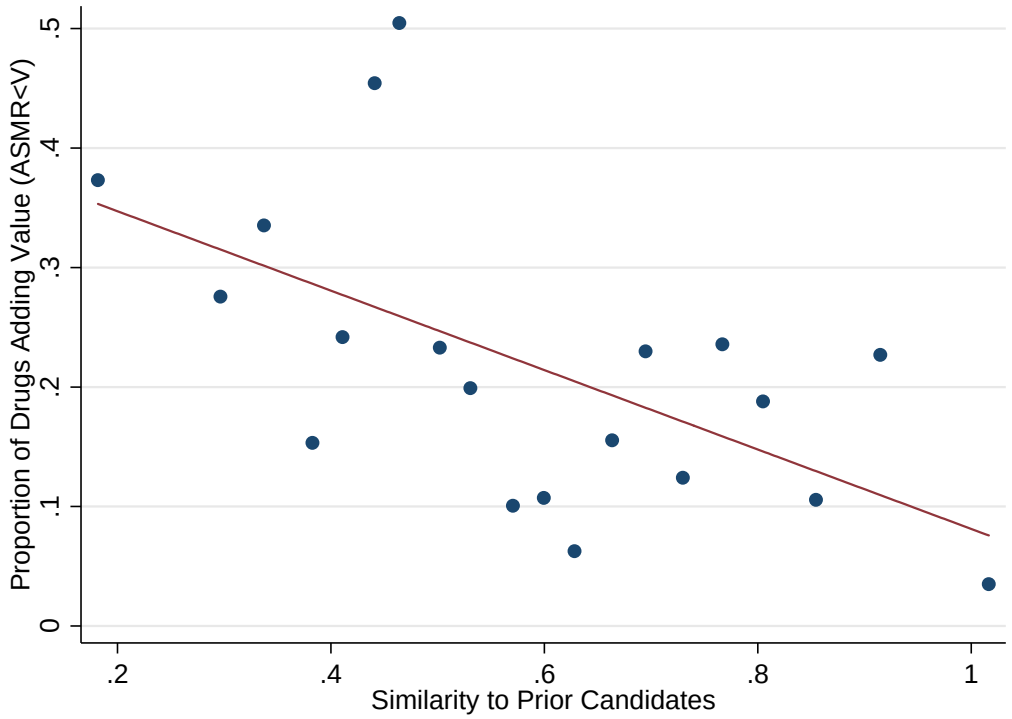
Notes: Figure A.14 presents a binned scatterplot of drug-level similarity against revenue conditional on approval. The plot corresponds to the regression in Column (4) of Table A.23, which includes controls for drug indication, drug age, and firm dummies.

Figure A.15: Drug Similarity and Stock Market reaction on FDA Approval



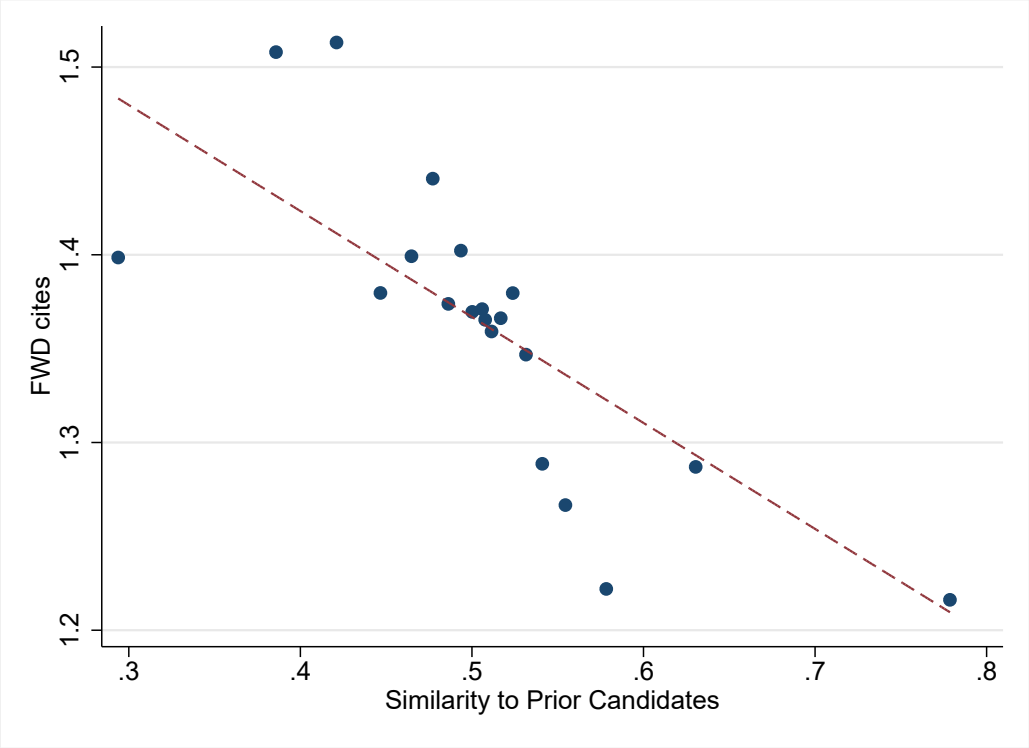
Notes: Figure A.15 presents a binned scatterplot of drug-level similarity against the logarithm of the estimated dollar reaction on the (first) approval of the drug by the FDA. The dollar reaction to the FDA approval is estimated following the methodology of Kogan et al. (2017) and uses a 5-day window 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.24. We adjust our estimates for differences in the ex-ante probability of approval using the point estimates of Column (9) of Table A.5.

Figure A.16: Drug Similarity and Drug Effectiveness



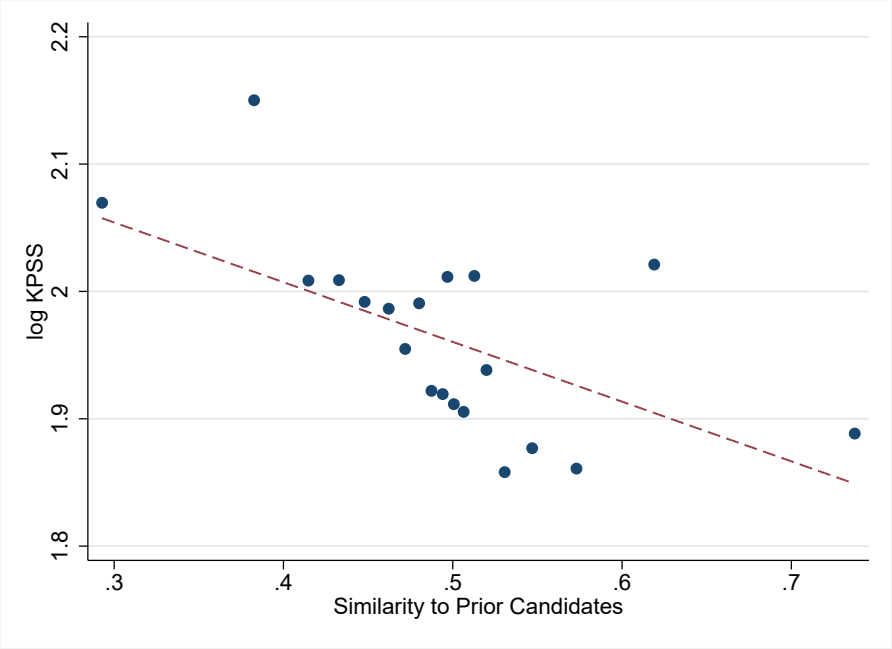
Notes: Figure A.16 presents a binned scatterplot of drug-level similarity against drug added benefits. A drug's added benefit is derived from the from the French Haute Autorité de Santé (HAS) health system's clinical added benefits scores (Amélioration du Service Medical Rendu, or ASMR), which range 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.17: Drug Similarity and Patent Citations



Notes: Figure A.17 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.7. Please see Table A.7 for additional specifications.

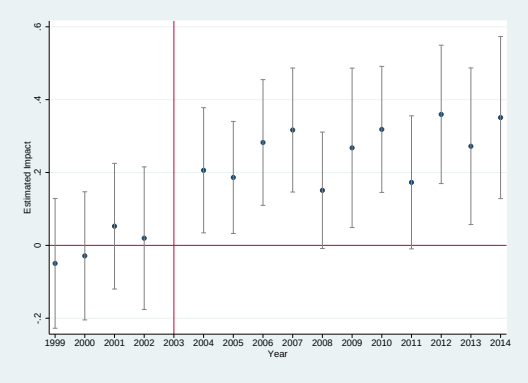
Figure A.18: Drug Similarity and Market Value of Patents



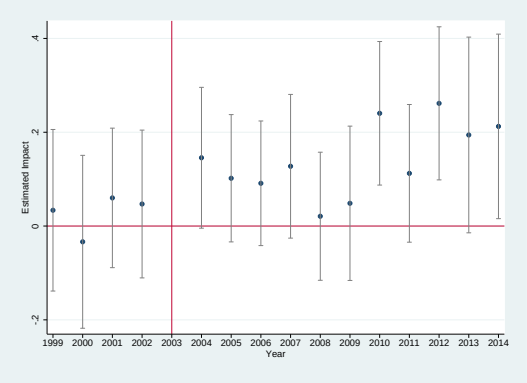
Notes: Figure A.18 presents a binned scatterplot of drug-level similarity against the logarithm of the Kogan et al. (2017) estimated patent values. Each dot represents mean log value, among all candidates within a given similarity score bin, conditional on disease (ICD9); patent issue year; firm and year of development fixed effects. This specification corresponds to Column (4) of Table A.6. Please see Table A.6 for additional specifications.

Figure A.19: Event Studies: # of New Candidates, by Stages of Development

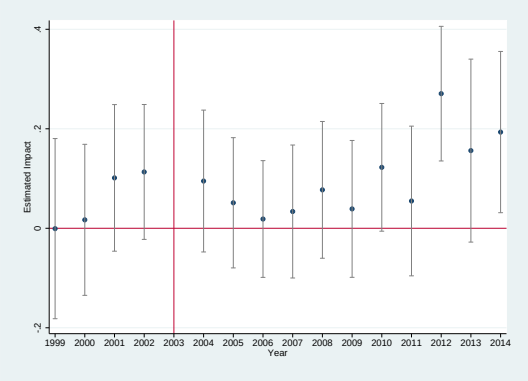
(a) Pre-clinical Development



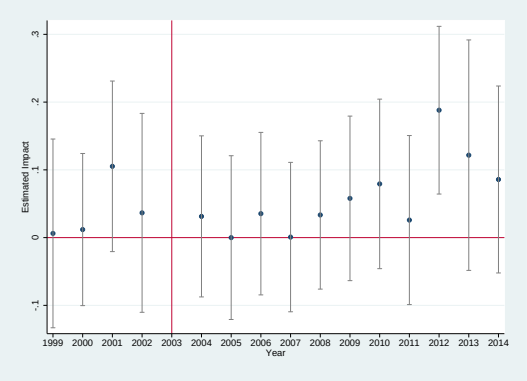
(b) Phase 1



(c) Phase 2

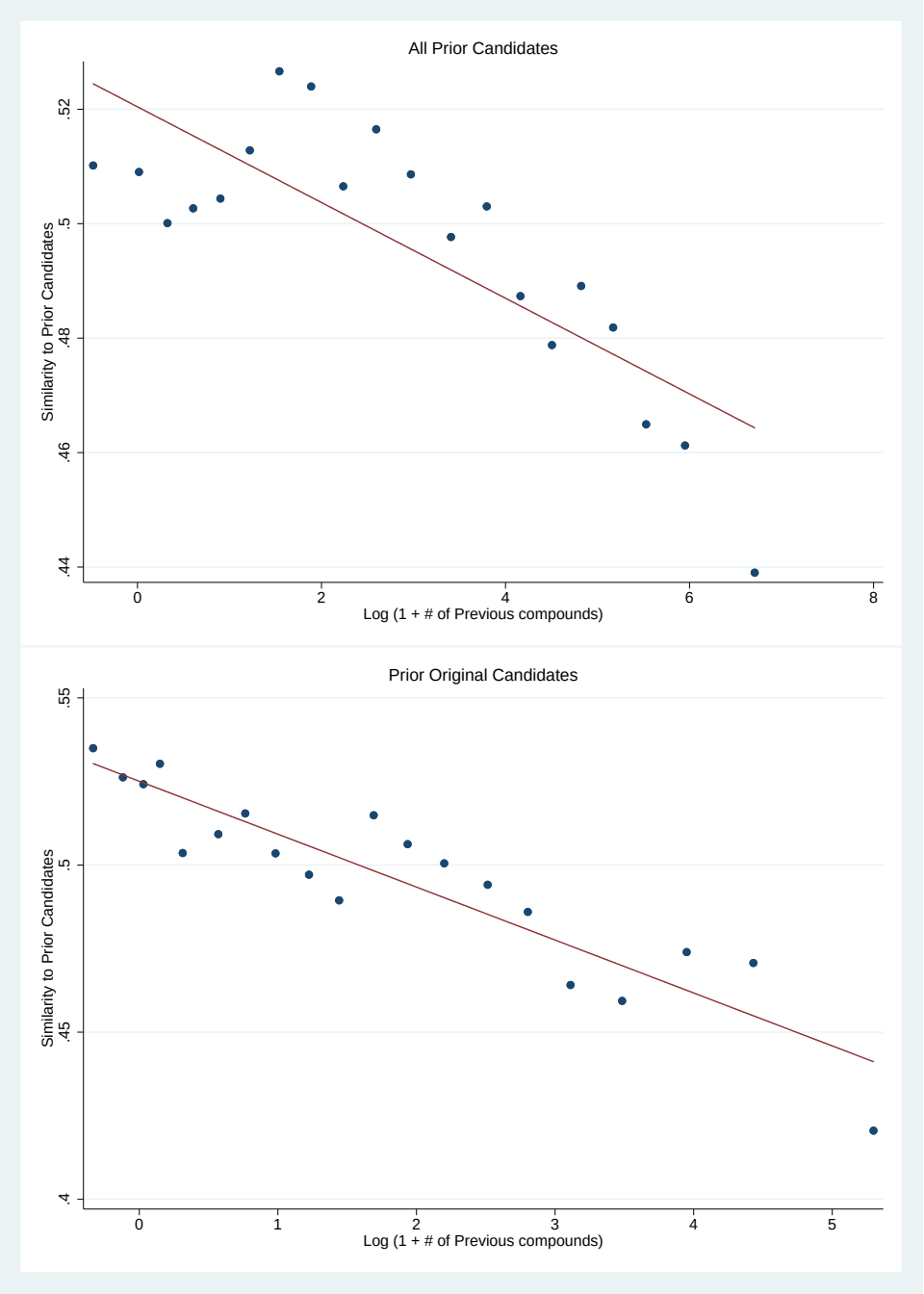


(d) Phase 3



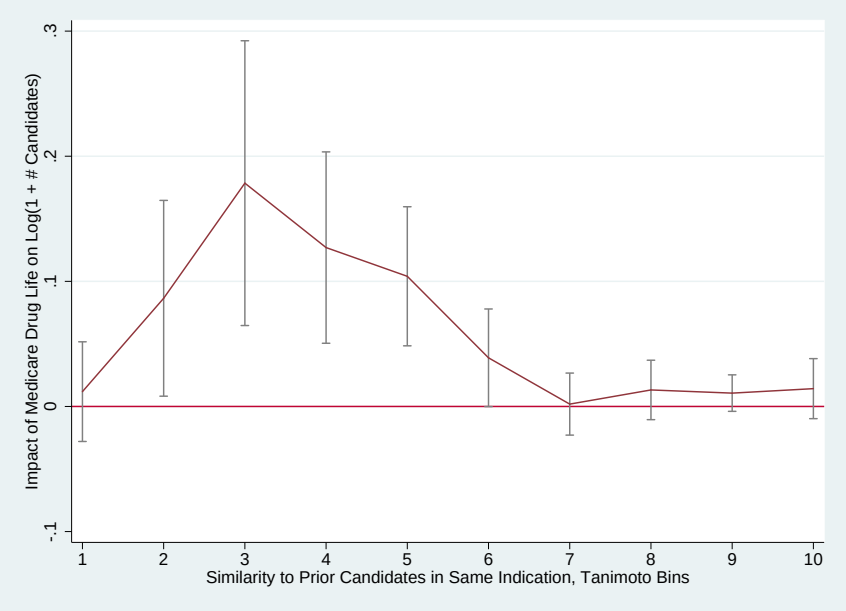
Notes: Figure A.19 reports event studies for number of novel drugs. Our outcome variables are the number of new candidates in different stages of development for each quarter. Each dot represents the coefficient on Medicare Drug Life$_{f,2003}$ interacted with an indicator variable for that given year. 2003 is the omitted year, and 90th percentile confidence intervals are reported.

Figure A.20: Firm Experience, by Drug Similarity



Notes: Figure A.20 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.21: Impact of Additional Resources on Novelty, within Indication



Notes: Figure A.21 plots the estimated coefficients on Post × Medicare Drug Life$_{f,2003}$ from our main regression specification defined by Equation (3). This figure is analogous to the bottom panel of Figure 5 of the main text, except that similarity is measured with respect to other drugs in the same indication (disease).

Table A.1: Drug Candidates Summary Statistics

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

Notes: Table A.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 A.2: Firm–Quarter Summary Statistics

	Mean	p10	p25	p50	p75	p90
Firm-Quarter Output						
# 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
Firm Characterisitics (2003)						
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 A.2 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 A.3: Drivers of Pairwise Drug Similarity

	Drug Candidate Pairwise Similarity			
	Mean = 0.106			
	(1)	(2)	(3)	(4)
Share Target-Action	0.167***	0.122***		
Mean: 0.022	*(6.24e-05)*	*(0.00838)*		
Share Indication			0.0102***	0.0285***
Mean: 0.149			*(8.51e-06)*	*(0.00200)*
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.3 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.4: Proportion First in Target, by Drug Similarity

	First in Narrow Target		**First in Broad Target**	
	Mean: 0.194		*Mean: 0.068*	
	(1)	(2)	(3)	(4)
Similarity Measure	-0.210***	-0.175***	-0.144***	-0.141***
	(0.0148)	*(0.0153)*	*(0.00858)*	*(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.4 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.5: Proportion FDA Approved, by Drug Similarity

	All			Phase 1		Phase 2		Phase 3	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Maximum Similarity	0.269***	0.227***	0.208***	0.300***	0.254***	0.312***	0.249***	0.271***	0.123
	(0.033)	(0.031)	(0.040)	(0.045)	(0.060)	(0.051)	(0.071)	(0.073)	(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.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 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.1. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table A.6: Patent market value and Drug Similarity

log(KPSS value)	US patents			
	(1)	(2)	(3)	(4)
Maximum Similarity	-1.428***	-1.662***	-1.618***	-0.469**
	(0.447)	(0.386)	(0.361)	(0.196)
N	5130	5130	5090	5031
R^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.6 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.18. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table A.7: Patent citations and Drug Similarity

log(1 + citations)	A. All patents			
	(1)	(2)	(3)	(4)
Maximum Similarity	-0.022	-0.160*	-0.130*	-0.173**
	(0.081)	(0.084)	(0.078)	(0.078)
N	119080	119080	119069	118765
R^2	0.268	0.287	0.301	0.404
log(1 + citations)	B. US patents only			
	(1)	(2)	(3)	(4)
Maximum Similarity	0.213	0.011	-0.002	-0.565***
	(0.154)	(0.148)	(0.136)	(0.196)
N	11,557	11,557	11,536	11,324
R^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.7 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.17. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table A.8: Size and Length of Clinical Trials versus Drug Novelty

	# Patients		Average Length	
	(1)	(2)	(3)	(4)
	P2	P3	P2	P3
Maximum Similarity	-0.024	-0.360	0.201	0.573
	(0.300)	(0.509)	(0.154)	(0.468)
R^2	0.854	0.944	0.899	0.976
Company FEs	Yes	Yes	Yes	Yes
ICD9 X Qtr of Development FEs	Yes	Yes	Yes	Yes
Observations	9275	4267	8637	1524

Notes: This table relates drug-level similarity proxies of clinical development costs: number of patients and average length of trials. We have data on larger Phase 2 and Phase 3 trials (Phase 1 data is less reliable).

Table A.9: Pharmaceutical firms: Leverage and Dividend Payout

	A. Leverage (debt-to-assets)			B. Cash Dividends (1/0 dummy)			C. Share Repurchases (1/0 dummy)		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Pharmaceutical	-0.067	-0.176**	-0.403***	-0.247***	-0.127***	-0.133***	-0.140***	-0.116***	-0.111***
	(-1.84)	(-3.21)	(-4.60)	(-13.04)	(-9.49)	(-9.73)	(-14.41)	(-14.40)	(-13.76)
Size, log		-0.076***	0.034***		0.083***	0.086***		0.017***	0.014***
		(-3.86)	(6.22)		(32.92)	(32.51)		(7.56)	(5.83)
Profitability (ROA)			-0.831***			-0.020***			0.019***
			(-5.51)			(-5.96)			(5.59)
N	425028	425028	425028	425028	425028	425028	425028	425028	425028
R^2	0.000	0.001	0.006	0.095	0.292	0.293	0.023	0.033	0.034

Notes: Table A.9 compares leverage ratios and payout propensity between pharmaceutical firms (SIC 3-digit code of 283) and other publicly traded firms in Compustat. Firm size is book assets (Compustat: at); profitability is income before extraordinary items (Compustat: ib) plus depreciation (Compustat: dp) over book assets. In Panel A, the dependent variable is book leverage (Compustat: dltt divided by at); Panel B the dependent variable is the propensity to pay cash dividends (a dummy taking the value of 1 if Compustat: dv is positive); in Panel C the dependent variable is a dummy taking the value 1 if firms repurchase shares (the sum of the change in common equity (Compustat: ceq) plus the change in deferred taxes (Compustat: txdb) minus retained earnings (Compustat: re) is negative. All specifications include year fixed effects. We report t-statistics in parentheses, with standard errors clustered by firm and year. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table A.10: 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**	0.106**	0.093**	0.118**	0.028*
	(0.098)	(0.054)	(0.046)	(0.052)	(0.037)
Post 2003 X Overall Drug Life	-0.214**	-0.101*	-0.075*	-0.090*	-0.030*
	(0.098)	(0.053)	(0.047)	(0.052)	(0.037)
Post 2003 X Firm MMS	-0.056*	-0.020*	-0.022*	-0.015*	-0.016*
	(0.042)	(0.022)	(0.017)	(0.020)	(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**	0.107*	0.111**	0.129**	0.048
	(0.103)	(0.056)	(0.048)	(0.059)	(0.040)
Post 2003 X Overall Drug Life	-0.218**	-0.110**	-0.092*	-0.103*	-0.039
	(0.105)	(0.055)	(0.049)	(0.061)	(0.041)
Post 2003 X Firm MMS	-0.052	-0.021	-0.020	-0.013	-0.014
	(0.043)	(0.022)	(0.016)	(0.020)	(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.10 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.11: 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*	0.116**	0.095*	0.074	0.010
	(0.099)	(0.057)	(0.049)	(0.050)	(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.11 shows that our results are not driven by company-specific trends. The table reports the main specification coefficient for Post × 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 Post × Overall Drug Life$_{f,2003}$ and Post × 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.12: 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**	0.830	0.962**	0.693	0.631
	(0.389)	(0.593)	(0.445)	(0.514)	(0.577)
Post 2003 X Overall Drug Life	-0.397	-0.592	-0.312	0.208	-0.607
	(0.429)	(0.614)	(0.513)	(0.547)	(0.659)
Post 2003 X Firm MMS	-0.495	-0.147	-0.592	-0.125	-0.622
	(0.354)	(0.477)	(0.462)	(0.428)	(0.591)
R^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.12 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 candiates, 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 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. 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.13: 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	0.167***	0.111***	0.079**	0.084**	0.065**
Medicare Drug Life	(0.059)	(0.040)	(0.035)	(0.035)	(0.028)
Post 2003 X Overall Drug	-0.138**	-0.104**	-0.060*	-0.054	-0.062**
Life	(0.063)	(0.041)	(0.035)	(0.036)	(0.030)
Post 2003 X Firm MMS	-0.048	-0.014	-0.019	-0.014	-0.012
	(0.042)	(0.022)	(0.018)	(0.020)	(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.13 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.14: 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**	0.130*	0.098*	0.143**	0.110*
	(0.141)	(0.077)	(0.063)	(0.068)	(0.056)
Post 2003 X Overall Drug Life	0.111*	0.043*	0.035*	0.134*	0.077*
	(0.166)	(0.085)	(0.084)	(0.080)	(0.067)
Post 2003 X Firm MMS	-0.179*	-0.143*	-0.061*	-0.089*	0.048*
	(0.167)	(0.088)	(0.088)	(0.082)	(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.14 shows that our results are robust to excluding firms with extreme values of Medicare exposure of 0 or 1. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table A.15: New Investments by Stage, Company Quarter

A) Most Novel

	Log(1 + New Candidates), Most Novel, by Stage			
	Pre-Clinical	Phase 1	Phase 2	Phase 3
Post 2003 X Medicare Drug Life	0.134**	0.046*	0.028	0.025
	(0.053)	(0.025)	(0.021)	(0.016)
R^2	0.394	0.250	0.196	0.108
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) Least Novel

	Log(1 + New Candidates), Least Novel, by Stage			
	Pre-Clinical	Phase 1	Phase 2	Phase 3
Post 2003 X Medicare Drug Life	0.054	0.029	0.008	0.009
	(0.035)	(0.027)	(0.024)	(0.019)
R^2	0.300	0.252	0.232	0.189
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 /refstagesbynovelty shows the impact of the Medicare Drug Life shock on number of new drugs, by phase of development. We report the main specification coefficient for Post $\times$ Medicare Drug Life$_{f,2003}$. 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. Panel A restricts the outcome to the most novel (top quartile) drugs, while Panel B reports the results for the least novel (bottom quartile) drugs. Robust standard errors in parentheses, clustered around company identifiers. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table A.16: Effect of Cashflows on Number of Drug Candidates, by Firm Cash Holdings in 2002

(a) Firms above the median in terms of Cash-to-Assets

	Log(1 + New Candidates), by Similarity Decile			
	1	2	3	4
Post 2003 X Medicare Drug Life	-0.044	-0.001	-0.096	-0.018
	(0.115)	(0.073)	(0.106)	(0.091)
R^2	0.302	0.388	0.293	0.238
Company FEs	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes	Yes
Observations	3391	3391	3391	3391

(b) Firms below the median in terms of Cash-to-Assets

	Log(1 + New Candidates), by Similarity Decile			
	1	2	3	4
Post 2003 X Medicare Drug Life	0.381*	0.436***	0.339**	0.175*
	(0.211)	(0.143)	(0.140)	(0.103)
R^2	0.489	0.549	0.485	0.397
Company FEs	Yes	Yes	Yes	Yes
Qtr of Development FEs	Yes	Yes	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes	Yes	Yes
Observations	3515	3515	3515	3515

Notes: Table A.16 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 × Medicare Drug $\text{Life}_{f,2003}$. 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 adolescants and young adults. All models include a full set of company and quarter indicator variables, with Post × Overall $\text{Drug Life}_{f,2003}$ and Post × $\text{Firm MMS}_{f,2003}$ 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.17: Effect of Cashflows on Number of Drug Candidates, by Firm Revenues

	Log(1 + New Candidates), by Size		
	(1) All	(2) Top 50	(3) Bottom 50
Post 2003 X Medicare Drug Life	0.263***	0.299	0.192*
	(0.096)	(0.214)	(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 A.17 examines how the treatment effect of cashflows on number of developed drugs varies by firm size—that is, 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 × Medicare Drug $\text{Life}_{f,2003}$. We estimate the model with the full set of company and quarter indicator variables, including Post × Overall Drug $\text{Life}_{f,2003}$ and Post × Firm $\text{MMS}_{f,2003}$, 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 A.18: 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*	0.084*	0.051	0.026	0.091**	0.050*	0.055	0.049*	0.014	0.009
	(0.027)	(0.043)	(0.035)	(0.034)	(0.037)	(0.026)	(0.036)	(0.028)	(0.025)	(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	0.011	-0.007	0.000	0.001	-0.005	0.050***	0.003	0.003	0.016**
	(0.017)	(0.010)	(0.008)	(0.002)	(0.002)	(0.006)	(0.017)	(0.004)	(0.005)	(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.18 reports the main specification coefficient for Post × 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 bottome three quartiles of firm experience. All models include a full set of company and quarter indicator variables, with Post × Overall Drug Life$_{f,2003}$ and Post × 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.19: In-House vs. Acquired Drug Candidates

	(1) All	(2) In House	(3) Acquired
Post 2003 X Medicare Drug Life	0.263***	0.223**	0.094*
	(0.096)	(0.086)	(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.19 reports the main specification coefficient for Post $\times$ Medicare Drug Life$_{f,2003}$. Model 1 repeats the result from our main regression specification (Column 6 of table 3). 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 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 A.20: New Biologics

	Log(1 + New Biologics)		
	(1)	(2)	(3)
	All	Past Exp.	No Past Exp.
Post 2003 X Medicare Drug Life	0.045	0.352**	0.007
	(0.048)	(0.152)	(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.20 reports the main specification coefficient for Post × 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 Post × Overall Drug Life$_{f,2003}$ and Post × 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.21: New Targets

	Log(1 + New Targets)			
	(1)	(2)	(3)	(4)
	All Drugs New Target-Action	All Drugs Coarse Target (6-level)	Biologics New Target-Action	Biologics Coarse Target (6-level)
Post 2003 X Medicare Drug Life	0.028*	0.025*	0.002**	0.002**
	(0.017)	(0.014)	(0.001)	(0.001)
R^2	0.217	0.162	0.052	0.026
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.21 reports the main specification coefficient for Post × Medicare Drug Life$_{f,2003}$. The dependent variables in Columns 1 and 2 count all new drugs, including both small molecules and biologic drugs. Columns 3 and 4 display the results for the subset of biologic drugs only. The dependent variable in Columns 1 and 3 is the log of one plus the number of drugs that the focal firm developed (in the given quarter) using 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 3 and 4 use coarser definitions of targets, based on the Cortellis target tree ontology. The "coarse" definition of targets 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. All models include a full set of company and quarter indicator variables, with Post × Overall Drug Life$_{f,2003}$ and Post × 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.22: Drug candidates are patented prior to pre-clinical testing

	Quarters between testing date and patent priority date				
	% > 0	Mean	25th	50th	75th
Pre-clinical	93.90	34.22	13	29	53

Notes: This table shows the lag between a drug candidate's earlier date of preclinical development in the United States and the earliest date of USPTO patent priority.

Table A.23: Revenue, by Drug Similarity

	Log(Annual US Revenue)			
	(1)	(2)	(3)	(4)
Maximum Similarity	-1.449***	-1.307***	-1.253***	-0.641*
	(0.280)	(0.286)	(0.297)	(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.23 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 (ICD9); drug cohort (the year the drug is launched); and firm. We cluster the standard errors clustered at the calendar year and ICD9 level. The accompanying binned scatterplot of results is shown in Figure A.14. $^{*}p < 0.10,^{**} p < 0.05,^{***} p < 0.01$.

Table A.24: Market reaction to FDA approval, by Drug Similarity

	(1)	(2)	(3)
Maximum Similarity	-1.321***	-2.191***	-1.100***
	(0.453)	(0.592)	(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.24 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.15. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table A.25: Drug Novelty and Drug Effectiveness

	(1) Any Value Added	(2) Any Value Added	(3) High Importance	(4) High Importance	(5) ASMR Value	(6) ASMR Value
	ASMR<V	ASMR<V	ASMR<IV	ASMR<IV		
Maximum Similarity	-0.343***	-0.263***	-0.100**	-0.064	0.347***	0.208**
	(0.058)	(0.053)	(0.045)	(0.041)	(0.122)	(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.25 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 recieved 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.16. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table A.26: Firm Experience, by Drug Similarity

	Maximum Similarity					
	(1)	(2)	(3)	(4)	(5)	(6)
Log(1 + All Prior Candidates)	-0.007***	-0.007***	0.005			
	(0.002)	(0.002)	(0.011)			
Log(1 + Prior Original Candidates)				-0.014***	-0.012***	-0.004**
				(0.002)	(0.002)	(0.002)
R^2	0.070	0.156	0.419	0.065	0.161	0.400
Qtr of Development FEs	Yes	Yes	Yes	Yes	Yes	Yes
ICD-9 FEs		Yes	Yes		Yes	Yes
Company FEs			Yes			Yes
Observations	28521	28486	27886	21220	21182	20820

Notes: Table A.26 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.20. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.

Table A.27: 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	0.074**	0.046*	0.042	0.064**	0.048**	0.053**	0.035**	0.011	0.005
	(0.015)	(0.030)	(0.023)	(0.027)	(0.028)	(0.020)	(0.025)	(0.018)	(0.017)	(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**	0.016	0.012	-0.010	0.019	0.007	0.013	0.019	0.005	0.005
	(0.014)	(0.013)	(0.018)	(0.015)	(0.012)	(0.009)	(0.012)	(0.013)	(0.012)	(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.27 reports the main specification coefficient for Post × 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 Post × Overall Drug Life$_{f,2003}$ and Post × 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.28: 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	0.000	0.054**	0.134**	0.123***	0.059**	0.028	0.010	0.012	0.008
	(0.003)	(0.005)	(0.022)	(0.058)	(0.044)	(0.028)	(0.020)	(0.016)	(0.011)	(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**	0.084**	0.053*	0.029	0.083***	0.051**	0.064**	0.052**	0.017	0.009
	(0.023)	(0.035)	(0.029)	(0.028)	(0.031)	(0.022)	(0.029)	(0.024)	(0.020)	(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.28 reports the main specification coefficient for Post × 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 to 0.6). In Panel B, the dependent variable is split into bins that represent new drugs' deciles of maximum similarity score. All models include a full set of company and quarter indicator variables, with Post × Overall Drug Life$_{f,2003}$ and Post × 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.29: 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	0.050	0.089**	0.072*	0.094**	0.080**	0.092***	0.069**	0.103***	0.056*	0.030
Life	(0.036)	(0.044)	(0.040)	(0.041)	(0.038)	(0.030)	(0.033)	(0.034)	(0.032)	(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.29 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 Post $\times$ 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.30: 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**	0.130***	0.113**	0.108**	0.068*
	(0.078)	(0.048)	(0.048)	(0.053)	(0.037)
Post 2003 X Overall Drug Life	-0.166**	-0.123**	-0.091*	-0.070*	-0.063*
	(0.078)	(0.049)	(0.048)	(0.055)	(0.039)
Post 2003 X Firm MMS	-0.046*	-0.015*	-0.018*	-0.010*	-0.011*
	(0.040)	(0.023)	(0.018)	(0.023)	(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.30 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.31: 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***	0.119***	0.105***	0.111***	0.038**
	(0.035)	(0.021)	(0.019)	(0.019)	(0.019)
Post 2003 X Log(1 + Total Patent Life)	-0.085***	-0.066***	-0.051***	-0.048***	-0.021**
	(0.014)	(0.010)	(0.010)	(0.009)	(0.008)
Post 2003 X Firm MMS	-0.036	-0.004	-0.011	-0.006	-0.010
	(0.039)	(0.020)	(0.016)	(0.019)	(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.31 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 Medicare Part D by scale of firm more directly than controlling for the proportion of drugs with patent life remaining. $^{*}p < 0.10,^{**}p < 0.05,^{***}p < 0.01$.