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# Missing Novelty in Drug Development*

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We provide evidence that risk aversion leads pharmaceutical firms to underinvest in radical innovation. We introduce a new measure of drug novelty based on chemical similarity and show that firms face a risk-reward trade-off: novel drug candidates are less likely to obtain FDA approval but are based on more valuable patents. Consistent with a simple model of costly external finance, we show that a positive shock to firms' net worth leads firms to develop more novel drugs. This suggests that even large firms may behave as though they are risk averse, reducing their willingness to investment in potentially valuable radical innovation. (*JEL* G31, G32, O31, O32, I1)

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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 (R&D) are characterized by considerable uncertainty. As a result, the forces that limit firms' willingness to take risks may lead them to forgo innovative

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investments and focus instead on safer but more marginal projects.[1] Our goal in this paper is to understand the extent to which firms' risk aversion limits their investment in innovative projects. To do so, we focus on the pharmaceutical industry, an important setting in which these frictions are likely to be particularly salient.

Using detailed data on firms' drug development decisions, we provide evidence suggesting that risk aversion keeps even large firms from investing in 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 trade-off when considering investments in novelty: novel drug candidates are less likely to be approved by the U.S. Food and Drug Administration (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 cash flows. A positive cash flow 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 pairwise chemical similarity to prior drug candidates using a metric known as a "Tanimoto score" or "Jaccard coefficient." Tanimoto scores are designed to

[1] This intuition goes back to at least Arrow (1962), who writes "any unwillingness or inability (by firms) to bear risks will give rise to a nonoptimal allocation of resources, in that there will be discrimination against risky enterprises as compared with the optimum." Agency frictions may lead firms to discriminate against risky projects for several reasons, even if risks are diversifiable. For instance, modern finance theory posits that agency frictions may lead firms to exhibit risk-averse behavior. In the classic model of Froot, Scharfstein, and Stein (1993), firms invest conservatively to avoid states of the world in which they need to raise costly external funds; agency frictions between investors and managers makes external finance costly (Myers and Majluf 1984). More recently, dynamic agency models make a similar prediction: managers invest conservatively to avoid dismissal if their investments perform poorly (DeMarzo et al. 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 about the innovativeness of the pharmaceutical industry: Dr. Marcia Angell (2010), 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 variations of top-selling drugs already on the market, sometimes called "me-too" drugs.

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% of newly developed candidates have a maximum similarity score of over 0.8, meaning that they share more than 80% of their chemical substructures with a previously developed candidate. For example, Mevacor and Zocor, two very similar statins, share an 82% 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% 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 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 net present value (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, and the value a firm may derive from a failed candidate due to learning-by-doing.

Our findings suggest that novel drugs are higher NPV investments than are 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 et al. 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% increase in the estimated value of associated patents and an 8%–18% 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 outsiders; 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 cash flow risk leads firms to favor more conservative development strategies by underinvesting in riskier projects, even if the underlying cash flows can be diversified away by investors. In the model, a positive shock to net worth (either current or expected cash flows) 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 1 in 10 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% increase, correcting for inflation, over the estimate the center made in 2003 (DiMasi, Grabowski, and Hansen 2016). Pharmaceutical firms have significantly lower leverage and are less likely to pay out to investors than the average firm in Compustat (see the Internet 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 more valuable. In the Internet Appendix (Section 4), we provide an example of such a model in which novel drugs are "missing" because concerns about managing cash flow risk discourage firms from investing in novel candidates.

The second part of this paper explores this idea by examining how cash flow shocks affect firms' development decisions.[5] We construct shocks to firm net worth using the introduction of Medicare Part D, which expanded U.S. 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 preexisting 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 novel drugs, not because they are responsive to cash flows, but because they may see an opportunity for 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 cash flows. 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 cash flow 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 cash flow shock are on average more valuable. These findings are consistent with a model in which risk management considerations lead firms to underinvest in riskier (novel) drug candidates, relative to the frictionless benchmark.

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[5] Anecdotal evidence indeed suggests pharmaceutical firms fund innovation from internal cash. One notable example is AbbVie, a large publicly traded firm that 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 per 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 (Carroll 2014; Reuters 2017). 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.

[6] Our primary analysis tackles 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).

A key assumption in our identification strategy is that we are able to isolate a cash flow 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 observe 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 treat 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 cash flows. 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 cash flow shock even among publicly traded firms, which suggests that the prospect of facing R&D failure and uncertain cash flows 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, a voluminous literature studies the impact of financing frictions on the level of physical investment (for instance, Lin and Paravisini 2013; Almeida et al. 2011; Frydman, Hilt, and Zhou 2015); hiring decisions (Chodorow-Reich 2014; Duygan-Bump et al. 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 cash flows 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 that used in most of the literature, our data allow 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 Blanchardde, 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 cash-flow-investment relation exists in our setting. Our view is that a positive cash flow 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 cash flow 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 alternative set of policies that can incentivize radical innovation without a significant transfer of liquidity, for instance, by improving the relative risk-return trade-off 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, Garthwaite, and Hermosilla (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 cash flow shocks on firm-level investment decisions; that is, we isolate a cash flow 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 cash flow 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, Garthwaite, and Hermosilla 2014). Similarly, crediting drugs as novel if they are the first to treat a particular indication ignores innovation in common disease categories for which treatments already exist (see, e.g., DiMasi and Paquette 2004; Dranove, Garthwaite, and Hermosilla 2014; DiMasi and Faden 2010; Lanthier et al. 2013). By contrast, 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 tend 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 that 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 data set 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, because 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 preclinical drugs as most of these will be patented, but may miss early-stage preclinical 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).

### 1.2 Similarity based on chemical structure

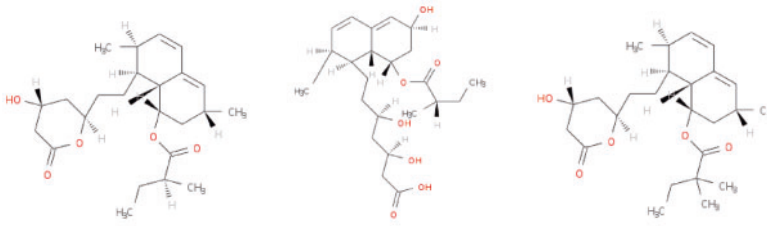
The first step in measuring novelty requires us to estimate the similarity of two molecules. We follow the chemical informatics literature and measure similarity using the Tanimoto distance (Jaccard coefficient) between two sets of chemical fragments (Nikolova and Jaworska 2004),

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

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

[7] In our sample, we see the number of reported molecules sharply increase 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 provide fuller coverage post-1999.

[8] Section 2.2 provides more detail about the construction of similarity scores using the simplified molecular-input line-entry system (SMILES) and ChemMine Tools.



Mevacor
(Similarity Score=0.25)

Pravachol
(Similarity Score =0.61)

Zocor
(Similarity Score =0.82)

**Figure 1**
**Example of Tanimoto Similarity: Statins**
This figure visualizes the molecular structure and lists the 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 FDA-approved statin (approved in October 1991); its pairwise similarity to Mevacor is 0.61, and its overall maximum similarity is also 0.61. Finally, Zocor (Simvastatin) is the third FDA-approved statin (approved in December 1991); its pairwise similarity to Mevacor is 0.82, and its pairwise similarity to Pravachol is 0.52. Zocor's overall maximum similarity to prior molecules is 0.82.

distance of zero implies that the pair of drugs have no common fragments; a score of one means they have the same set of atoms and bonding. However, a Tanimoto score of one 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 pairwise 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.

[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 one.

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).

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 bimodal; 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, a second peak is close to one (zero novelty). Approximately 10% of our sample candidates share the same structure as a prior candidate that has also entered development. These include molecules that are stereoisomers, meaning that they differ only in orientation, as well as combination therapies that involve multiple compounds that were previously developed as separate therapies. Table A.1 in the Internet Appendix provides more details on the underlying distribution of novelty across phases of development.

### 1.3 Which firms develop more novel drugs?

Next, we 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 or not the firm is publicly listed (can be matched to Compustat). 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 the firm has at a given point in time. The advantage of this measure is that, unlike sales revenue, it 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% of new drug candidates being developed are novel. By contrast, over 55% 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:

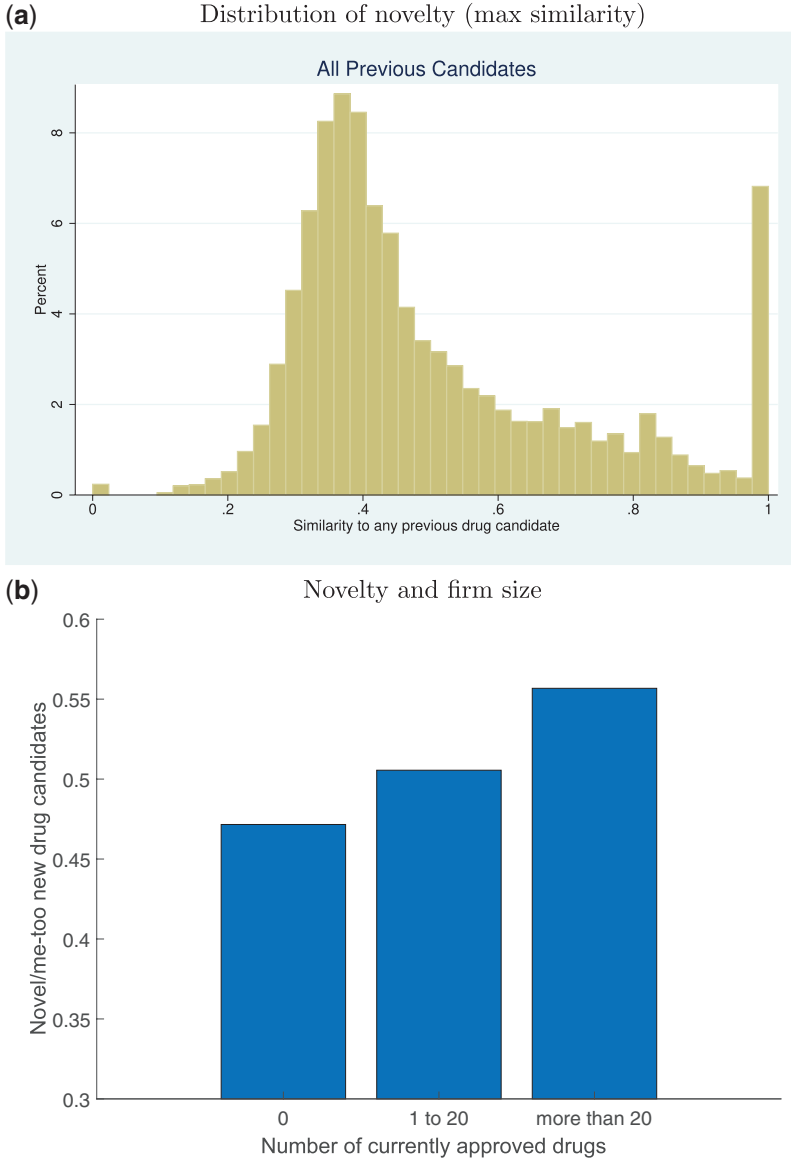



**Figure 2**
**Drug novelty, descriptive statistics**
This figure displays descriptive statistics for our novelty measure. Panel A displays the distribution of our drug similarity measure. A drug's similarity is measured as its similarity to the most similar drug candidate that had previously entered 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).

**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) |
| $R^2$ | .061 | .143 | .043 | .135 | .065 | .146 | .084 | .159 | .071 | .149 | .091 | .166 |
| Observations | 41,055 | 41,027 | 18,691 | 18,642 | 41,055 | 41,027 | 16,264 | 16,197 | 5,701 | 5,628 | 16,264 | 16,197 |
| Fixed effects | | | | | | | | | | | | |
| Dev. qtr. | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| ICD-9 | | Yes | | Yes | | Yes | | Yes | | Yes | | Yes |

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. $^{*}p < .10$; $^{**}p < .05$; $^{***}p < .01$.

a one-standard-deviation increase in (log) firm revenue is associated with a 0.1- to 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- to 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 Internet Appendix Section 1.4 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 cash flow 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 cash flows. Larger firms have higher net worth and are therefore better able to weather adverse development outcomes than small firms; having a safety net allows 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 toward developing more novel drugs. The rest of the section tests this prediction using an exogenous shock to firm cash flows exploiting the passage of Medicare Part D in 2003.

### 1.4 Validation and caveats

Several important caveats should be kept in mind about 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, comprises two mirror-image molecules, one that is a safe sedative and the other that 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. Table A.3 in the Internet Appendix shows that pairs of drugs that 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%. Figure 3 further shows 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%.[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 zero, 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) that cannot be compared with Tanimoto scores. Although biologics make up for only 20% of drug development, their share is increasing, and they are often considered to be a source of innovation in the drug industry (Otto, Santagostino, and Schrader 2014). In Section 3.7, we show that a positive cash flow shock also leads to greater development of biologics.

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

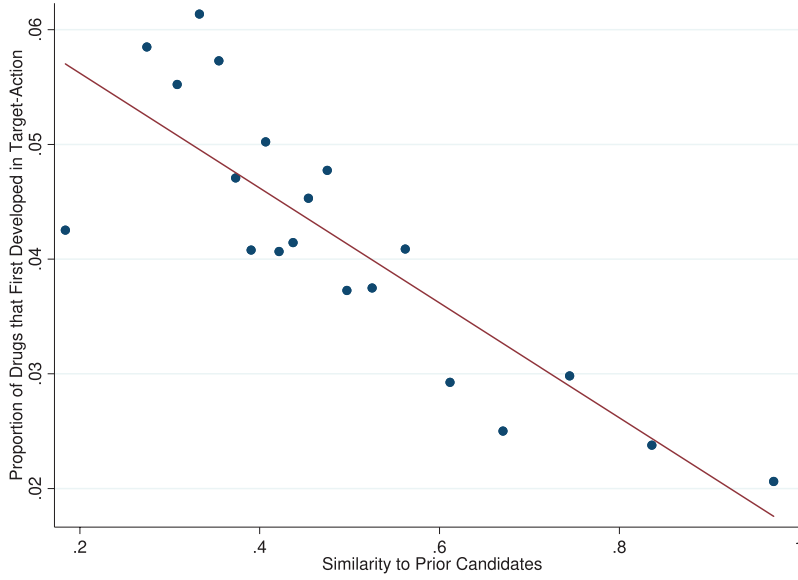



**Figure 3**
**Proportion first-in-target, by drug similarity**
Figure 3 presents a binned scatterplot of drug-level similarity against whether a drug is the first developed in its target action. Each dot represents the proportion of candidates that are the first to be developed in their target action,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

## 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 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 preclinical 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

**Table 2**
**Drug novelty, risk, and expected return: Summary table**

| | Risk | Measures of Expected Value | |
|---|---|---|---|
| | Likelihood of FDA approval (1) | Patent value (2) | Patent citations (3) |
| Maximum similarity | 0.208*** | −0.469** | −0.173*** |
| | (0.025) | (0.196) | (0.078) |
| Observations | 19,127 | 5,031 | 116,611 |
| Internet Appendix Table/column | A.5.(3) | A.6.(4) | A.7.(4) |

This table 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 by drug revenues, by 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 Internet Appendix tables referenced in this summary table (along with the relevant columns). For brevity, we report the coefficients for 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 legend to the relevant Internet Appendix tables for more details. * $p < .10$;** $p < .05$;*** $p < .01$.

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 ($\text{Outcome}_i$) 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 and report results separately conditioning on different stages in development. We will estimate versions of Equation (3) for a variety of other outcomes, which will be 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 $-0.21 \times 0.208 = 4.4$-percentage-point decrease in the likelihood of FDA approval. Given that the unconditional likelihood of FDA approval for candidates in our data is 18%, this estimate represents a 24% 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 Internet 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

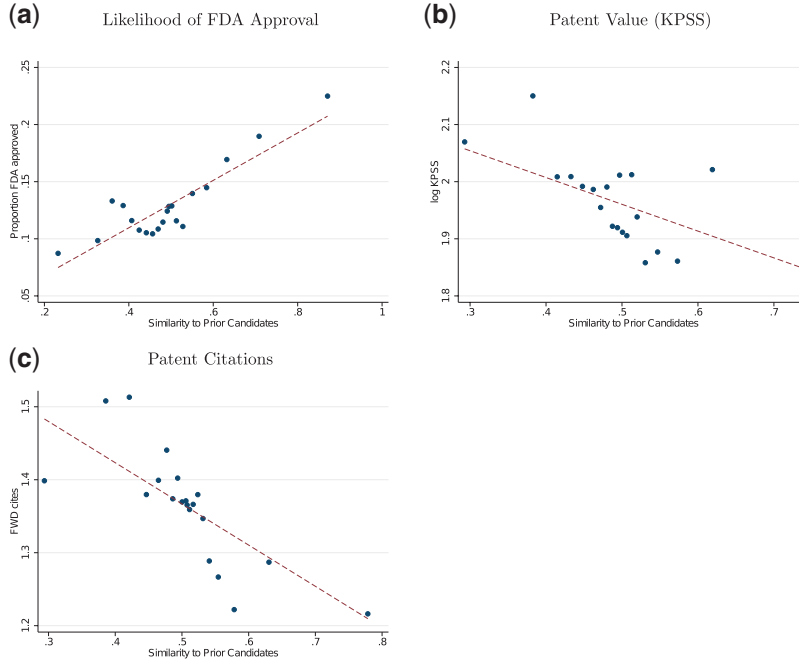



**Figure 4**
**Drug novelty: Risk and expected return**
This figure presents binned scatterplots of drug-level similarity against several drug characteristics. Panel A examines whether a drug is FDA approved. Panel B examines the logarithm of the Kogan et al. (2017) estimated patent values. Panel C examines 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 the legend to Internet Appendix Figures A.1 and A.14–A.18 for more details.

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 not only 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 NPV 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% of drugs entering preclinical development in our data have a patent application. The costs of discovery—in addition to being relatively small, see Section 1.3—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 number of forward citations received by the patent.[13] We restrict our attention to key patents, those 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 Section 2.6. The resultant data set has information on 31,915 patents, 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

[11] In Section 3.2 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, as the value depends on difficult to observe outcomes. For example, it is probable that firms learn more from developing novel drugs, rather than derivative ones. For example, working on 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 1.2 in the Internet Appendix discusses the patenting process in detail.

[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 U.S. patents in our sample, which ends in September 2016.

patent approval occurs very early in the drug development process, market reactions to patent approval incorporate the NPV 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 U.S. 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 B of Figure 4 shows the associated binned scatterplot; Table A.6 in the Internet Appendix 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% 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 3.2.2 which condition on drug approval (20%). Given the unlikeliness that the patent office applies a higher threshold for patents associated with novel drugs, our estimates of value are unlikely to be biased upward 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, Jaffe, and Trajtenberg (2005) argue that the number of forward citations a patent receives are significantly related to economic value. Harhoff et al. (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

[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 Section 1.2). If this were the case, then it would bias our results against finding a positive link between novelty and value. In particular, the stock price reaction following the (less surprising) 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.

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 scatterplot of the results. Panel A of Table A.7 in the Internet Appendix examines how the choice of controls affects our results.

We find that patents associated with novel drugs on average receive a larger number of forward citations. The correlation between our measure is both statistically and economically significant. Our estimates imply that a one-standard-deviation increase in drug novelty is associated with an increase of 0.12 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 United States. Panel B of Table A.7 in the Internet Appendix 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 U.S. 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 is 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 Table A.8 in the Internet Appendix, we consider how the number of patients and number of trials associated to a compound vary by its chemical novelty. We find no consistent relationship between these proxies of development cost and drug novelty.

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 and 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. Figure A.2 in the Internet Appendix plots 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% 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 that potentially arises because of 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. Cash Flow Shocks and Drug Development

We begin by discussing the channel through which shocks to firm cash flows affect drug development decisions. We then outline our empirical strategy and document our findings on the link between cash flow 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, cash flows 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 Internet 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, the model 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 the firm's net worth—that is, a shock to its current and future cash flows. Our model builds on that of Bolton, Chen, and Wang (2011), who provide a tractable framework to study dynamic investment, financing, and risk management decisions in continuous time. To simplify the 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 Internet Appendix 4.

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 cash flows 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 cash flows in the future.[15] A positive shock to expected cash flows makes these costly states of the world less

[15] Alternative interpretations of our modeling setup are possible. We view the underlying friction as an agency problem that leads to costly external finance: investors do not trust managers with their capital and hence impose a cost whenever managers access financial markets. This friction drives to a wedge between the cost of financing a project with internal cash flows and the cost of raising outside funds (Myers and Majluf 1984). Alternatively, investors may terminate the manager if the firm's economic performance is sufficiently low (Smith and Stulz 1985; DeMarzo et al. 2012); our model incorporates this case by reinterpreting the fixed cost of raising external capital as the manager facing the possibility of costly termination when cash flows 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

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 cash flows 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 cash flows, we utilize an additional source of preexisting variation, namely, the remaining life of a firm's patents. In particular, the extent to which a firm benefits from the introduction of Part D depends on not only the types of drugs it sells (elderly share) but also the amount of market exclusivity remaining on those drugs. Our empirical strategy makes use of both sources of variation to isolate the impact of Part D that comes through a shock to a firm's cash flows 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 cash flows because Part D ensures that its potential customers will now be reimbursed for their purchase of its products. By contrast, a firm that only sells drugs for pediatric conditions should not expect to see an increase in sales, except possibly through secondary factors, such as wealth effects. Following previous work (Blume-Kohout and Sood 2013; Duggan and Scott Morton 2010; Dranove, Garthwaite, and Hermosilla 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 data set to the Medical Expenditure Panel Survey (MEPS), which contains drug-level information on sales by patient demographics. Section 2.3 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

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 the members of the board.

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 the remaining exclusivity for each firm's drugs, we match drugs approved as of 2003 to their associated patents and, where possible, link the drugs to their key patent expiration dates and FDA exclusivity extensions. We then aggregate these drug-level measures to the firm level by defining a firm's overall drug life, $Overall\ drug\ life_{f,2003}$, as the proportion of its approved drugs with long remaining exclusivity as of 2003. Since our data on exclusivity periods is somewhat noisy, we minimize measurement error 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 Table A.10 in the Internet Appendix.

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 versus 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 cash flows 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

[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 7 years of market exclusivity. Other legislation also sets aside market exclusivity for additional drug designations (e.g., 5 years for New Chemical Entities, and 6 months for Pediatric Exclusivity). For more information on our drug-to-patent data and patent expiration dates, see the Internet Appendix, Section 2.6

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:

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

Our main coefficient of interest is $a_1$, which captures the *cash flow* 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 Internet Appendix), to ensure that our results are not driven by preexisting 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 cash flow 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

[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 zero or one. Figure A.3 in the Internet Appendix shows a smoother distribution of Medicare Drug Life for firms with nonextremal values, and Tables A.13 and A.14 in the Internet Appendix show that our results are robust to restricting to this subsample or to using a binary treatment measure.

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 Table A.1 in the Internet Appendix: our original sample included over 12,000 drug candidates from 3,108 firms, while our cash flow 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 data set 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 Internet Appendix, we show that our findings are robust to using alternative specifications, including count models (see A.12).

### 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 for $\text{Post} \times \text{Overall Drug Life}_{f,2003}$ indicates that firms with a newer set of drugs as of 2003 proceed to introduce fewer new candidates into development in the post-Part-D period, suggesting that controlling for differences in firm development cycles is important. Perhaps surprisingly, the inclusion of $\text{Post} \times \text{Firm MMS}_{f,2003}$ in column 6 does not materially affect our point estimates, suggesting that (in our sample) demand effects do not appear to increase development separately from cash flow

[18] That said, the descriptives that we report in Section 2 and in Section 3.2 of the Internet Appendix continue to hold for drugs associated with firms in our cash flow analysis sample. Indeed, our analysis of the relationship between novelty and measures of value for approved drugs is largely the same because over 90% of these drugs are associated with firms in our natural experiment sample.

**Table 3**
**Impact of resources on the number of 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) |
| $R^2$ | .556 | .556 | .557 | .594 | .595 | .595 |
| Company FEs | Yes | Yes | Yes | Yes | Yes | Yes |
| Qtr of development FEs | Yes | Yes | Yes | Yes | Yes | Yes |
| Observations | 16,442 | 16,442 | 16,442 | 16,442 | 16,442 | 16,442 |

This table 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 (Model 1–3) or the log of one plus the number of new drug candidates entering development (Model 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 × Overall Drug Life $_{f,2003}$ and Post × Firm MMS $_{f,2003}$ both included as independent variables. Robust standard errors are in parentheses, clustered around company identifiers. * $p < .10$;** $p < .05$;*** $p < .01$.

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% 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 the 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% of candidates have novelty scores in that range (see Table A.1).

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

[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 value, 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).

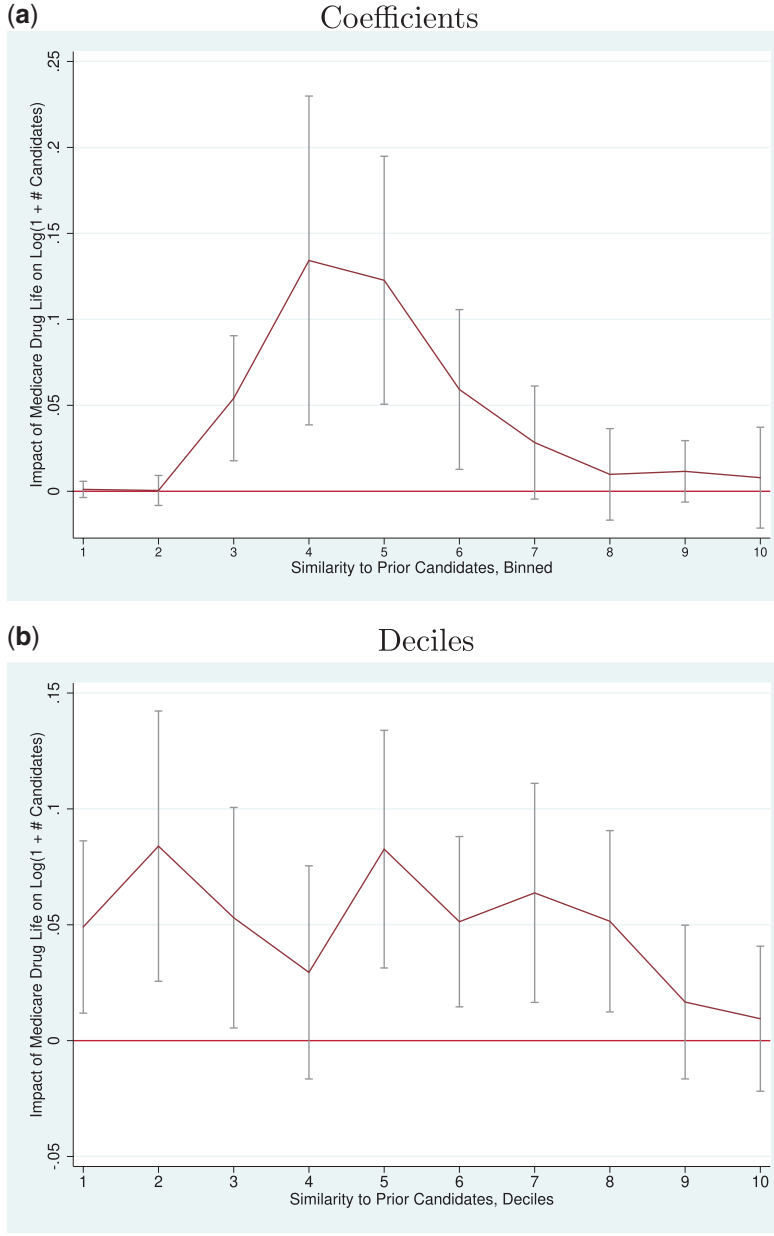



**Figure 5**
**Impact of additional resources on novelty of drug investments**
This figure plots the estimated coefficients for Post × Medicare Drug Life $_{f,2003}$ from our main regression specification defined by (6). Each point represents a different outcome variable: the number of new drug candidates 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.

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 cash flow 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 preexisting trends. To address this concern, Figures 6 and 7 show how the estimated effect of the cash flow 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 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 the 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, Table A.11 in the Internet Appendix 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 from higher expectations of future cash flows.[21]

[21] The model in Section 3 has i.i.d. cash flow 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 cash flow 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).

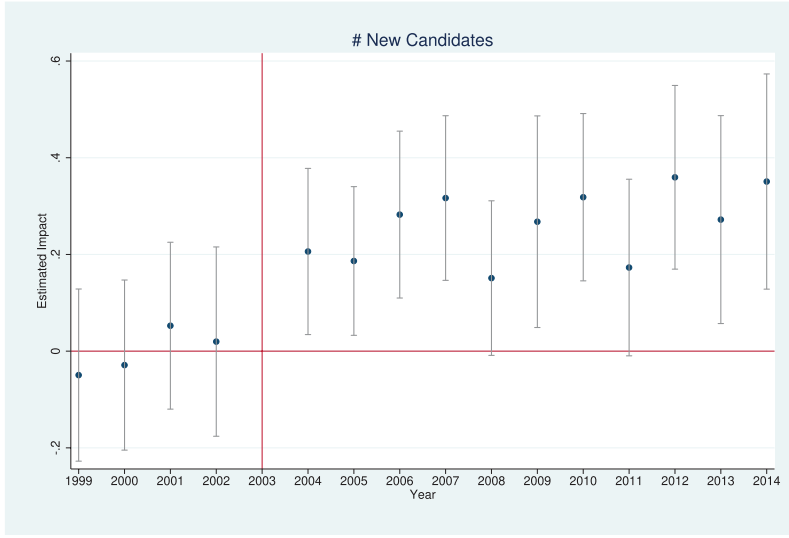



**Figure 6**
**Event studies: # of new candidates**
This figure reports the accompanying event study associated with Column 6 of Table 3. Each dot represents the coefficient for Medicare Drug Life $_{f,2003}$ interacted with an indicator variable for that given year. The omitted year is 2003, and 90th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

The fact that firms can quickly alter their development pipeline is not particularly surprising for our sample of firms, those with an approved drug in 2003. Since these firms are more established, they likely have a stock of potential drug candidates in the discovery phases of development at any given point in time. Indeed, the majority of drug candidates that entered development in 2004 or 2005 are based on at least one patent application that was filed prior to the introduction of Medicare Part D in late 2003 (86% and 66%, 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 cash flow 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 Internet Appendix show that firms respond to cash flow shocks primarily by increasing their investments in early-stage novel drugs. These patterns are consistent with treated firms engaging in more early-stage experimentation. Treated firms know 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.

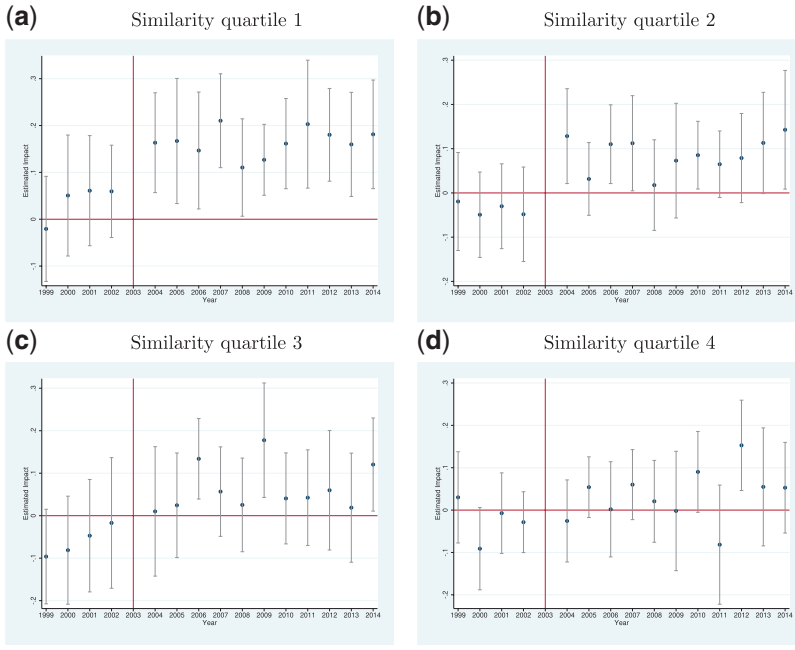



**Figure 7**
**Event studies: Number of new candidates, by similarity quartile**
This figure reports event studies coefficients for which the outcome variables are the number of new candidates in each quartile of similarity. Each dot represents the coefficient for Medicare Drug Life$_{f,2003}$ interacted with an indicator variable for that given year. The omitted year is 2003, and 90th percentile confidence intervals are reported.

**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 cash flow 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%. 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-Hirschman index. Columns 3 and 4 show that firms also diversify their portfolios by investing in drugs with different biological targets.

**Table 4**
**Portfolio expansion (candidates new to firm)**

| | New indications | | New targets | |
|---|---|---|---|---|
| | (1) log(1+ #) | (2) Δ HHI | (3) log(1+ #) | (4) Δ HHI |
| Post-2003 X Medicare drug life | 0.160** | −0.013* | 0.101* | −0.020*** |
| | (0.069) | (0.008) | (0.060) | (0.007) |
| $R^2$ | .260 | .029 | .440 | .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 | 16,442 | 12,220 | 16,442 | 12,220 |

This table 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 affected 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. $^{*}p < .10;^{**}p < .05;^{***}p < .01$.

**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 cash flow 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 cash flow 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. Columns 1 and 2 show that treated firms increase their development of drugs for conditions in which fewer than 5% or 10% of patients are elderly. In column 3, we consider the development of drugs for pediatric conditions, namely, those defined as indications for which an above-median share of drug trials requires enrollees to be newborns,

[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.

**Table 5**
**Drug development across drugs for elderly and nonelderly populations**

*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) |
| $R^2$ | .337 | .343 | .366 | .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 | 16,442 | 16,442 | 16,442 | 16,442 |

*B. Drugs for pediatric and young adult conditions*

| | log(1+ New candidates), nonelderly conditions | | | |
|---|---|---|---|---|
| | (1) < 5% MMS | (2) < 10% MMS | (3) Pediatric | (4) Youth |
| Post-2003 X Medicare drug life | 0.076** | 0.090** | 0.192** | 0.138** |
| | (0.038) | (0.041) | (0.080) | (0.066) |
| $R^2$ | .317 | .344 | .532 | .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 | 16,442 | 16,442 | 16,442 | 16,442 |

This table examines whether firms developing more drugs in response to cash flow shocks do so in areas that experience a greater increase in demand (depending on whether these drugs target elderly or nonelderly patients). The table reports the main specification coefficient for Post × 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) nonelderly conditions. Columns 1 and 2 define nonelderly as low MMS conditions, and 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, preschool children or children. The "youth" category is assigned similarly but expands this definition to include adolescents and young adults. All models include a full set of company and quarter indicator variables, with Post × 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. * $p <$ .10; ** $p <$ .05; *** $p <$ .01.

infants, preschool-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 cash flows 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.

**Table 6**
**Novelty for nonelderly drugs**

*A. Below-median MMS drugs*

| | log(1+ Nonelderly 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) |
| $R^2$ | .233 | .303 | .238 | .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 | 16,442 | 16,442 | 16,442 | 16,442 |

*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) |
| $R^2$ | .322 | .407 | .311 | .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 | 16,442 | 16,442 | 16,442 | 16,442 |

*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) |
| $R^2$ | .292 | .377 | .295 | .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 | 16,442 | 16,442 | 16,442 | 16,442 |

This table reports the main specification coefficient for Post × Medicare Drug Life $_{f,2003}$ but focuses 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 drug candidate outcomes to "pediatric" drugs, that is, 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. * $p < .10$;** $p < .05$;*** $p < .01$.

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

**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) |
| $R^2$ | .650 | .576 | .370 | .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 |

This table examines the average value of the drugs developed in response to cash flow shocks do so in areas that experience a greater increase in demand (depending on whether these drugs target elderly or nonelderly 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. Columns 1 and 2 evaluate the value of all new drugs, and 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. * $p < .10$;** $p < .05$;*** $p < .01$.

**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 toward more novel (i.e., riskier) drugs. Here, we examine whether these marginal novel drugs being developed in response to the cash flow shock are also more valuable on average (as is the case in our model). To do so, we reestimate. Equation (5), but now the main outcome variable is the average value of drugs being developed in a given quarter,

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

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 *cash flow* 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 cash flow 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 and imprecisely estimated due to the small sample: the 90% 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

**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) |
| $R^2$ | .934 | .930 | .800 | .463 |
| Company FEs | Yes | Yes | Yes | Yes |
| Year of development FEs | Yes | Yes | Yes | Yes |
| Observations | 1,774 | 1,572 | 1,657 | 1,925 |

This table examines the response of firm-level research spending, operating cash flow, and debt to our main treatment variable, Post × Medicare Drug Life $_{f,2003}$. The dependent variable is the logarithm of R&D spending; the logarithm of operating cash flows (Compustat: ib + dp); the logarithm of long-term debt (Compustat: dltt); or the logarithm of leverage (Compustat: dltt scaled by at). The sample period is 1999–2013. 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. Standard errors clustered by firm are reported in parentheses.* $p < .10$;** $p < .05$;*** $p < .01$.

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 do not find an 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 underinvestment 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% increase in the development of new and novel drugs. To assess the magnitude of this effect and benchmark it to the existing literature, we need to express our estimates in terms of the implied elasticity of drug development with respect to firm R&D spending. Hence, we need a measure of how much firm resources increase as a result of this policy.

To assess the response of R&D investment to our main treatment variable, we match the public firms in our data to Compustat North America and Compustat Global. We are able to match approximately 50% of 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. Table 8 reports these results. Columns 1 and 2 show that firms with higher Medicare Drug Life in 2003 experienced higher growth in R&D and operating cash flows

in the years following treatment. We find no evidence in Columns 3 and 4 that treated firms increase their borrowing.[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 1% increase in treatment leads to both a 0.53% increase in R&D and a 0.40% 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-one and top-two deciles of novelty, respectively, compared to an elasticity of 0.02 and 0.31 for the top-one and top-two deciles of similarity, respectively. These magnitudes are broadly consistent with the literature.[24]

### 3.6 Firm heterogeneity

Next, we examine how the impact of cash flows 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 Internet 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 Table A.16 in the Internet Appendix for more details).

We find some evidence that the response to treatment varies with the pretreatment level of cash holdings. Specifically, within the subsample 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

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[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 the Internet Appendix) given the relative difficulty of collateralizing their intellectual property.

[24] This analysis comes with several caveats. Because some of our firms include large conglomerates (for instance, firms, such as Dow Chemical), our R&D values 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 et al. (2019) 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 et al. (2015) use variation in demographic trends and find a smaller elasticity of innovation to market size of 0.23. We may find a larger impact in part because the increase in novel drug development that we document may reflect the development of preexisting research ideas, which were unexplored by choice (for instance, because of risk aversion).

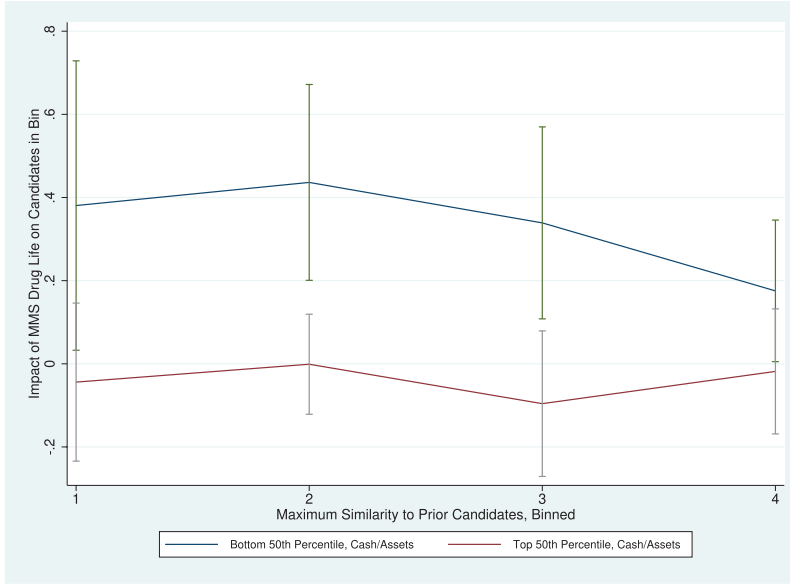


**Figure 8**
**Response to treatment, as a function of the level of cash holdings**
This figure reports the coefficient for our main treatment variable (Medicare Drug Life in Equation (5) in the main text) estimated across two different subsamples: firms in Compustat that are above (red line) or below (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 subsample. The points on the horizontal axis correspond to groups of drugs of different levels of novelty: quartile 1 refers to drugs that are most novel (lowest maximum similarity, and quartile 4 refers to drugs that are least novel (highest maximum similarity). Error bars represent 95% confidence intervals.

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, caveats subsist: 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 Section 3.4 for an extensive list of robustness and specification checks.

In Section 3.3, we showed that firms that experienced an increase in cash flows 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 discussed in Section 1.2, novel molecules are easier to patent than derivative ones. Nevertheless, to dispel any remaining doubts, we restrict our primary analysis to those drug candidates that already have a U.S. patent issued prior to their earliest development date. These drugs account for approximately 41% of the sample. For this set of drugs, it is clearly the case that both discovery and patenting costs are sunk and should not be factored into their decision to pursue development. Figure A.7 in the Internet Appendix shows that our findings are qualitatively similar when we restrict in this subsample.

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 Internet 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 cannot be applied to complex biological entities, known as biologics, which make up a smaller fraction of pharmaceutical output but are a growing area for R&D.

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 Internet 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). We find 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 trade-off 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 cash flow shock we identify. Our results suggest that increased cash flows 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 trade-off 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, Stein, and Lo (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 lend 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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