INSURANCE DESIGN AND PHARMACEUTICAL INNOVATION

Leila Agha
Soomi Kim
Danielle Li

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ABSTRACT

This paper studies how insurance coverage policies affect incentives for pharmaceutical innovation. In the United States, the majority of drugs are sold to Pharmacy Benefit Managers (PBMs), which administer prescription drug plans on behalf of insurers. Beginning in 2012, PBMs began adopting “closed formularies”, excluding coverage for certain drugs, including many newly approved drugs, when adequate substitutes were available. We show that this policy reshaped upstream R&D activity and led pharmaceutical firms to shift investment away from therapeutic classes at greater risk of facing coverage exclusions. This move translated into a relative decline in the number of drug candidates that appear more incremental in their therapeutic contribution: that is, those in drug classes with more pre-existing therapies and less scientifically novel research.

Leila Agha
Department of Economics
Dartmouth College
6106 Rockefeller Hall
Hanover, NH 03755
and NBER
leila.agha@dartmouth.edu

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

Soomi Kim
Massachusetts Institute of Technology
skim20@mit.edu
Technological innovation is a large driver of rising health spending, raising questions as to whether our current payment systems deliver the right balance between incentives to innovate and incentives to contain costs. While some argue that broad insurance coverage and generous pricing policies are necessary to sustain valuable R&D investment, others believe that these same policies generate perverse incentives to create expensive products with little incremental clinical value.\footnote{For example, Stanford (2020) and Zycher (2006) have argued that the innovation benefits of generous drug payment policies are large, while Bagley et al. (2015) and Frank and Zeckhauser (2018) highlight the risk that generous drug payments may yield excessive incremental innovation.} The policy relevance of this debate has grown as politicians have increasingly called for the federal government to implement value-based pricing that limits insurance coverage for high-cost, low-value treatments. Despite its importance, there is limited empirical evidence on how the structure of insurance coverage shapes incentives for upstream medical innovation.

In this paper, we study the impact of a major change in coverage policies for private sector prescription drug plans on upstream pharmaceutical R&D. In the United States, prescription drug plans are typically managed by intermediary firms, known as Pharmacy Benefit Managers (PBMs). Traditionally, PBMs provide coverage for all FDA-approved drugs, but assign them to different tiers of patient cost-sharing. Beginning in 2012, however, PBMs began refusing to provide any coverage for some high price drugs (including many newly approved drugs) when cheaper generic or branded substitutes already existed. Over the next five years, 300 drugs were excluded by at least one of the three largest PBMs.

This practice of excluding coverage entirely, known as maintaining a “closed formulary,” can substantially reduce the expected profitability of new drugs. For example, the high blood pressure medication Edarbi received FDA approval in 2011 but was almost immediately excluded by the two largest PBMs, CVS Caremark and Express Scripts. By September 2013, Edarbi’s manufacturer, the Japanese firm Takeda, had decided to sell off its US distribution rights, despite keeping these rights in Japan and in other countries.\footnote{In an analysis described in Section 4.2, we test whether this example generalizes. Our results show that for each PBM that excludes coverage, a drug’s sales (as proxied by Medicare Part D claims) falls by 24%.}

Understanding how the downstream policies of PBMs shape upstream pharmaceutical innovation can inform our understanding of how to design insurance plans that balance incentives for innovation and cost-containment. These lessons, gleaned from the policies of private sector firms, provide insight into the possible effects of new policy proposals governing...
how public insurers interact with drugmakers.\textsuperscript{3} The largest PBM, CVS Caremark, manages benefits for 75 million Americans—more than the number of enrollees in either Medicare or Medicaid.

We begin by showing that the risk of being excluded from a PBM’s formulary varies systematically and predictably across drug classes: in particular, exclusions are more common in drug classes with more pre-existing therapeutic options, and in classes with a larger number of patients. In the case of Edarbi, CVS and Express Scripts both pointed to a variety of other popular angiotensin II receptor blockers (ARBs) as viable alternatives, even though they were not molecularly equivalent. Further, the cost savings associated with excluding Edarbi were potentially very large because they could be realized over many patients suffering from hypertension. Indeed, we show show that the greatest number of exclusions were for drugs aimed at treating diabetes and cardiovascular diseases, both areas responsible for a large share of insurance spending.

Next, we use this information to build a measure of each drug class’s ex-ante risk of facing exclusions based on its market characteristics prior to the introduction of closed formularies. We show that pharmaceutical R&D fell markedly in drug classes at high risk of exclusions, relative to trends in low risk classes, following the introduction of closed formulary policies. We document a 5% decline in the number of new clinical trials and announcements of early stage development for a one standard deviation increase in ex-ante exclusion risk. These declines impact drug candidates in all phases of development, but are largest among earlier stage drugs.

We go on to explore the nature and value of this foregone innovation. We first document a change in the composition of drugs under development: R&D declined the most in drug markets with a high number of existing therapies, serving common diseases such as diabetes and cardiovascular diseases. Second, we show that exclusions depressed R&D investments in the least scientifically innovative drug classes: those where drug patents are based on older and less “disruptive” underlying science (Funk and Owen-Smith 2017).

Taken together, our results suggest that closed formulary policies altered the demand risks that drugmakers consider when making R&D investment decisions. Prior to this policy

\textsuperscript{3}Congressional Budget Office (2007) predicts that the government will not be able to negotiate lower prices with drug manufacturers unless it adopts a PBM-pioneered model of providing preferential access for specific drugs on publicly-run formularies.
change, pharmaceutical firms could expect that their drugs would be covered by insurers if approved by the FDA. In this world, firms had strong incentives to develop incremental drugs aimed at large disease markets because such drugs were the most likely to receive FDA approval and generate a large base of revenues if approved. With the introduction of closed formularies, these incremental drugs became precisely the ones at greatest risk of being excluded from formularies. Our results show that pharmaceutical firms responded to this change in incentives by shifting resources away from drug classes serving common diseases with many incumbent therapies. Further, our results suggest that exclusion policies shifted research investments away from areas with more “me-too” development activity and lower scientific novelty.

An important caveat to note is that our econometric approach is based on a difference-in-differences specification that identifies a relative decline in investment in drug classes at high exclusion risk compared to lower risk classes. A natural, welfare-relevant question is whether this constitutes a total decline in innovative activity or a reallocation of R&D investment. While we cannot answer this question empirically (since it would rely purely on time series identification), recent research suggests that even large pharmaceutical firms may face financial frictions. In this case, a decline in R&D spending in high exclusion risk classes may generate some degree of reallocation toward other drug classes that face lower exclusion risk. In the absence of frictions, exclusion policies would decrease total investment in new drug innovation.

Our paper contributes to a broad literature examining how market incentives shape the rate and direction of innovative output.4 Prior empirical research has documented that increased demand for drugs spurs new drug development: several studies have measured the impact of public insurance expansions (Acemoglu et al. 2006; Blume-Kohout and Sood 2013; Clemens 2013; Dranove et al. 2020; Finkelstein 2004; Krieger et al. 2017) and demographic changes (Acemoglu and Linn 2004; Dubois et al. 2015). Other research has investigated the role of patent protection, showing that stronger patent protection (Kyle and McGahan 2012) and longer periods of market exclusivity (Budish et al. 2015) increase innovation. Both “push” and “pull” incentives have demonstrated effects on medical R&D, including

4Here we summarize some of the recent work in this area that focuses on healthcare innovation. Directed technical change is also an active area of research in environmental economics, which studies how investment in clean and dirty technologies responds to market incentive (e.g., Aghion et al. 2016; Acemoglu et al. 2012).
tax credits (Yin 2008), and public procurement incentives (Clemens and Rogers 2020). Our findings build on this earlier empirical work by focusing on a new angle: how changes in the structure of insurance coverage affect the direction of innovative activity. Further, our paper provides an empirical analysis of tradeoffs raised by a theoretical literature on insurance design and innovation (Garber et al. 2006; Lakdawalla and Sood 2009).

The rest of the paper proceeds as follows. Section 1 introduces the institutional context. Section 2 describes the negotiation between PBMs and drugmakers in more detail, summarizing a theoretical model of how R&D investments may respond to the introduction of formulary exclusions. Section 3 provides an overview of our key data sources covering exclusions, drug development, and market characteristics. Section 4 describes which drug classes contain formulary exclusions and reports evidence that exclusions suppress drug demand. Section 5 presents our main findings on how formulary exclusions have reshaped investments in drug development. Section 6 discusses the welfare implications, and Section 7 concludes.

1 Institutional Background

In the United States, many parties are involved in the process of bringing a drug from manufacturer to patient: wholesalers, pharmacies, pharmacy benefit managers (PBMs), and insurers. Historically, PBMs were only responsible for processing patient claims at the pharmacy: i.e., verifying the patient’s coverage, obtaining payment from the insurer, and transmitting that payment to the pharmacy. However, over time and in concert with a wave of mergers (Werble 2014), PBMs began playing a more active role in designing prescription drug plans on behalf of insurers, determining which prescription drugs would be covered under a plan’s formulary.

Figure 1 illustrates the flow of both goods and payments for prescription drugs. The physical path of drugs is simple: they are bought by wholesalers who then deliver and sell them to pharmacies, where they are distributed to patients. PBMs do not generally enter the physical supply chain for drugs, but they play a major role in coordinating payments. PBMs serve as an intermediary between the insurer and the pharmacy. The pharmacy is paid by two parties: it receives a drug co-pay from the patient and a reimbursement from
the PBM. Meanwhile, the PBM collects revenue in two ways. First, it is reimbursed for the drug by the patient’s insurer, who is still the ultimate payee. Second, the PBM also receives a rebate from the pharmaceutical firm: this is a payment that the pharmaceutical firm negotiates in return for having their drug included (ideally in a preferred position) on the PBM’s formulary. The PBM may pass on a portion of this rebate to the insurer.

By 2012, the PBM industry had consolidated to the point that the largest three companies controlled 62% of the market, a share which has continued to grow (Lopez 2019). In this paper, we track the exclusion policies of the three largest firms: CVS Caremark, Express Scripts, and OptumRx. Given their ability to pool patient demand across plans administered on behalf of multiple insurance companies, as well as their influence on formulary design, PBMs have substantial negotiating power with drug manufacturers. PBMs may place drugs into formulary tiers, setting higher cost sharing for less preferred drugs. Coverage for certain drugs may require prior authorization from the patient’s insurance company. Further, PBMs may use step-therapy restrictions, and only cover more expensive drugs after cheaper options have been proven ineffective.

Beginning with CVS in 2012, major PBMs began implementing closed formularies. Rather than providing coverage (potentially with some tiering or restrictions) for all drugs as long as they are FDA-approved, PBMs began publishing lists of drugs that their standard plans would not cover at all, directing potential users to lists of recommended alternatives including similar branded or generic drugs. Some major PBMs also designated closed formularies the default choice, implementing a system where PBM customers (i.e., insurers) would have to opt out if they wanted to avoid the standard closed formulary (Reinke 2015). Industry experts describe PBM formulary exclusions as an “integral part of contract negotiations” with drug manufacturers (Reinke 2015).

Patients enrolled in prescription drug plans with closed formularies typically receive an annual mailing notifying them of exclusions for the upcoming year, and urging them to change medications if they are currently taking a drug that is on this list. With few exceptions, patients wishing to take an excluded drug would be responsible for paying the full cost at the pharmacy.\(^5\)

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\(^5\)While patients may be able to access drugs that are excluded by their PBM’s formulary, the exclusions introduce new barriers. The patient’s insurer may entertain patient-specific appeals for coverage outside of the PBM’s standard policies. The patient may choose to purchase the drug without insurance coverage,
The PBM industry argues that formulary restrictions reduce insurers’ costs (Brennan 2017), but advocates counter that exclusions harm patients by decreasing access to treatment. A 2017 survey conducted by the Doctor-Patients Rights Project reports that a quarter of insured Americans were denied treatment for chronic illnesses; the most common denial reason was the treatment’s formulary exclusion (The Doctor-Patient Rights Project 2017). Furthermore, while PBMs’ closed formularies policies implicitly rely on a “one-size-fits-all” approach—choosing one preferred treatment over other similar treatments—drugs that appear therapeutically equivalent may vary in efficacy and side effects, and a drug that works well for one patient may not be the best drug for another patient with the same disease (Celgene 2016). We provide more detail on exclusion practices in Section 4.

A natural question is why PBM formulary exclusions became common after 2012. A complete investigation is beyond the scope of this paper, but there is evidence that existing policies such as prior authorization requirements and the use of “step therapies” were not effective at limiting the use of certain expensive medications. For example, Miller and Wehrwein (2015) suggest that exclusions may have arisen in response to the growing use of “co-pay cards,” which are discounts offered by pharmaceutical companies to subsidize patients’ drug costs. Because the insurer still has to pay its share of the drug price, co-pay cards diminished PBMs’ ability to steer patients to cheaper drugs. In contrast, exclusions provide PBMs with a stronger tool for utilization management that cannot be directly countered by co-pay cards and other consumer discounts.

2 Formulary Exclusions and Upstream Innovation

In this paper, we analyze the effect of PBM formulary exclusions on investments in drug development. While closed formularies have direct effects on demand for excluded drugs, they are also likely to affect the pricing of other drugs that face exclusion risk but were not ultimately excluded. Steve Miller, the chief medical officer of Express Scripts, described the process of negotiating with pharmaceutical manufacturers as follows:

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paying the full price out-of-pocket. Finally, some patients may be able to choose between insurance plans serviced by different PBMs, and so could switch to an alternative plan that has not excluded the drug.
“We are going to be pitting you all against each other. Who is going to give us the best price? If you give us the best price, we will move the market share to you. We will move it effectively. We’ll exclude the other products” (Miller and Wehrwein 2015).\(^6\)

Consistent with the market dynamics described by Garthwaite and Morton (2017), the exclusion threat increases the PBM’s ability to shift consumers across rival products, strengthening their bargaining position. In its marketing analysis, CVS explicitly argues that “[f]ormulary is foundational to cost control” and suggests that the introduction of formulary exclusions in 2012 led to lower price growth for pharmaceuticals.\(^7\)

In Appendix A, we provide a simple model that formalizes how drug exclusion policies impact drug firms’ R&D decisions. In this model, a potential pharmaceutical entrant faces a choice: invest in developing a drug for a “new” drug class—that is, one in which no prior treatments exist—or invest in developing a drug for an “old” class, in which there is an incumbent therapy available. In the absence of exclusions, PBMs are required to provide coverage for all approved drugs: if successful, a pharmaceutical entrant would become a monopolist in the new drug class and a duopolist in the old drug class. We model closed formularies as permitting exclusions when a similar substitute is available. In the old drug class, the two firms bid on rebate payments to the PBM in order to win exclusive formulary coverage. Exclusions therefore reduce drug revenues in the old drug class, where entrants face exclusion risk and will pay high rebates to the PBM if they succeed in obtaining formulary coverage. These reduced revenues lower the returns to investing R&D dollars into the old drug class, without changing the returns to investing in the new class. Our model predicts that we should see a relative drop in new drug candidates entering markets in which existing therapies are already available.

The welfare implications of this change in drug development incentives are theoretically ambiguous. First, losses to pharmaceutical firms can be cast as gains to the PBMs, in the form of higher rebates. If PBMs pass some of these cost savings onto consumers, then exclusion policies create a tradeoff between incentives for future innovation and

\(^6\)In line with this description, observers note that within a therapeutic class, PBMs are increasingly selecting a single brand for coverage (Cournoyer and Blandford 2016).

affordability of current prescription drug coverage. Second, an overall decrease in drug development can be welfare enhancing if business stealing effects dominate the benefits of expanding treatment options (Mankiw and Whinston 1986). This is a possibility in our setting, especially if foregone drug candidates would have otherwise been entrants into already crowded therapeutic areas.

Finally, another welfare-relevant consideration is how R&D investment is allocated within pharmaceutical firms. In our model, the potential entrant chooses between investing in the old versus the new class. This is likely to be the case when firms face financial or organizational frictions that limit their ability to invest in all net present value (NPV) positive projects. Under this assumption, the introduction of closed formularies generates a reallocation of R&D dollars away from older drug classes toward newer classes. An alternative model, however, would have firms investing in all drug candidates with a positive NPV. In this case, the introduction of closed formularies would instead lead to an aggregate decline in R&D investments, since exclusions decrease the NPV of investments in older classes but have no effect in newer classes. Our empirical strategy allows us to identify only the relative change in development across drug classes, making it difficult to distinguish between these possibilities. Section 6 discusses the welfare implications and limitations of our analysis in more depth.

3 Data

Our analysis focuses on tracking changes in drug development activity over time and across drug classes. We have assembled four primary data sources: (1) PBM formulary exclusion lists, (2) time-varying characteristics of drug markets, (3) prescription drug sales volume, and (4) new drug development activity. The data we draw from each of these sources is summarized briefly below.

1. **Formulary Exclusions**: We hand-collected data on formulary exclusions published by CVS Caremark, Express Scripts, and OptumRX through 2017. Together, these firms account for approximately 70% of the PBM market.\textsuperscript{8} Our data cover “standard”

\textsuperscript{8}When it first closed its formulary in 2012, CVS had a 20% share of the PBM market (Lopez 2018). Express Scripts followed suit in 2014, when its market share was 33.8% (Health Strategies Group 2015).
formulary exclusions: these exclusions apply to most health plans administered by a particular PBM. Insurers may elect to provide more expansive coverage by opting out of the standard formulary, but we do not have information on exclusions within these custom plans.\footnote{Custom plans are less common because they are likely to be substantially more expensive. For example, on its payer-facing website, CVS encourages insurers to choose its standard (closed) formulary, for an estimated 29\% savings in per member per month drug costs (Brennan 2017).} We match the excluded drugs to their 4-digit Anatomical Therapeutic Chemical (ATC4) drug class using the First Data Bank data (described below). These exclusions form the basis of our analysis.

2. First Data Bank: In order to better understand the characteristics of drugs and drug classes that experience exclusions, we collect data on drug markets and drug pricing from First Data Bank (FDB). FDB is a commercial dataset primarily marketed to healthcare organizations that manage formularies. It contains information on a drug’s ATC4 classification, pricing, and the existence of generic substitutes. We use this information to construct additional data on drug markets at the ATC4 level: the number of approved branded and generic drugs in an ATC4 class and measures of the price of already approved branded and generic drugs.\footnote{We use unit price provided by the manufacturer to FDB. Specifically, wholesale acquisition unit cost (manufacturer’s published catalog or list price to wholesalers) was used, where available. If this was unavailable, suggested wholesale unit price (manufacturer’s suggested price from wholesalers to their customers) was used. If this was unavailable, then direct unit price (manufacturer’s published catalogue or list price to non-wholesalers) was used. Unit refers to the NCPDP billing unit of the product, where a unit is defined as a gram, each, or milliliter.} We use these variables to predict which drug classes face exclusion risk and as control variables to account for time-varying market attributes in certain specifications.

3. Medicare Part D Data: To establish that formulary placement affects drug demand, we document the impact of exclusions on a drug’s insurance claim volume in Section 4.2. Because sales volume is not measured by FDB, we turn to publicly available data on annual Medicare Part D claims volume by drug.\footnote{This data is published annually by the Center for Medicare and Medicaid Studies. We accessed it online at \url{https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/Historical_Data}, in November 2019.} Most Medicare Part D plan sponsors contract with PBMs for rebate negotiation and benefit

Finally, OptumRx began publishing formulary exclusions in 2016, when its market share was 22\% (Fein 2017).
management (Government Accountability Office 2019), and many Part D plans feature closed formularies (Hoadley et al. 2011), making Medicare Part D a suitable context to study the impact of exclusions. This data is available from 2012-2017 and reports the annual number of claims for all drugs with at least 11 claims.

4. **Cortellis Investigational Drugs**: Our main analysis studies the impact of formulary exclusions on drug development. We obtain data on pipeline drugs, including both small molecule and biologic drugs, from Clarivate Analytics’ Cortellis Investigational Drugs database (Cortellis). Cortellis tracks drug candidates using data it compiles from public records: company documents, press releases, financial filings, clinical trial registries, and FDA submissions. Drug candidates typically enter the Cortellis database when they enter preclinical development; this is often when a drug candidate will appear in patents or in other documents describing a firm’s research pipeline. Similarly, because all firms are required to apply for and receive FDA approval to begin human clinical trials, Cortellis has near complete coverage of drug candidates that advance into human testing.

Using Cortellis, we track each drug’s US-based development across five stages: pre-clinical development, phase 1 trials, phase 2 trials, phase 3 trials, and launch. Our primary outcome is the total number of drug candidates within a class that entered any stage of development each year. Table 1 Panel A reports the summary statistics of development activity across different stages.

Throughout most of the paper, our unit of analysis is a narrowly defined drug class, following the Anatomical Therapeutic Chemical (ATC) classification system. ATC codes are used to organize medicinal compounds; we use an ATC4 (four-digit) level classification, which identifies chemical subgroups that share common therapeutic and pharmacological properties.

Appendix Table A.1 lists several examples of ATC4 designations. For example, diabetes drugs fall into 3 distinct ATC4 categories depending on whether the drug is an insulin or

12 In cases where we observe a drug in development at a later stage without a recorded date for prior development stages, we fill in the earlier stage date to equal the subsequent recorded stage. Because the FDA requires each new drug to move through each phase before receiving approval, seeing a drug at a later stage in development is strong evidence that it previously moved through the earlier stages. We never fill drug development “forward,” because many drug candidates fail to progress at each stage.
insulin analogue (ATC4 A10A), a non-insulin blood glucose lowering drug (A10B), or other diabetes drug (A10X). Cardiovascular drugs span 28 distinct ATC4 categories. Narrowing in on the subgroup of cardiovascular drugs that are beta blocking agents, Appendix Table A.1 reports 6 distinct ATC4 classes for beta blockers, distinguishing whether the beta blocker is present in isolation or in combination with various other drug types.

We interpret an ATC4 drug class as a “market,” where drugs within the class will typically be partial substitutes for one another. We drop ATC4 categories that are not categorized as drugs in FDB, such as medical supplies. We also restrict to ATC4 categories that contain at least one branded drug on the market as of 2011. Finally, we drop ATC4 categories with missing data on prices or the availability of generic and branded drugs as measured in FDB and ATC4s with missing data on prescription volume as measured in the 2011 Medicare Expenditure Panel Survey, as we need to be able to predict exclusion risk as a function of these market attributes for our main specification. After making these restrictions, our primary sample has 127 ATC4 classes. Table 1 Panel B shows the summary statistics of various market characteristics for our sample ATC4s, separately based on whether or not they experienced exclusions in 2012 or 2013.

4 Formulary Exclusions

4.1 Descriptive statistics

Figure 2 illustrates the rise of drug exclusions over time and across PBMs. CVS is the first major PBM to implement a closed formulary, starting with the exclusion of 38 drugs in 2012. CVS advertises on its payer-facing website, “[W]e were the first pharmacy benefit manager...to remove certain high-cost drugs from our Standard Formulary and give preference to lower-cost, clinically appropriate alternatives leading to cost savings for clients.”\(^{13}\) Over the next six years, CVS oversaw a sustained expansion of exclusions, with more drugs being added to its exclusion lists each year. Express Scripts introduced its exclusion list in 2014, followed by OptumRx in 2016. By 2017, a total of 300 drugs were ever excluded by at least one of the three major PBMs. 75% of these excluded drugs had

\(^{13}\)https://payorsolutions.cvshealth.com/programs-and-services/cost-management/formulary-management
no molecularly equivalent generic substitute on the market. Figure 3 plots exclusions by
disease category at the drug level. Each bubble represents a disease category in a year, and
the size of the bubble reflects the number of drugs excluded by at least one PBM in that
category. From the outset, diabetes drugs have consistently been the most frequently
excluded. Other diseases with high numbers of exclusions include cardiovascular,
endocrine, and respiratory diseases.

The introduction of exclusion policies represented a major shift in market facing drug
manufacturers, with the scope and frequency of exclusions expanding steadily over time. For
instance, PBMs began to contravene a prior “gentlemen’s agreement” to keep cancer drugs
off exclusion lists (The Doctor-Patient Rights Project 2017). Starting in 2016, CVS and
Express Scripts excluded fluorouracil creams (which treat skin cancer and pre-cancer skin
conditions). In 2017, CVS expanded its exclusion list to oncology drugs, excluding drugs
such as Gleevec and Tasigna (which treat chronic myelogenous leukemia) and Nilandron and
Xtandi (which treat prostate cancer).14

In the remainder of this section, we analyze the effect of exclusions on drug sales and
describe how exclusion risk differs across markets, as defined by drug therapeutic classes.

4.2 The impact of exclusions on drug sales

A PBM’s formulary choice has a substantial impact on patients’ drug utilization. A
large body of work has documented that patient demand for drugs is elastic to the
out-of-pocket price, suggesting that eliminating insurance coverage for excluded drugs will
suppress demand.15 Recent evidence from plans that switch to the restrictive CVS
formulary find evidence of therapy discontinuation for patients on excluded drugs
(Shirneshan et al. 2016). While CVS was the first PBM to implement a closed formulary
in 2012, an older literature examined individual insurance plan’s formulary choices. These
earlier formulary coverage decisions affect many fewer patients than the national PBM

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14 Coverage of cancer drugs was mandated for privately administered Medicare Part D plans, but was not
mandated for private plans in general. When CVS began excluding cancer drugs in 2017, the PBM stipulated
that this restriction would only affect new patients (The Doctor-Patient Rights Project 2017).

15 For example, the following papers find evidence of negative price elasticities for drugs, as a function
formularies we study here, but are likely to have similar effects on the drug choices of enrolled patients. This research has found that closed formularies induce patients to switch away from excluded drugs (Motheral and Henderson 1999; Huskamp et al. 2003) and reduced healthcare spending (Chambers et al. 2016). Further, doctors who treat many patients insured with restrictive formularies are less likely to prescribe excluded drugs even to patients with open formulary insurance plans (Wang and Pauly 2005).

To test whether these patterns hold in our setting, we investigate the link between PBM formulary exclusions and drug sales, using data on prescription drug claims from Medicare Part D from 2012-2017. We estimate the impact of exclusions on claims for drugs that were already on the market and had Part D claims, using a model that includes drug fixed effects and controls for year and time-varying market characteristics. Because Medicare Part D regulation over this period disallowed formulary exclusions from six protected drug classes, this analysis studies the 161 excluded drugs that are not in a protected class.\(^\text{16}\)

The distribution of Part D claims per drug is highly right-skewed. Appendix Table A.2 reports that the mean number of annual Part D claims per drug is 158,298 for non-excluded drugs, while the median is 4,357. Drugs that eventually receive an exclusion have an even higher mean (454,433), consistent with the evidence from our FDB analysis that exclusions typically target high-volume drugs. Due to the high variance of prescription volume, our primary outcome in the regression analysis is the natural log of the drug’s claim count.

Regression results reported in Table 2 find that each additional excluding PBM decreases a drug’s prescription volume by 24% \(\left( e^{-0.274} - 1 \right) \). This coefficient is identified from within-drug changes in formulary exclusion status, since the estimating equation includes drug-specific fixed effects to control for the drug’s baseline popularity, and as well as drug age \( \times \) calendar year fixed effects to capture lifecycle patterns. Additional controls for time-varying demand for the drug class, captured with ATC4 \( \times \) calendar year fixed effects, do not attenuate the estimate; these results are reported in Column 2. As an alternative outcome, we consider the impact of exclusions on the excluded drug’s market share (i.e., share of total Medicare Part D claims) within the ATC4 class. We find very

\(^{16}\)The protected classes are antidepressants, antipsychotics, anticonvulsants, antineoplastic agents, antiretroviral agents, and immunosuppressants. Of the 181 excluded drugs prescribed in Part D, only 20 fall into these classes.
similar results: each additional excluding PBM reduces a drug’s market share by 20% percent.

This analysis of exclusion impact will tend to overstate the magnitude of these effects on excluded drugs if patients substitute from excluded drugs to non-excluded drugs within the same ATC4 category. These spillovers will inflate prescription volume in the “control group” of non-excluded drugs, increasing the difference between excluded and non-excluded drugs. We take these results as informative of the direction of exclusion impact, but measuring the full set of cross-drug substitution elasticities (which are likely to be very heterogeneous across drug classes) is beyond the scope of this project. Another limitation of this analysis is that it cannot measure prescription drug sales that are not claimed in Medicare Part D; if formulary exclusions leads patients to pay fully out-of-pocket for the drugs without requesting insurance coverage, we will not have a record of it in our data.

In Appendix Table A.3, we investigate whether the immediate exclusion of newly released drugs depresses drug diffusion, relative to the diffusion of other drugs in the same ATC4 class. These estimates suggest that formulary exclusion depresses prescription volume of new drugs by 68% ($e^{-1.147} - 1$), although the estimates are noisier because they focus on a small set of 13 drugs that face immediate exclusion by at least one PBM within 1 year of FDA approval.

### 4.3 Predictors of formulary exclusion risk

Twelve percent of ATC4 drug classes experienced exclusions in 2012 and 2013, the first two years of the closed formulary policy. Having provided evidence that exclusions harm revenues, we next examine the factors that predict exclusion risk. Prior descriptions of PBMs’ exclusion strategy have, for example, argued that exclusions target drugs that have escalated price increases, limited clinical evidence, or target an overly broad patient population (Cournoyer and Blandford 2016).

To examine which characteristics predict exclusions at the drug-market level, we regress an indicator for whether a drug class experiences exclusions in 2012 or 2013 on various ATC4 level market characteristics. Using data from FDB described in Section 3, we construct the following measures of potential predictors of exclusion risk for 127 ACT4 classes: measures of the availability of therapeutic alternatives such as the number of existing branded drugs approved within an ATC4, the number of existing generics within the same class, or the
number of finer-grained ATC7 subclasses (which indicate specific chemical substances). We also measure the expected size of the patient population by using information on total prescription volume across all drugs in a given ATC4 class; this information is calculated from the 2011 Medicare Expenditure Panel Survey. Finally, we collect data on the price of already approved branded and generic drugs, keeping in mind that price data do not reflect the rebates that manufacturers often pay to PBMs. All of these market characteristics are from 2011, before the introduction of first exclusions in 2012.

Figure 4 plots the coefficients of bivariate linear regressions of exclusion on each drug class characteristic; these regressions estimate how standardized market characteristics predict the probability of having at least one exclusion in the ATC4 class in 2012 or 2013. We find that drug classes with higher prescription volume and more existing treatment options (measured as the number of distinct drugs on the market) are more likely to experience exclusions. These patterns are consistent with the contemporaneous analysis of industry experts. Mason Tenaglia, vice president of IMS Health described formulary exclusions as targeting “me-too drugs” with multiple therapeutic substitutes (Reinke 2015). In an interview, the chief medical officer of Express Scripts echoed this strategy of targeting me-too drugs, and further described a focus on excluding drugs with a larger number of prescribed patients: “[T]here’s no reason to go after trivial drugs that aren’t going to drive savings” (Miller and Wehrwein 2015). We find no statistically significant relationship between drug prices in the class and exclusion risk, but because our data does not measure prices net of rebates, these correlations are difficult to interpret.

Having shown that these market characteristics have predictive power, we use them to construct an index of an ATC4 drug class’s likelihood of facing exclusions. To do so, we fit a logistic regression to predict whether a drug class experience exclusions in 2012 or 2013 as a function of all of the ATC4 market characteristics (measured as of 2011). For this regression, the unit of observation is a single ATC4 drug class \(c\). We then use the regression’s fitted values to construct the predicted exclusion risk of each ATC4: \(\Pr(\text{Excluded})_c\). Appendix Table A.4 shows the results of this exercise and Appendix Figure A.1 plots the resulting distribution of predicted exclusions.

The goal of our analysis is to understand how exclusion risk affects upstream R&D decisions. Our theory predicts that changes to upstream investments are shaped by the
expected net present value (NPV) of projects in a drug class: exclusions can decrease NPV either because firms anticipate that the new drug may be excluded, or because firms anticipate that they will have to pay high rebates in order to avoid exclusions. Our primary analysis defines treatment exposure as predicted exclusion risk in order to consider the impact of exclusions not only on drug classes with realized exclusions but also on classes with similar market characteristics where high rebates may be paid to avoid exclusions.

We test whether our measure of exclusion risk has empirical validity by asking whether predicted exclusion risk fit from 2012 and 2013 exclusion lists correlates with subsequent exclusions in 2014-2017. Table 3 shows that our measure of exclusion risk has out-of-sample prediction power. In Column 1, we show that a 1 standard deviation increase in exclusion risk (estimated based on 2012 and 2013 exclusions) correlates with a 17 percent point increase in the likelihood that an ATC4 class experiences exclusions in later periods. In Column 2, we repeat this exercise restricting to the subset of ATC4s that do not experience any exclusions during the first wave of exclusions in 2012 and 2013. This set includes drug classes that are actually at a very low risk of experiencing exclusions (in which case we would not expect them to see future exclusions) as well as those that were at high risk, but which were able to avoid early exclusions perhaps by offering higher rebates. Among this set of drug classes with no early exclusions, our measure of predicted exclusion risk is still significantly correlated with future exclusions. This result suggests that exclusions followed a consistent and predictable pattern over our study period, and that market characteristics can form valid out-of-sample predictions of at-risk drug classes.

5 The Impact of Exclusion Risk on Subsequent Drug Development

In our model, we predict that exclusion risk decreases the NPV of projects in more affected drug classes, and therefore dampens upstream investments in these areas. This logic is echoed by pharmaceutical executives: AstroZeneca leaders, for example, describe meeting “payer criteria required for global reimbursement” as a crucial input into their decisions about R&D investment (Morgan et al. 2018). In this section, we use our measure
of drug-class exclusion risk to study how upstream firms’ investment strategies respond to exclusion risk.

5.1 Empirical strategy

Our main specification compares drug development behavior across ATC4 drug classes that vary in their ex-ante risk of exclusion, before and after the rise of closed formulary policies:

\[
\text{Development}_{ct} = \beta_1 \Pr(\text{Excluded})_c \times I(\text{Year}_t \geq 2012) + X_{ct} \gamma + \delta_c + \delta_t + \epsilon_{ct}
\]  

(1)

In Equation (1), Development\(_{ct}\) refers to various measures of the number of new drug candidates in drug class \(c\) at year \(t\). We define a drug class’s extent of treatment using \(\Pr(\text{Excluded})_c\), described above in Section 4.3. In Section 5.3, we show that our results are robust to an alternative definition of treatment that uses data on realized exclusions, rather than exclusion risk. The regressions control for drug class fixed effects (\(\delta_c\)), year fixed effects (\(\delta_t\)), and time-varying drug market controls (\(X_{ct}\)).

To interpret our primary coefficient of interest, \(\beta_1\), as the causal impact of drug exclusions on development activity, we must assume that development activity in ATC4s with different predicted degrees of exclusion risk would have followed parallel trends in the absence of formulary exclusions. We use event study graphs over a 5 year pre-period to assess the plausibility of this assumption. These graphs are based on a modified version of Equation (1), which replaces the single indicator variable for being in the post period (\(I(\text{Year}_t \geq 2012)\)) with a vector of indicator variables for each year before and after the introduction of PBM exclusion lists in 2012.

5.2 Main results

We begin by studying how trends in drug development activity vary across ATC4 classes as a function of formulary exclusion risk. Figure 5 shows the difference-in-differences results in an event study framework. There appears to be little difference in drug development across excluded and non-excluded ATC4s prior to 2011, suggesting that the parallel trends assumption is supported in the pre-period. Development
activity across excluded and non-excluded drug classes begins to diverge in 2012, and these differences grow until 2017, the last full year of our sample.

Table 4 presents our main regression results. The outcome is the total number of drug candidates within a class that entered any stage of development each year. In Column 1, we estimate that a one standard deviation increase in the risk that the class has formulary exclusions leads to 3.6 fewer advanced drug candidates each year, from a mean of 30.6 advancing candidates.\textsuperscript{17} In Column 2, we include controls for a variety of time-varying market conditions at the ATC4 class level: the number of approved drugs in that class, the number of approved generic drugs, the mean price of branded drugs minus the mean price of generic drugs, and the number of ATC7 subclasses (which indicate specific chemical substances) with approved drugs. Adding these controls lowers our estimate slightly from 3.6 to 3.3 fewer drug candidates per 1 standard deviation increase in class exclusion risk. We find similar results after log-transforming the outcome, suggesting that development activity declines by 5-6\% in excluded classes for every 1 standard deviation increase in class exclusion risk, as reported in columns 3 and 4.

Table 5 decomposes the total effect by drug development stage. In Table 5, we find the largest percent declines for earlier stage drugs. Exponentiating the reported coefficients, we estimate a 7\% decline in new pre-clinical candidates for every 1 standard deviation increase in the probability that the class has exclusions, as compared to a decline in advancing candidates of 5\% in Phase 1, 5\% in Phase 2, and 4\% in Phase 3. We find consistent results when measuring the outcome in levels (rather than logs), and report these results in Appendix Table A.5 and Appendix Figure A.2. The patterns in the event study difference-in-differences plots are very similar across development stages.

We interpret these findings in the context of the drug development process, where Phase 1 trials generally assess safety, Phase 2 trials provide preliminary evidence of efficacy, and Phase 3 trials are the large-scale expensive trials that firms rely upon to generate data for FDA approval. Of these investment stages, Phase 3 trials are the most costly, with average costs estimated over $250 million per drug in 2013 dollars (DiMasi et al. 2016). Given that the marginal cost of continuing to develop a candidate drug remains high through the end of

\textsuperscript{17}As reported in Appendix Figure A.1, the standard deviation of the probability the class faces exclusions is 0.15. Using the coefficient reported in Table 4, we calculate $-24.03 \times 0.15 = -3.6$. 
phase 3 trial stage, it is sensible that firms would be more likely to drop drug candidates even at this relatively late stage. Further, a drug is more likely to be excluded from formularies if it offers few benefits relative to existing treatments. Phase 2 trials provide the first evidence of clinical efficacy. If a drug shows only marginal promise, then a firm concerned about the possibility of exclusions may choose to end its development efforts rather than committing to very expensive Phase 3 trials.

In contrast, we find no effect for new drug launches; at the point when a drug has completed Phase 3 trials, the bulk of R&D expenses are already sunk. As a result, concerns about coverage would be less likely to impact a firm’s launch decisions. Over time, we would expect that launches would also fall in affected drug classes as the pipeline narrows, but, given the long time lags in bringing a drug through each development stage, this effect would not be immediate.

5.3 Robustness checks

In this section, we show that our results are robust to alternative choices for defining exclusion risk, linking drug candidates to drug classes, and calculating standard errors.

First, we show that our results are consistent when we apply an alternative definition of a drug class’s exclusion risk. In our primary analysis, we use 2011 ATC4 market level characteristics to predict exclusion risk. An alternative approach would be to look at realized exclusions and ask whether drug classes that actually experienced exclusions saw reductions in development. Appendix Figure A.3 and Appendix Table A.6 presents results using a binary definition of treatment (whether or not an ATC4 class actually experienced an exclusion in 2012 or 2013) and show a similar pattern of results as our main analysis.

Second, we show that our results are robust to the method we use to match drug candidates to drug classes. In our primary analysis, we match drug candidates to ATC4 drug classes using a direct linkage when Cortellis provides it (in 43% of cases); in cases where direct linking is not possible, we rely on indirect linking based on using a drug candidate’s area of therapeutic application (ICD9) combined with an ICD9-ATC4 crosswalk. Appendix B provides further details on how we linked the drug candidates from Cortellis to ATC4 classes. Appendix Tables A.7 and Appendix Figure A.4 show that our
results are similar when either using only direct linkages (Panel A) or only indirect linkages (Panel B).

Finally, conventional inference can over-reject when the number of treated clusters is small, so we also implement a correction using the wild cluster bootstrap (Cameron et al. 2008; Djogbenou et al. 2019). In Appendix Table A.8, we report 95% confidence intervals calculated with the wild cluster bootstrap for our main regression results; our findings remain statistically significant. In this table, we also present robustness to using the inverse hyperbolic sine function rather than log transformation to better account for ATC4 categories with no development in some years. Results are very close to the log transformed outcomes reported in the main text, and remain statistically significant.

5.4 Classifying foregone innovation across drug classes

In this section, we describe the drug classes and types of projects that experienced the greatest declines in R&D as a result of formulary exclusions. To assess the decline in drug development for each ATC4 drug class, we compare the number of candidates we predict would have been developed in the absence of exclusions to the number we predict in the presence of exclusions. This analysis examines how exclusions impact the allocation of R&D resources across drug classes that vary in their size, competitiveness, or level of scientific novelty. We focus on allocation across drug classes because our theoretical framework, formalized in Appendix A, predicts that exclusions will affect the relative investments in drug development across classes.18

Our analysis is based on the specification reported in Table 4 Column 4; this is our preferred specification because it controls for a battery of time-varying drug class observables and generates the most conservative point estimate. To measure predicted new drug candidates in the presence of exclusions, we calculate the fitted value prediction of drug development activity for every year of the post-period. To recover the predicted new drug candidates absent exclusions, we repeat this exercise after setting the treatment variable \( \Pr(\text{Excluded}) \times I(\text{Year}_t \geq 2012) \) equal to zero for all observations. We use these

18The impact of exclusion policies within a drug class are less obvious; while it is possible that exclusions may change the characteristics of promoted molecules within a drug class, these effects may be smaller and more difficult to measure. Because ATC4 drug classes already represent relatively narrow categories, there is limited scope to change the scientific novelty of investment within the class, for example.
predictions as the basis for calculating the percent decline in development activity attributable to exclusion risk. We then compare the predicted decline in development activity across several ATC4 drug class characteristics, measured before the introduction of the formulary exclusions.

**Availability of existing therapies & market size**

For our first counterfactual comparison, we divide drug classes into terciles based on the number of existing therapies, as measured by the number of distinct drugs available within that class as of 2011. Figure 6 Panel A compares predicted drug development activity to the counterfactual development levels predicted to have occurred absent exclusions. Consistent with our model, we see the largest declines in drug classes with more existing therapies: among drug classes in the top tercile of available therapies, exclusions depress development by nearly 8%. By contrast, exclusions depress development by less than 2% for drug classes in the bottom tercile of pre-existing therapies. This result indicates that formulary exclusions lead firms to reduce their investments in drugs that are more likely to be incremental entrants to more crowded therapeutic areas.

In Figure 6 Panel B, we perform the same analysis splitting drug classes by market size, as measured by the volume of prescriptions filled in 2011 (estimated from the MEPS data). We find that formulary exclusions disproportionately impact drug development in therapeutic classes with many patients. For drug classes in the top tercile of prescription volume, drug development is predicted to decline by more than 10% after the introduction of formulary exclusions.

**Disease category**

Next, Figure 7 explores the extent of foregone innovation across therapeutic areas. To do so, we map ATC4 drug classes into disease categories and calculate the percentage change in drug development from the counterfactual predicted absent exclusions. Our results indicate that closed formulary policies generated substantial declines in development across a range of disease classes, led by diabetes, where we predict more than a 20% decline in the number of new drug candidates. The next set of affected disease categories, predicted to lose 8-10% of new drug candidates, includes cardiovascular,
respiratory, autonomic & central nervous system, and pain/inflammation related conditions. Meanwhile, we find little evidence of significant declines in development activity for many acute diseases, such as infections, viruses, and cancers.

This set of evidence is consistent with the hypothesis that closed formulary policies reduce firms’ incentives to develop additional treatments in large markets, where new drugs may face a high likelihood of exclusion. This creates a tension: while foregone innovations are likely to be incremental in the sense that the most impacted drug classes already have many existing treatment options, they are also likely to have benefited more patients because the most impacted drug classes also had the largest base of prescribed patients.

**Scientific novelty**

Finally, we examine the relative effect that formulary exclusions had on R&D investment across areas with differing measures of scientific novelty. To assess scientific novelty, we match drug candidates within an ATC4 class to the scientific articles cited by their underlying patents, making use of patent-to-science linkages created by Marx and Fuegi (2020). We then create two measures of the scientific novelty of research in a drug class (averaged over 2007-2011). First, we calculate how often patents in a drug class cited recent science, defined as articles under 5 years old as of 2011. In Panel A of Figure 8, we find that exclusions generate twice as large a decline in R&D in drug classes that were rarely citing recent science in the policy pre-period, compared to those that were (8% vs. 4% predicted declines, respectively).

Second, we measure how “disruptive” research in a drug class is likely to be. To do this, for each of the scientific article cited by the underlying patents of the drugs, we follow Funk and Owen-Smith (2017) and measure how many of a focal article’s forward citations also cite the focal article’s backward citations. This “disruptiveness” index, ranging from -1 (consolidating) to 1 (destabilizing), captures the idea that a research article that represents a paradigm shift will generate forward citations that will not cite the breakthrough article’s backward citations. In contrast, a review article that consolidates a knowledge domain will receive forward citations that will also cite the same citations as the review article. In Figure 8 Panel B, we report predicted changes in drug development as a function of how
disruptive the patents underlying the drugs were in this class over the pre-period (proxied by the average disruptiveness index of the cited science). Formulary exclusions spurred larger reductions in development in drug classes citing the least disruptive research.

Together, these results suggest that exclusions encouraged a relative shift in R&D dollars toward investment in drug classes engaging with more recent, novel science.

6 Discussion

So far, we have shown that closed formulary policies lead pharmaceutical firms to invest less in R&D for areas more likely to face exclusions. This response results in a shift in development across drug classes: away from large markets (in terms of available therapies and prescription volume) and common disease classes treating chronic conditions such as heart diseases and diabetes. Moreover, our evidence also indicates that R&D effort shifts away from drug classes with older and less disruptive underlying science. Overall, these results suggest that exclusions direct upstream research away from more incremental treatments.

As discussed in Section 2, the welfare implications of this behavior are theoretically ambiguous. There are two key considerations. First, exclusions reduced development of drugs for crowded markets; what is the value of this sort of forgone incremental innovation? Second, when investment declines in high-exclusion risk classes relative to other classes, does this contribute to an aggregate decline in pharmaceutical R&D, or is some of the investment redirected to innovation in other drug classes within the sector?

Regarding the first question, assessing the value of late entrants to a drug class is difficult because even incremental drugs can reduce side effects, improve compliance by being easier to take, or generate price competition and improve access (Regnier 2013; Hult 2014). Further, even if the new drugs never make it to market, incremental drug candidates may generate scientific spillovers, leading to further innovation over a longer time horizon.

Second, our empirical approach cannot test for aggregate changes in development activity, which would be identified solely by time-series trends. By estimating equation (1), we isolate the relative change in development activity in drug categories with exclusions, compared to the changes in non-excluded categories. These differences could come from a combination of
absolute declines in R&D for excluded classes or it could come from a shift in development from classes with high- to low-exclusion risk.

Absent financial frictions, we would expect that the introduction of closed formularies would decrease the expected value of investments in drug classes at high risk of facing exclusions, but should have little to no impact on the net present value for drugs in classes at low risk of facing exclusions. In such a world, we would interpret our results as leading to an absolute decline in drug R&D. However, a large finance literature has shown, both theoretically and empirically, that even publicly traded firms often behave as though they face financial frictions (Myers and Majluf 1984; Froot et al. 1993; Brown et al. 2009). This is especially true in pharmaceuticals and other R&D intensive sectors where intellectual property is more difficult to collateralize or value (Fernandez et al. 2012; Kerr and Nanda 2015; Krieger et al. 2019). For example, it is common for firms to set their R&D budgets by allocating a percentage of revenues from the previous year.

In the event that exclusion policies generate some degree of reallocation away from older drug areas toward newer ones, a welfare analysis would need to take into account the relative value of research in these areas. In our case, this would require weighing the value of additional incremental innovations aimed at larger markets against the value of earlier-in-class innovations for less common conditions.

7 Conclusion

Amid rising public pressure, government and private payers are looking for ways to contain drug prices, while maintaining incentives for innovation. In this paper, we study how the design of downstream insurance policies—namely, those related to drug coverage—impact upstream investments in pharmaceutical R&D.

We find that drug classes facing a one standard deviation greater risk of experiencing exclusions see a 5% decline in drug development activity following the introduction of closed formulary policies. These declines in development activity occur at each stage of the

\[19\]Moreover, if exclusion policies have positive spillovers on development in non-excluded categories (e.g., due to within-firm investment reallocation), our estimates will tend to overstate the magnitude of the total decline in R&D investment in excluded categories. By contrast, if exclusion policies have negative spillovers on non-excluded categories (e.g., due to a fall in revenue reducing available development dollar), our estimates will tend to understate the magnitude of the investment decline in excluded categories.
development process, from pre-clinical through Phase 3 trials. In aggregate, our results suggest that PBMs wielded the threat of formulary exclusion in a way that shifted the relative allocation of R&D effort away from incremental treatments for common conditions such as heart diseases and diabetes, as well as away from drug classes with many existing therapies on the market and older, less novel underlying science.

Taken together, our results provide strong evidence that insurance design influences pharmaceutical R&D. Leaving aside the specifics of which drug classes faced greater exclusion risk in our setting, an overarching point that our paper makes is that pharmaceutical firms anticipate downstream payment policies and shift their upstream R&D efforts accordingly. Viewed from a public policy perspective, this finding opens the door for insurance design to be included as a part of the broader toolkit that policymakers use to encourage and direct investments in innovation. In particular, public policy related to innovation has almost exclusively focused on ways that the public sector can directly influence the returns to R&D, such as through patents, tax credits, research funding, or other direct subsidies. Our results suggest that, in addition, managers and policymakers can use targeted coverage limitations—for example, those generated by value-based pricing—to shift R&D efforts away from drugs with limited incremental clinical value.

The limitations of our analysis suggest several important directions for future work. First, our identification strategy allows us to document a relative decline in R&D in high exclusion risk categories; more research is needed in order to assess the extent to which policies that limit the profitability of a specific class of drugs generate aggregate declines in R&D or induce reallocations toward other areas. Second, it remains a challenge to place an accurate value on the innovation that is forgone as a result of the exclusion practices we study. While we focus on the availability of existing treatments, prescription volume, and measures of scientific novelty, these are not complete descriptions of the clinical and scientific importance of potentially foregone drugs. Third, because we cannot directly observe drug price rebates, we cannot directly quantify the reductions in revenue precipitated by formulary exclusion policies. Finally, as formulary exclusion policies continue to expand—toward smaller drug markets and those in which there are fewer therapeutic substitutes—additional research will be needed to see if our findings extrapolate to those settings.
References


Figure 1: Pharmaceutical Payment and Supply Chain Example

Notes: Illustration of the flow funds and prescription drugs for a prescription drug purchase covered by a Medicare Part D Insurance plan. Other private insurance plans using PBMs have similar flow of funds. Figure credit to Government Accountability Office (2019).
Figure 2: Number of Excluded Drugs by PBMs

Notes: This figure plots the number of drugs excluded by each of the three Pharmacy Benefit Managers. CVS was the first to begin excluding drugs in 2012, followed by Express Scripts in 2014 and OptumRx in 2016.
Figure 3: Number of Excluded Drugs by Disease Categories

Notes: Each bubble represents a disease category in a year, and the size of the bubble reflects the number of drugs that were excluded by CVS, Express Scripts, or OptumRx in that disease category. There were a total of 300 drugs that were ever excluded from 2012-2017 by at least one of the three PBMs. Of these 300 excluded drugs, we were able to match 260 of them to the First Data Bank data, from which we obtained the ATC4 data. We manually matched each ATC4 to a disease category; this disease taxonomy was adapted from the disease categories provided by the PBMs in their exclusion lists.
Figure 4: Predictors of Exclusion Risk

Notes: We used the 2011 market characteristics of the ATC4 class to predict exclusion risk. The plotted coefficients were generated by conducting bivariate linear regressions of whether an ATC4 class had at least one drug excluded in 2012 or 2013 on each characteristic of the ATC4 class. Independent variables were standardized (divided by their standard deviation). All of the coefficients, except the price variable, were significant at the 5% level. Since not every ATC4 class had data on all of the characteristics, sample size differed across the regressions: 197 ATC4 classes when predicting exclusion risk using the number of brand NDCs, generic NDCs, or ATC7s, 134 when using brand price premium, and 165 when using total prescription volume. Data on prices, the number of brand and generic NDCs, and the number of ATC7s are from FDB; data on total prescription volume are from the 2011 Medical Expenditure Panel Survey.
Figure 5: Impact of Predicted Exclusion Risk on New Drug Development: Event Study

Notes: Figure displays coefficient estimates and 90% confidence intervals from a modified version of Equation (1). The outcome variable is the annual count of new development activity (across all stages). To generate the event study graph, we replace the single post-period indicator variable ($I(Year \geq 2012)$) with a vector of indicator variables for each year before and after the introduction of PBM exclusion lists in 2012. We plot the coefficients on the interaction of these year indicators and a continuous measure of predicted exclusion risk. (Exclusion risk is predicted using 2011 market characteristics, prior to the introduction of PBM formulary exclusions. Details on the prediction of exclusion risk can be found in Appendix Table A.4.) The regression controls for ATC4 fixed effects and year fixed effects. The sample includes 1,397 ATC4-year observations.
Figure 6: Counterfactual Development Activity by Pre-Period Availability of Existing Therapies & Market Size

A. Reduction in development by number of drugs in class

B. Reduction in development by number of prescriptions in class

Notes: This figure displays the percent decrease in annual development attributable to exclusions. Predictions are based on our estimation of equation (1); we match the specification reported in Table 4 column 4. The figure shows the percent difference between predictions at the ATC4 × year with and without exclusions, averaged over the post-period (2012-2017). In Panel A, we group ATC4 drug classes by terciles of the number of existing drugs in the class (in 2011); data on existing drugs is from First Data Bank. In Panel B, we group ATC4 drug classes by the number of prescriptions written in the class (in 2011); data on prescriptions is from the 2011 Medical Expenditure Panel Survey. Drug classes are weighted by the number of drugs with advancing development over the pre-period.
Notes: This figure plots the predicted percent decline in drug development activity attributable to formulary exclusions, by disease class. Predictions are based on our estimation of equation (1); we match the specification reported in Table 4 column 4. We manually matched each ATC4 to a disease category; this disease taxonomy was adapted from the disease categories provided by the PBMs in their exclusion lists.
Figure 8: Counterfactual Development Activity by Pre-Period Measures of Scientific Novelty

A. % Citing Recent Science

B. Average “Disruptiveness” Index

Notes: This figure displays the percent decrease in annual development attributable to exclusions. Drug classes are divided into terciles according to attributes of patents associated with drug development activity over the pre-period, averaged from 2007-2011. Panel A groups drug classes by the share of pre-period patents in a drug class citing recent science as of 2011 (recent is therefore defined as publications between 2006 and 2011). Panel B groups drug classes by the average “disruptiveness” index of patents in the drug class over the pre-period, which is a measure that captures how disruptive the scientific articles associated with the patent are; the index ranges from -1 (least disruptive) to 1 (most disruptive) and was originally developed by Funk and Owen-Smith (2017).
Table 1: Summary Statistics

(A) New Drug Development

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<th>Mean</th>
<th>Std. Dev.</th>
<th>Median</th>
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<tbody>
<tr>
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<tr>
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<td>Launch</td>
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(B) ATC4 Characteristics

<table>
<thead>
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<th>ATC4 market characteristics in 2011</th>
<th>ATC4s with early exclusions</th>
<th>ATC4s without early exclusions</th>
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<tbody>
<tr>
<td>Mean N of generic NDCs</td>
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<tr>
<td>Mean N of brand NDCs</td>
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<tr>
<td>Mean N of ATC7s within ATC4</td>
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<td>Mean brand price - mean generic price</td>
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<td>Mean total prescription volume (millions)</td>
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<td>Number of ATC4s</td>
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</table>

Notes: Panel A summarizes the annual drug development activity from 2007-2011 in the Cortellis data. The sample includes 1,397 ATC4-year observations. The panel reports the annual number of drug candidates within an ATC4 class that entered different development stages. Panel B summarizes ATC4 market characteristics in 2011. Column 1 reports results for ATC4 classes with at least one excluded drug in 2012-2013; Column 2 reports results for ATC4s with no exclusions in 2012-2013. Data on pricing and the number of available drugs are from First Data Bank; data on on total prescription volume are from the 2011 Medical Expenditure Panel Survey.
Table 2: Impact of Exclusions on Prescription Volume

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<th>(3) Log(Mkt. Share)</th>
<th>(4) Log(Mkt. Share)</th>
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<tbody>
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<td>-0.220***</td>
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</tr>
<tr>
<td>Cohort X Year FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Market Controls</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

Notes: This table estimates the impact of PBM formulary exclusion on the volume of Medicare Part D insurance claims; each column reports a different regression specification. The unit of observation is a drug × year. The outcome variable in columns (1) and (2) is the natural log of the total number of annual claims; the outcome in columns (3) and (4) is the annual market share of the index drug relative to all other drugs in the ATC4 class. The key independent variable of interest is the number of formularies excluding the drug that year. All regressions include drug fixed effects and drug age X calendar year fixed effects. (Drug age is measured as number of years elapsed since market entry.) Specifications (2) and (4) include additional controls for ATC4 class × calendar year fixed effects to account for trends in demand for different drug classes. Data on prescription volume is from Medicare Part D 2012-2017 public use files. We analyze exclusions on 161 excluded drugs that are prescribed to Medicare Part D enrollees and are not in a protected class. Standard errors are clustered at the drug level. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.
### Table 3: Early Exclusion Risk and Later Exclusions

<table>
<thead>
<tr>
<th></th>
<th>(1) Pr(Exclusion)</th>
<th>(2) Late Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pr(Exclusion)</td>
<td>0.167***</td>
<td>0.150**</td>
</tr>
<tr>
<td></td>
<td>(0.0413)</td>
<td>(0.0624)</td>
</tr>
<tr>
<td>Observations</td>
<td>127</td>
<td>112</td>
</tr>
<tr>
<td>Sample</td>
<td>All ATC4s</td>
<td>ATC4s without early exclusions</td>
</tr>
</tbody>
</table>

Notes: Using a linear probability model, we regressed whether ATC4 classes that were highly predicted to be excluded by 2013 were more likely to be actually excluded later after 2013. Early exclusion risk is a continuous measure defined using the same specification underlying Table 4; we used 2011 market characteristics of the ATC4 class to predict whether the ATC4 class was at risk of exclusion by 2013. We then standardized this early exclusion risk variable. The outcome variable, late exclusion, is a binary variable that indicates whether the ATC4 was on any of the PBM’s exclusion list at least once in 2014-2017. Column 1 includes all ATC4s, while Column 2 drops ATC4s that were actually excluded by 2013. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.
### Table 4: Impact of Predicted Exclusion Risk on New Drug Development

<table>
<thead>
<tr>
<th></th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New Development</td>
<td>New Development</td>
<td>Log(1+New Dev.)</td>
<td>Log(1+New Dev.)</td>
</tr>
<tr>
<td>Post X Pr(Exclusion)</td>
<td>-24.03*** (5.894)</td>
<td>-21.98*** (6.571)</td>
<td>-0.382*** (0.108)</td>
<td>-0.333*** (0.115)</td>
</tr>
<tr>
<td>Observations</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
</tr>
<tr>
<td>Year FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ATC FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Market Controls</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Notes: This table reports results from estimation of equation (1); each column reports a different regression specification. The unit of observation is an ATC4 drug class × year. The outcome variable “New Development” is the annual count of new development activity (across all stages). The treatment variable is a continuous measure of predicted exclusion risk. (Exclusion risk is predicted using 2011 market characteristics, prior to the introduction of PBM formulary exclusions. Details on the prediction of exclusion risk can be found in Appendix Table A.4.) The “Post” period comprises years 2012 and later, after the introduction of PBM formulary exclusions. All specifications include year fixed effects and ATC4 fixed effects. Columns 2 and 4 include time-varying controls for each of the drug class characteristics listed in Table 1. Standard errors are clustered at the ATC4 level. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.
### Table 5: Impact of Predicted Exclusion Risk on New Drug Development By Stages

<table>
<thead>
<tr>
<th></th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
<th>(6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Log(1+All)</td>
<td>Log(1+Preclinical)</td>
<td>Log(1+P1)</td>
<td>Log(1+P2)</td>
<td>Log(1+P3)</td>
<td>Log(1+Launch)</td>
</tr>
<tr>
<td>Post X Pr(Exclusion)</td>
<td>-0.333***</td>
<td>-0.449***</td>
<td>-0.331***</td>
<td>-0.310***</td>
<td>-0.259**</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>(0.115)</td>
<td>(0.101)</td>
<td>(0.103)</td>
<td>(0.106)</td>
<td>(0.101)</td>
<td>(0.138)</td>
</tr>
<tr>
<td>Observations</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
</tr>
<tr>
<td>Year FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ATC FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Market Controls</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>N of Drug Candidates</td>
<td>Mean 30.61</td>
<td>17.39</td>
<td>6.54</td>
<td>4.57</td>
<td>2.11</td>
<td>1.02</td>
</tr>
</tbody>
</table>

**Notes:** See notes to Table 4. Each column reports a regression with a different outcome variable. Column 1 replicates the result reported in Table 4 column 4 on total development activity. The additional columns decompose this effect to explore how drug development changes at each phase, moving from the earliest observed preclinical activity in column 2 through the each phase of clinical trials and eventual launch on the market. Standard errors are clustered at the ATC4 level. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.
Figure A.1: Distribution of Predicted Exclusion Risk

Notes: This histogram plots the distribution of predicted exclusion risk of the 127 ATC4s in our main analyses. Summary statistics are also provided. See notes to Appendix Table A.4 for details on how the exclusion risk was calculated.
Figure A.2: Impact of Predicted Exclusion Risk on New Drug Development: Event Study By Stages

A. Pre-clinical

B. Phase 1

C. Phase 2

D. Phase 3

Notes: See notes to Figure 5. Each panel displays results from estimating the same equation with a distinct outcome variable. The outcome variables correspond to the number of drug candidates tested at the indicated phase within the ATC4 category and year. The sample includes 1,397 ATC4-year observations.
Figure A.3: Impact of Exclusions on New Drug Development: Event Study

Notes: These results parallel the specification underlying Figure 5, but with a new definition of exclusion exposure. Instead of defining exclusion risk as a continuous measure predicted using the 2011 market characteristics, the exclusion risk here is a binary variable that equals one if any drug in the ATC4 class was on a PBM exclusion list in 2012 or 2013. The sample includes 1,397 ATC4-year observations.
Figure A.4: Impact of Predicted Exclusion Risk on New Drug Development: Event Study, Alternative ATC4 Linking

(A) Directly Linked Approach Only

(B) Indirect Linking Approach Only

Notes: These results parallel the specification underlying Figure 5, but with alternative methods for linking drug candidates to ATC4 classes. In these figures, we have replaced our baseline outcome measure of development activity with two alternative outcomes that take different approaches to matching. In Panel A, we only count track development activity among the subset of drug candidates for which Cortellis directly reports the drug class. In Panel B, we impute ATC4s from ICD9 codes for all drug candidates, rather than relying on Cortellis’ reporting of drug class. Appendix B provides more details on how the drug candidates are linked to ATC4s.
### Table A.1: Examples of ATC4 Codes Defining Drug Markets

<table>
<thead>
<tr>
<th>ATC4 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A10</td>
<td>Diabetes drugs</td>
</tr>
<tr>
<td>A10A</td>
<td>Insulins and analogues</td>
</tr>
<tr>
<td>A10B</td>
<td>Blood glucose lowering drugs, excluding insulins</td>
</tr>
<tr>
<td>A10X</td>
<td>Other drugs used in diabetes</td>
</tr>
<tr>
<td>C07</td>
<td>Beta blocking drugs</td>
</tr>
<tr>
<td>C07A</td>
<td>Beta blocking agents</td>
</tr>
<tr>
<td>C07B</td>
<td>Beta blocking agents and thiazides</td>
</tr>
<tr>
<td>C07C</td>
<td>Beta blocking agents and other diuretics</td>
</tr>
<tr>
<td>C07D</td>
<td>Beta blocking agents, thiazides and other diuretics</td>
</tr>
<tr>
<td>C07E</td>
<td>Beta blocking agents and vasodilators</td>
</tr>
<tr>
<td>C07F</td>
<td>Beta blocking agents, other combinations</td>
</tr>
</tbody>
</table>

**Notes:** This table provides examples of ATC4 classes for illustrative purposes. Our sample includes 127 distinct ATC4 classes. A complete listing of the ATC4 class definitions that guided this analysis can be found in WHO Collaborating Centre for Drug Statistics Methodology (2010).
# Table A.2: Summary Statistics, Part D Claims per Drug

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Median</th>
<th>No. of obs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claims for non-excluded drugs (all ages)</td>
<td>158,298</td>
<td>842,241</td>
<td>4,357</td>
<td>3,923</td>
</tr>
<tr>
<td>Claims for excluded drugs (all ages)</td>
<td>454,433</td>
<td>1,193,389</td>
<td>45,374</td>
<td>867</td>
</tr>
<tr>
<td>Market share, non-excluded drugs (all ages)</td>
<td>0.187</td>
<td>0.305</td>
<td>0.027</td>
<td>3,923</td>
</tr>
<tr>
<td>Market share, excluded drugs (all ages)</td>
<td>0.113</td>
<td>0.211</td>
<td>0.028</td>
<td>867</td>
</tr>
<tr>
<td>Claims for new drugs, not excluded on entry</td>
<td>125,826</td>
<td>395,623</td>
<td>7,123</td>
<td>1,811</td>
</tr>
<tr>
<td>Claims for new drugs, excluded on entry</td>
<td>193,731</td>
<td>452,800</td>
<td>27,799</td>
<td>59</td>
</tr>
<tr>
<td>Market share of new drug, not excluded on entry</td>
<td>0.147</td>
<td>0.264</td>
<td>0.027</td>
<td>1,811</td>
</tr>
<tr>
<td>Market share of new drug, excluded on entry</td>
<td>0.063</td>
<td>0.183</td>
<td>0.004</td>
<td>59</td>
</tr>
</tbody>
</table>

**Notes:** This table reports summary statistics from the Medicare Part D public use file. Data tracks annual claims per drug in 2012-2017; the unit of observation is the drug-year pair. Market share is calculated as the fraction of prescription drug claims in the ATC4 class that are for the index drug. The first four rows report results for all drugs, comparing those that were ever excluded to those that were never excluded during the sample period. The last four rows report results for the subset of “new drugs,” defined as drugs that enter the market in 2007 or later, and so are ten years old or younger for the duration of the sample. These final rows compare new drugs that were excluded within a year of entry to those that were not excluded in the first year.
### Table A.3: Impact of Immediate Exclusion on Prescriptions of New Drugs

<table>
<thead>
<tr>
<th></th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Log(No. of Claims)</td>
<td>Log(No. of Claims)</td>
<td>Log(Market Share)</td>
<td>Log(Market Share)</td>
</tr>
<tr>
<td>Excluded at Entry</td>
<td>-1.147**</td>
<td>-1.193**</td>
<td>-1.094**</td>
<td>-1.099*</td>
</tr>
<tr>
<td></td>
<td>(0.573)</td>
<td>(0.591)</td>
<td>(0.546)</td>
<td>(0.564)</td>
</tr>
<tr>
<td>Observations</td>
<td>1,846</td>
<td>383</td>
<td>1,846</td>
<td>383</td>
</tr>
<tr>
<td>ATC4 FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Cohort X Year FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Limited sample</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

**Notes:** This table investigates the impact of immediate exclusion by one or more PBM on claims for a new prescription drug. Each column reports results from a separate regression. The regressions include ATC4 fixed effects, and drug age X calendar year fixed effects. Identifying variation comes from the debut of multiple drugs within an ATC4 drug class, some of which are immediately excluded and others are not. Immediate exclusion is defined as exclusion in the calendar year immediately following market entry. The sample is restricted to drugs that enter the market in 2007 or later, and so are ten years old or younger for the duration of the sample. In columns 2 and 4, the sample is further restricted to only ATC4 categories that have at least one immediately excluded drug. See notes to Appendix Table A.2 for more details on the data. Standard errors are clustered at the drug level. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.
Table A.4: Predicting Exclusion Risk

<table>
<thead>
<tr>
<th></th>
<th>(1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exclusion</td>
</tr>
<tr>
<td>Log(1 + N of generic NDCs)</td>
<td>-0.674**</td>
</tr>
<tr>
<td></td>
<td>(0.317)</td>
</tr>
<tr>
<td>Log(1 + N of brand NDCs)</td>
<td>0.656</td>
</tr>
<tr>
<td></td>
<td>(0.511)</td>
</tr>
<tr>
<td>Log(1 + N of ATC7s)</td>
<td>1.069</td>
</tr>
<tr>
<td></td>
<td>(0.665)</td>
</tr>
<tr>
<td>Mean brand price - mean generic price</td>
<td>-0.00862</td>
</tr>
<tr>
<td></td>
<td>(0.00761)</td>
</tr>
<tr>
<td>Total prescription volume</td>
<td>1.70e-08**</td>
</tr>
<tr>
<td></td>
<td>(8.16e-09)</td>
</tr>
<tr>
<td>Observations</td>
<td>128</td>
</tr>
<tr>
<td>Pseudo R2</td>
<td>0.243</td>
</tr>
</tbody>
</table>

Notes: We used the above 2011 market characteristics of the ATC4 class to predict exclusion risk. Using a Logit model, we regressed whether an AT4 class had at least one drug excluded in 2012 or 2013 on all of the characteristics of the ATC4 class reported above. We then used the regression’s fitted values to construct predicted exclusion risk of each ATC4. Data on prices, the number of brand and generic NDCs, and the number of ATC7s are from FDB; data on total prescription volume are from the 2011 Medical Expenditure Panel Survey.
Table A.5: Impact of Predicted Exclusion Risk on New Drug Development By Stages, Non-Logged

<table>
<thead>
<tr>
<th></th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
<th>(6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Preclinical</td>
<td>Phase 1</td>
<td>Phase 2</td>
<td>Phase 3</td>
<td>Launch</td>
</tr>
<tr>
<td>Post X Pr(Exclusion)</td>
<td>-21.98***</td>
<td>-11.05***</td>
<td>-6.010***</td>
<td>-3.830***</td>
<td>-1.098**</td>
<td>0.220</td>
</tr>
<tr>
<td></td>
<td>(6.571)</td>
<td>(3.403)</td>
<td>(2.077)</td>
<td>(1.349)</td>
<td>(0.422)</td>
<td>(0.496)</td>
</tr>
<tr>
<td>Observations</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
</tr>
<tr>
<td>Year FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ATC FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Market Controls</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>N of Drug Candidates Mean</td>
<td>30.61</td>
<td>17.39</td>
<td>6.54</td>
<td>4.57</td>
<td>2.11</td>
<td>1.02</td>
</tr>
</tbody>
</table>

Notes: This table parallels the results reported in Table 5 but using non-logged outcomes. Each column explores how drug development changes at each stage, moving from the earliest observed preclinical activity in column 2 through the different stages of clinical trials. Standard errors are clustered at the ATC4 level. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.
<table>
<thead>
<tr>
<th></th>
<th>(1) New Development</th>
<th>(2) New Development</th>
<th>(3) Log(1+New Dev.)</th>
<th>(4) Log(1+New Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post X Excluded Class</td>
<td>-5.824**</td>
<td>-4.534**</td>
<td>-0.161*</td>
<td>-0.137</td>
</tr>
<tr>
<td></td>
<td>(2.568)</td>
<td>(2.290)</td>
<td>(0.0838)</td>
<td>(0.0891)</td>
</tr>
<tr>
<td>Observations</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
</tr>
<tr>
<td>Year FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ATC FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Market Controls</td>
<td>YES</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: This table reports results from estimating a modified version of equation (1). Instead of defining exclusion risk as a continuous measure predicted using the 2011 market characteristics, the exclusion risk here is a binary variable that equals one if any drug in the ATC4 class was on a PBM exclusion list in 2012 or 2013. For further details on the regression specifications, see notes to Table 4. Standard errors are clustered at the ATC4 level. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.
Table A.7: Impact of Predicted Exclusion Risk on New Drug Development: Alternative ATC4 Linking

(A) Directly Linked Approach Only

<table>
<thead>
<tr>
<th></th>
<th>(1) New Dev.</th>
<th>(2) New Dev.</th>
<th>Log(1+New Dev.)</th>
<th>Log(1+New Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post X Pr(Exclusion)</td>
<td>-20.98***</td>
<td>-18.59***</td>
<td>-0.370***</td>
<td>-0.269*</td>
</tr>
<tr>
<td></td>
<td>(6.048)</td>
<td>(6.745)</td>
<td>(0.132)</td>
<td>(0.146)</td>
</tr>
<tr>
<td>Observations</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
</tr>
<tr>
<td>Year FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ATC FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Market Controls</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

(B) Indirect Linking Approach Only

<table>
<thead>
<tr>
<th></th>
<th>(1) New Dev.</th>
<th>(2) New Dev.</th>
<th>Log(1+New Dev.)</th>
<th>Log(1+New Dev.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post X Pr(Exclusion)</td>
<td>-4.301***</td>
<td>-4.454***</td>
<td>-0.229***</td>
<td>-0.246***</td>
</tr>
<tr>
<td></td>
<td>(1.329)</td>
<td>(1.473)</td>
<td>(0.0836)</td>
<td>(0.0877)</td>
</tr>
<tr>
<td>Observations</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
</tr>
<tr>
<td>Year FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ATC FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Market Controls</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Notes: These results parallel the specification underlying Table 4, but with alternative methods for linking drug candidates to ATC4 classes. We have replaced our baseline outcome measure of development activity with two alternative outcomes that take different approaches to matching. In Panel A, we only count track development activity among the subset of drug candidates for which Cortellis directly reports the drug class. In Panel B, we impute ATC4s from ICD9 codes for all drug candidates, rather than relying on Cortellis’ reporting of drug class. Appendix B provides more details on how the drug candidates are linked to ATC4s. Standard errors are clustered at the ATC4 level. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.
## Table A.8: Impact of Predicted Exclusion Risk on New Drug Development: Wild Cluster Bootstrap

<table>
<thead>
<tr>
<th></th>
<th>(1) New Development</th>
<th>(2) Log(1+New Dev.)</th>
<th>(3) IHS New Dev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post X Pr(Exclusion)</td>
<td>-21.98***</td>
<td>-0.333***</td>
<td>-0.316**</td>
</tr>
<tr>
<td></td>
<td>[-37.97, -8.378]</td>
<td>[-.5357, -.03624]</td>
<td>[-.5549, .01335]</td>
</tr>
<tr>
<td>Observations</td>
<td>1,397</td>
<td>1,397</td>
<td>1,397</td>
</tr>
<tr>
<td>Year FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>ATC FE</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Market Controls</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Notes: Columns 1 and 2 of this table repeat the specifications reported in Table 4 columns 2 and 4, but now using wild cluster bootstrap to calculate the 95% confidence interval (rather than using conventional inference). Clustering is performed at the ATC4 level. Column 3 reports results with the outcome variable defined as the inverse hyperbolic sine transformation of development activity; this transformation can be interpreted similarly to the log transformation, but better accounts for ATC4-year categories with no development activity. Column 3 also uses wild cluster bootstrap for inference. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.
A Theoretical Model

We focus on a potential pharmaceutical entrant that makes R&D decisions on the basis of expected profitability. This firm can make investments in one of two drug classes: class $o$ is “old” in the sense that there is already an approved treatment in that class; class $n$ is “new” in the sense that there are no existing treatments. For tractability, we assume that there is exactly one incumbent drug in the old class. The pharmaceutical firm pays a fixed cost of drug development, $K$, that is the same for both classes. If the firm invests in class $o$, it produces an FDA approved drug with probability $\phi^o$; for class $n$ this probability is given by $\phi^n$. If successful, the entrant competes as a monopolist in the new drug class and as a Bertrand duopolist in the old drug class. For simplicity, we follow Dixit (1979) and adopt a linear demand system with horizontally differentiated products.

We assume there is a single PBM that facilitates access to FDA approved drugs by administering an insurance plan formulary. Patients pay a coinsurance fraction $\lambda \in (0, 1)$ for drugs included in the PBM’s formulary but must bear the full cost of drugs that are not.

We begin in Section A.1 by characterizing pharmaceutical profits in both the old and new drug classes when formulary exclusions are prohibited. Next, in Section A.2, we introduce formulary exclusions as a policy change in which PBMs begin granting exclusive contracts to pharmaceutical firms in exchange for a fixed fraction $(1 - \alpha) \in (0, 1)$ of sales revenue from the included drug. When there are two drugs on the market, we show that ex post profits are lower for drugmakers when their drug is excluded from the PBM’s formulary; because of this, they are willing to offer higher rebates ex ante in order to win the exclusive contract. Finally, after characterizing downstream profits associated with approved drugs, both with and without exclusions, we analyze how the exclusion policy impact firms’ upstream investment decisions, and provide an informal discussion of welfare implications.

A.1 Downstream profits without exclusions

In our baseline case, we do not allow for exclusions; PBMs facilitate access to all FDA approved drugs. If the entrant drug is approved, it competes as either a monopolist in class $n$ or as a differentiated Bertrand duopolist in class $o$. In both cases, its drug is included on the PBM’s formulary. Because formulary inclusion is guaranteed, the PBM cannot extract rebate payments in the absence of a credible exclusion threat, in the context of our simple model.\footnote{In reality, PBMs could negotiate rebates in exchange for placement on a preferred formulary tier, even in the absence of exclusions. For simplicity, we do not include these other tools in our model. Crucially,}
We denote the entrant’s downstream profits as $\Pi_{e,n}$ in the new class and as $\Pi_{e,o}^{\text{open}}$ in the old class. The subscript $e$ indicates the entrant; the subscript $o$ or $n$ indicates the old or new class, respectively; the superscript open describes the open formulary policy state where no drugs are excluded.

In drug class $n$, the entrant faces a standard monopoly pricing problem:

$$\max_{p_{e,n}} (p_{e,n} - m) (A - B \lambda p_{e,n})$$

Here, $A$ is a parameter describing the level of demand in this drug class and $B$ is a parameter describing consumer’s elasticity with respect to price. Marginal costs of production are denoted as $m$. Demand also depends on $\lambda p$ because we assume consumers are partially insured. The relevant price consumers face is $\lambda p \leq p$, even though the drugmaker receives $p$. Solving this problem yields equilibrium prices $p_{e,n}$, quantities $q_{e,n}$, and profit $\Pi_{e,n}$.

Meanwhile, in class $o$, the entrant $e$ would be two competing with the incumbent $i$. We assume that the demand system is symmetric and the drugs are horizontally differentiated but of equivalent quality, so that $b > d$.

$$q_{e,o}^{\text{open}} = a - b \lambda p_{e,o}^{\text{open}} + d \lambda p_{i,o}^{\text{open}}$$
$$q_{i,o}^{\text{open}} = a - b \lambda p_{i,o}^{\text{open}} + d \lambda p_{e,o}^{\text{open}}$$

Here, the parameters $a$ and $b$ denote potentially different levels and elasticities of demand, relative to class $n$. The entrant and incumbent symmetrically choose price to maximize profits:

$$\max_{p_{e,o}^{\text{open}}} (p_{e,o}^{\text{open}} - m) (a - b \lambda p_{e,o}^{\text{open}} + d \lambda p_{i,o}^{\text{open}})$$
$$\max_{p_{i,o}^{\text{open}}} (p_{i,o}^{\text{open}} - m) (a - b \lambda p_{i,o}^{\text{open}} + d \lambda p_{e,o}^{\text{open}})$$

We take the first order conditions and solve for the optimal duopoly pricing.

Exclusions are the strongest tool available to PBMs for restricting drug access, and are thus a significant departure from the earlier forms of control over formulary structure.
Proposition A.1 The incumbent and entrant face symmetric demand and will choose identical prices and then produce identical quantities. Production will occur as long as $2b - d > 0$.

$$p_{e,o}^{\text{open}} = p_{i,o}^{\text{open}}, \quad q_{e,o}^{\text{open}} = q_{i,o}^{\text{open}}, \quad \Pi_{e,o}^{\text{open}} = \Pi_{i,o}^{\text{open}}$$

This proposition is proved by deriving equilibrium price, quantity, and profit. These expressions are given below:

$$p_{e,o}^{\text{open}} = p_{i,o}^{\text{open}} = \frac{a}{\lambda(2b - d)} + \frac{bm}{(2b - d)}$$

$$q_{e,o}^{\text{open}} = q_{i,o}^{\text{open}} = \frac{ab}{(2b - d)} - \frac{\lambda b (b - d) m}{(2b - d)}$$

$$\Pi_{e,o}^{\text{open}} = \Pi_{i,o}^{\text{open}} = \frac{b (a - \lambda(b - d) m)^2}{\lambda(2b - d)^2}$$

A.2 Downstream profits with exclusions

We now consider the case in which PBMs are able to exclude approved drugs when there is a viable alternative. In our model, this means that there can be no exclusions in class $n$, so that prices, quantities, and profits are unaffected.

In class $o$, however, drugs can be excluded. Excluded drugs can still be marketed, but would not be covered by insurance, meaning that consumers face the full price $p$ rather than the subsidized $\lambda p$. The firm again enters differentiated Bertrand competition, but with another firm whose drug is covered. For the purposes of this exposition, we assume that the entrant is excluded and the incumbent is covered. The demand functions will then become:

$$q_{e,o}^{\text{excluded}} = a - b p_{e,o}^{\text{excluded}} + d \lambda p_{i,o}^{\text{included}}$$

$$q_{i,o}^{\text{included}} = a - b \lambda p_{i,o}^{\text{included}} + d p_{e,o}^{\text{excluded}}$$

Each firm will choose prices to maximize profits. Here, we assume that the term $(1 - \alpha)$ is the pre-negotiated rebate that the incumbent pays in order to be included in a PBM’s formulary. We will endogenize $\alpha$ in the following section. If the entrant is excluded, then it no longer pays the
(1 − α) revenue share to the PBM.

\[
\max_{p_{excluded}^{e,o}} (p_{excluded}^{e,o} - m) \left( a - b p_{excluded}^{e,o} + d \lambda p_{included}^{i,o} \right) \\
\max_{p_{included}^{i,o}} (\alpha p_{included}^{i,o} - m) \left( a - b \lambda p_{included}^{i,o} + d p_{excluded}^{e,o} \right)
\]

Taking first order conditions, we can solve for the optimal price, quantity and profits for entrant and incumbent.

**Proposition A.2** When \( \lambda \leq \alpha \), we have the following expressions for prices and quantities.

\[
p_{excluded}^{e,o} \leq \alpha p_{included}^{i,o}, \quad q_{excluded}^{e,o} \leq q_{included}^{i,o}
\]

The condition \( \lambda \leq \alpha \) means that the share of revenue retained by the pharmaceutical company after rebates is greater than the drug coinsurance rate paid by insured consumers.\(^{21}\) Under this assumption, the included drug is able to charge a higher price to insurers and still sell more quantities because formulary placement leads consumers to face a lower out-of-pocket price. The more generous the insurance coverage, the larger the price wedge between the included and excluded drug. If marginal costs of production are zero, then the two drugs will sell equal quantities: the excluded drug’s lower prices will be exactly the amount needed to offset the insurance coverage. If marginal costs are positive, then the excluded drug will sell at a lower quantity than the included drug. Finally, the expressions above assumed the entrant is excluded, but flipping the identity of the excluded drug will simply swap the comparative statics: the excluded drug will have a lower revenue per unit and lower quantity sold in equilibrium.

To prove these propositions, we solve for the equilibrium price and quantities, taking the rebate level \((1 - \alpha)\) required for formulary inclusion as given. We then solve for the optimal rebate bidding

\(^{21}\)Empirical estimates suggest this sufficient condition holds in practice. The Kaiser Family Foundation reports average insurance subsidy rates \((1 - \lambda)\) for prescription drugs ranging between 62% and 83%, depending on the drug tier, for employer-sponsored insurance plans in 2017 (Claxton et al. 2017). These estimates imply coinsurance rates \(\lambda\) in the range of \([0.17, 0.38]\). In comparison, Kakani et al. (2020) estimate rebates of 48% in 2017, suggesting the share of retained revenue \(\alpha\) as 0.52.
strategy in the second stage. Prices are as follows:

\[
 p_{e,o}^{excluded} = \frac{a}{(2b - d)} + \frac{b(2\alpha b + \lambda d)m}{\alpha(4b^2 - d^2)}
\]

\[
 p_{i,o}^{included} = \frac{a}{\lambda(2b - d)} + \frac{b(2\lambda b + \alpha d)m}{\alpha\lambda(4b^2 - d^2)}
\]

Recall that the included drug does not receive the full price \( p_{i,o}^{included} \) in additional revenue for each unit sold, because it owes a cut \((1 - \alpha)\) of its revenue to the PBM. As a result, the effective revenue per unit sold is \( \alpha p_{i,o}^{included} \) for the included drug. As a result, we compare \( \alpha p_{i,o}^{included} \) to \( p_{e,o}^{excluded} \) to calculate the difference in revenue per unit across the included and excluded drug.

\[
 \alpha p_{i,o}^{included} - p_{e,o}^{excluded} = \frac{(\alpha - \lambda)a}{\lambda(2b - d)} + \frac{(\alpha + \lambda)(\alpha - \lambda)bdm}{\alpha \lambda(4b^2 - d^2)}
\]

As long as \( \lambda \leq \alpha \) and \( 2b - d > 0 \), it will hold that:

\[
 \alpha p_{i,o}^{included} \geq p_{e,o}^{excluded}
\]

We can calculate equilibrium quantities as follows:

\[
 q_{e,o}^{excluded} = \frac{ab}{(2b - d)} - \frac{b (2\alpha b^2 - \lambda bd - \alpha d^2) m}{\alpha(4b^2 - d^2)}
\]

\[
 q_{i,o}^{included} = \frac{ab}{(2b - d)} - \frac{b (2\lambda b^2 - \alpha bd - \lambda d^2) m}{\alpha(4b^2 - d^2)}
\]

From these quantity expressions, we calculate:

\[
 q_{i,o}^{included} - q_{e,o}^{excluded} = \frac{(\alpha - \lambda)b(b + d)m}{\alpha(2b + d)}
\]

Maintaining the assumption that \( \lambda \leq \alpha \), it follows that:

\[
 q_{i,o}^{included} \geq q_{e,o}^{excluded}
\]
A.3 Profits and bidding on rebates

From the PBM’s perspective, exclusions allow it to extract positive rebates $1 - \alpha$ by leveraging the exclusion threat. From the drug company’s perspective, exclusions reduce the profitability of entry into the old class; we discuss these profitability comparisons in this section. A corollary of Proposition A.2 is that profits will be higher when a drug is included rather than excluded from an PBM’s formulary, as long as the final rebate level is not too high. Because of this, drugmakers would be willing to provide an ex ante payment in order to avoid exclusion ex post. We model this process as a second price auction in which pharmaceutical firms bid for the exclusive right to be included in a PBM’s formulary by offering rebates of the form $\alpha pq$. The drug offering the highest rebate offer will be included on the formulary; in cases with tied bids, one drug will be selected at random for inclusion. The following pins down rebates in equilibrium:

**Proposition A.3** In the old drug class, firms will be bid a rebate level $1 - \alpha = 1 - \lambda$, so that:

$$\Pi_{e,o}^{excluded} = \Pi_{i,o}^{included} \text{ and } \Pi_{e,o}^{excluded} > \Pi_{e,o}^{open} \quad (2)$$

At the time a drug is approved, each pharmaceutical firm would be willing to set the rebate up to the level that would equalize profits when included on formulary to the profits when excluded. As shown in Appendix A, excluded profits equal included profits when the rebate share $(1 - \alpha)$ equals the insurance coverage share $(1 - \lambda)$. Assuming that the entrant and incumbent have symmetric demand and marginal costs, the incumbent’s bid is the same as the entrant’s and we assume that the PBM uses a coin toss to break the tie. Because the firm’s bid leaves it indifferent between being included and being excluded, the firm receives its outside option profits in either case, and the PBM retains the extra rebate payment.\(^{22}\)

To compare profit of the entrant to the old drug class, see the expressions below:

$$\Pi_{e,o}^{excluded} = (P_{e,o}^{excluded} - m)q_{e,o}^{excluded}$$

$$\Pi_{i,o}^{included} = \left( p_{i,o}^{excluded} \frac{\alpha - \lambda}{\lambda(2b - d)} + \frac{(\alpha^2 - \lambda^2)bdm}{\alpha\lambda(4b^2 - d^2)} - m \right) \left( q_{e,o}^{excluded} + \frac{(\alpha - \lambda)b(b + d)m}{\alpha(2b + d)} \right)$$

\(^{22}\)For simplicity, we do not model demand for PBM services. In practice, some of the PBM’s rebate may be passed on to consumers or retained as PBM profit.
As shown above, as long as $\alpha > \lambda$, the included drug makes higher profits. Further, profits for the included drug are increasing in $\alpha$, and the difference in profitability between the included and excluded drug is also increasing in $\alpha$. Profits for the included drug are equal to profits for the excluded drug when $\lambda = \alpha$, since at this point the marginal revenue per unit sold is the same for included and excluded drugs, as is the quantity sold. The drug company would be willing to bid a maximum rebate level of up to $1 - \alpha = 1 - \lambda$ for inclusion on the formulary.

Now, we can compare price, quantity, and profitability of the entrant under the open formulary regime compared to the closed formulary regime. The entrant’s price net of the PBM rebate under the open formulary is higher than the price of the excluded drug in the closed formulary.

$$p_{e,o}^{open} - p_{e,o}^{excluded} = \frac{(1 - \lambda)a}{\lambda(2b - d)} + \frac{(\alpha - \lambda)bdm}{\alpha(4b^2 - d^2)}$$

Under the sufficient condition that $\lambda \leq \alpha$, it will hold that the the entrant’s drug price is strictly higher under the open formulary than if it were excluded from coverage.

$$\alpha p_{e,o}^{open} > p_{e,o}^{excluded}$$

Further, the entrant’s quantity sold is also strictly larger under the open formulary than when it is excluded.

$$q_{e,o}^{open} - q_{e,o}^{excluded} = \frac{(1 - \lambda)b(b - d)m}{(2b + d)} + \frac{(\alpha - \lambda)b^2dm}{\alpha(4b^2 - d^2)}$$

As long as $\lambda \leq \alpha$ and $b > d$, it will also hold that:

$$q_{e,o}^{open} > q_{e,o}^{excluded}$$

Because the entrant’s price and quantity are both strictly larger under the open formulary than when the entrant is excluded, it follows that entrant’s strictly profits are higher under the open formulary:

$$\Pi_{e,o}^{open} > \Pi_{e,o}^{excluded}.$$ 

### A.4 Upstream investment decisions

A firm will choose whether to invest in the old or new drug class by comparing expected profits and success rates of drugs in each class. When there are no exclusions, a potential entrant’s expected
returns at the time of its R&D decision are given by:

\[ E[\Pi^e] = \begin{cases} \\
\phi^n \Pi_{e,o}^\text{open} & \text{if develop for class } o \\
\phi^n \Pi_{e,n} & \text{if develop for class } n \\
\end{cases} \]

The firm therefore chooses to develop for the old class as long as

\[ \Pi_{e,o}^\text{open} > \frac{\phi_o}{\phi_o} \Pi_{e,n}. \tag{3} \]

In general, the old drug class will be more attractive when the likelihood of successful development is higher, when there is a large base of potential consumer demand (e.g., if it is a common condition), or if the firm’s drug is more differentiated from that of the incumbent’s. However, when there is a threat of exclusion, the entrant anticipates needing to bid for access to the PBM’s formulary in the event it creates an FDA approved drug for the old class. The firm has a probably \( \phi_o \) of developing a successful drug in the old class, in which case it will enter its maximum rebate bid to be included in the formulary and win half the time. However, any ex post returns to being included in the formulary are bid away, so that the entrant expects to receive only its outside option: revenues in the case when its drug is excluded.

Meanwhile, profits from developing an entrant for the new drug class do not depend on whether the formulary is open or closed, because we assume that drugs can only be excluded when there is a viable alternative. The potential entrant’s new criterion for developing in class \( o \) when exclusions are permitted is given by:

\[ \Pi_{e,o}^\text{excluded} > \frac{\phi_n}{\phi_o} \Pi_{e,n}. \tag{4} \]

The criterion differs from the no-exclusion condition given in Equation (3) only in the lefthand side, which had a \( \Pi_{e,o}^\text{excluded} \) instead of \( \Pi_{e,o}^\text{open} \). As shown above profits are higher when there is an open formulary so that \( \Pi_{e,o}^\text{open} > \Pi_{e,o}^\text{excluded} \). The model therefore predicts that the introduction of an exclusion policy leads firms to develop relatively fewer drugs for the older class.
B Linking Drug Candidates to ATC4 Classes

We matched the pipeline drug candidates in Cortellis to ATC4 codes in two ways: directly via EphMRA codes and indirectly via ICD9 codes if the EphMRA codes were missing.

**Direct method**: matching via EphMRA codes. Cortellis links drug candidates to chemical drug classes (specifically the EphMRA code, which is a close derivative of the ATC classification). Using a manually created crosswalk of EphMRA codes to ATC4 codes, we used the EphMRA codes of the drug candidates to link the drugs to ATC4 classes. A drug can be linked to many ATC4 classes, and we assigned equal weights of 1 to all ATC4 classes that directly matched to a given drug through their EphMRA codes.

**Indirect method**: matching via ICD9 codes. An alternative way to link the drug candidates to ATC4 classes is through the drugs’ areas of therapeutic use (ICD9) provided by Cortellis. Using the drug to ICD9 crosswalk from Cortellis, we linked to a crosswalk of ICD9 to ATC4 codes created by Filzmoser et al. (2009), in which the authors assigned a probabilistic match score of ICD9-ATC4 pairs. Since this results in a drug being matched (indirectly via ICD9) to many ATC4s, we assigned the likelihood of an ATC4 matching to a drug based on the probabilistic match scores from Filzmoser et al. (2009), such that the assigned weights sum to 1 for each drug.

For our main analyses, we matched the drug candidates to ATC4 codes using the direct method via EphMRA codes and used the indirect method via ICD9 codes for drugs with missing EphMRA codes. As shown in Appendix Table A.7, our results are similar regardless of the linking method used.

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23 Filzmoser et al. (2009) merged a dataset of prescriptions (with ATC4 codes) and a dataset of hospital admissions (with ICD9 codes) at the patient-level. Since the ATC4 code of a patient’s drug matches to many diagnosis codes of the patient, the authors use a frequency-based measure to calculate a probabilistic match score of an ICD9-ATC4 pair. They conduct this match specific to gender/age group of the patients. For our analysis, we take the average match probability across the gender/age groups for a given ICD9-ATC4 pair.