Insurance Design and Pharmaceutical Innovation[*]

Leila Agha[†]   Soomi Kim [‡]   Danielle Li [§]

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Abstract

This paper studies how insurance coverage policies impact pharmaceutical innovation. In the United States, most patients obtain prescription drugs through insurance plans administered by Pharmacy Benefit Managers (PBMs). Beginning in 2012, PBMs began refusing to provide coverage for many newly approved drugs when cheaper alternatives were available. We show that this policy reshaped upstream pharmaceutical R&D, shifting investments away from therapeutic classes at greater risk of exclusion. This move translated into a relative decline in the development of drug candidates that appear more incremental: that is, those in drug classes with more pre-existing therapies and with less scientifically novel research.

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[†]Dartmouth College and NBER
[‡]MIT
[§]MIT and NBER

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 investments, others believe that these same policies generate perverse incentives to create expensive products with little incremental clinical value.[1] 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 of private sector prescription drug plans on upstream pharmaceutical R&D. Prior to 2012, private prescription drug insurance in the United States generally provided coverage for all FDA-approved drugs. To manage costs, plans used a combination of cost-sharing tiers and ordeal mechanisms (e.g., prior authorization requirements) to direct patients to less expensive drugs. These approaches, however, were insufficient to curb prescription drug spending, which grew rapidly during the 1990s and 2000s (Kamal et al. 2018). Beginning in 2012, Pharmacy Benefit Managers (PBMs), the intermediary firms that manage most private prescription drug insurance, dramatically shifted their policies to exclude any coverage for certain drugs in a new effort to contain spending. These exclusions applied to many newly approved drugs without generic equivalents. This practice of excluding coverage entirely, known as maintaining a "closed formulary," has since become standard, with over 300 branded drugs excluded by at least one of the three largest PBMs as of 2017.

Exclusions can substantially reduce the profitability of drugs. For example, when GlaxoSmithKline's blockbuster asthma inhaler, Advair, was excluded by Express Scripts in January of 2014, its US sales immediately fell by over 30% by that April (Pollack 2014). Exclusion risk also extends to calculations of *expected* profitability for new drugs. The high blood pressure medication Edarbi, for instance, received FDA approval in 2011 but was almost immediately excluded by CVS Caremark in 2012, suppressing demand before it

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[1]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.

could become established. By September 2013, Edarbi's manufacturer, the Japanese firm Takeda, decided to sell off its US distribution rights, despite keeping these rights in Japan and in other countries. Since then, Takeda has not developed any further drugs for hypertension, choosing instead to focus on oncology and rare diseases, areas which have seen far fewer exclusions.

Studying how the downstream decisions of drug buyers shape upstream pharmaceutical innovation can inform our understanding of how to design payment policies that balance incentives for innovation and cost containment. These lessons, gleaned from the choices of private sector firms, can provide insight into the possible effects of policy proposals governing how public insurers interact with drugmakers.[2] Indeed, the largest PBM, CVS Caremark, manages benefits for 75 million Americans—more than the number of enrollees in either Medicare or Medicaid.

We begin our analysis by showing that exclusions limited drug claims beyond what PBMs were able to achieve with prior approaches to managing patient demand. On average, we find that for each PBM that excludes coverage, a drug's sales, as proxied by Medicare Part D claims, falls by 24%, relative to comparable drugs that did not face exclusions.

Next, we show that a drug's risk of facing exclusions varies systematically and predictably according to the market characteristics of its therapeutic class. Specifically, exclusions are more common in drug classes with a greater number of pre-existing therapeutic options, as well as in classes with a large number of patients, as measured by prescription volume. These findings are consistent with the case of Edarbi, where CVS pointed to a variety of similar angiotensin II receptor blockers (ARBs) as viable alternatives. Further, because hypertension is such a common condition, the savings associated with excluding Edarbi in favor of lower cost alternatives could be realized over a large patient population. We use these patterns to generate an index of a drug class's ex-ante risk of facing exclusions, as predicted by its pre-2012 market characteristics.

Our main results explore how concerns over downstream coverage, as measured by predicted exclusion risk, shape the extent and type of upstream R&D. Following the introduction of closed formularies, pharmaceutical investments fell markedly in drug classes

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[2]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.

at high risk of exclusions, relative to trends in low risk classes. We document a 6% decline in the number of new clinical trials and announcements of early stage development for one standard deviation increase in ex-ante exclusion risk. These declines affect drug candidates in all phases of development, but are largest among earlier stage drugs. We find no evidence that drug classes at higher risk of exclusion were on different development trends in the five years prior to the introduction of exclusions.

Finally, we go on to explore the nature of this foregone innovation. After exclusions are introduced, the composition of drugs under development shifts: 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; Wu et al. 2019).

Taken together, our results suggest that closed formulary policies altered the economic considerations that drugmakers face when making R&D investment decisions. Prior to this policy 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. Our results show that pharmaceutical firms responded to this change in incentives by reducing R&D spending in drug classes serving common diseases with many incumbent therapies. This response shifted investments away from research areas with more incremental activity and lower scientific novelty.

Our econometric approach is based on a difference-in-differences specification that identifies a *relative* decline in R&D across drug classes at high vs. low exclusion risk. 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 (Kerr and Nanda 2015; Krieger et al. 2019). In this case, our paper can be interpreted as showing that

selective coverage limitations can act as a lever to shift R&D resources away from areas with more incremental research, toward areas with fewer existing treatments and more novel science. In the absence of frictions, our results would instead be interpreted as showing that selective exclusions generate targeted cuts in R&D spending in areas at high risk of exclusion. In either case, our results provide support for the idea that insurance design choices, such as coverage limitations, are powerful tools that can shape the direction of pharmaceutical R&D.

We contribute to a broad literature examining how market incentives shape the rate and direction of innovative output.[3] 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 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

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[3]Here 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).

investments in drug development. Section 6 discusses the welfare implications, and Section 7 concludes.

1 Institutional Background

1.1 The Role of Pharmacy Benefit Managers (PBMs)

In the United States, three key parties are involved in shaping payments and access to prescription drugs: manufacturers who develop and produce new drugs, institutional payers such as insurance companies and large employers, and pharmacy benefit managers (PBMs), who design and administer drug insurance plans.[4]

Historically, PBMs were only responsible for processing patient claims at the pharmacy: 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, PBMs began playing a more active role in designing prescription drug plans on behalf of insurers (Werble 2014). By 2016, the three largest PBMs—CVS Caremark, Express Scripts, and OptumRx—collectively designed and administered 70% of private prescription drug plans (Fein 2017).

Modern PBMs argue that they create value by lowering prescription drug spending for institutional payers. One way that PBMs limit spending is through prescription drug coverage that steers patients toward the lowest cost treatment options. Prior to the use of exclusions, PBMs employed three tools to reduce patient demand for expensive drugs. First, insurance plans assign drugs to different coverage tiers, with varying generosity of patient cost-sharing; expensive drugs would be placed in tiers with higher coinsurance or copayment rates. Second, prior authorization requirements imposed on select drugs require physicians to obtain advance approval from the PBM or insurer prior to coverage. Finally, step therapy requirements allow coverage for certain expensive drugs only after the patient has tried and failed cheaper alternatives.

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[4]There are, of course, other parties involved, such as physicians, wholesalers, and pharmacies. We focus on the parties above because they play the largest role in coverage and R&D decisions. See Appendix Figure A.1 for a more complete picture of the supply chain.

PBMs may also lower costs by pooling demand across multiple payers in order to negotiate bulk discounts for drugs. Given the concentration in the industry and their role in shaping patient demand via the tools described above, PBMs have substantial negotiating power with manufacturers. Drugmakers routinely offer large rebates in order to secure more favorable formulary positions for their drugs. PBMs may return a portion of this savings to institutional payers and keep a portion for themselves. Because rebates are highly secretive, we have little information on how they vary across drugs.

1.2   The Introduction of Formulary Exclusions

Existing formulary strategies had limited success reducing the use of expensive medications and containing prescription drug spending. Pharmaceutical firms employed a variety of techniques aimed at circumventing coverage restrictions. For example, to help patients shoulder co-pays for drugs placed in more expensive coverage tiers, drugmakers introduced "co-pay coupons" that insulate consumers from cost-sharing.[5] Similarly, drug sales representatives actively targeted drugs with prior authorization requirements, training and supporting physician practices to process prior authorization paperwork, in some cases by developing specialty software for the purpose of auto-filling authorization forms (Pinsonault 2002).[6]

Beginning with CVS in 2012, major PBMs responded by implementing closed formularies. Rather than providing coverage (potentially with some tiering or restrictions) for all FDA-approved drugs, 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.

Exclusions constituted a much more effective tool for formulary management. In an investor call, Helena Foulkes, the President of CVS Pharmacy at the time, highlighted the efficacy of exclusions:

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[5]Because the average implied co-insurance rate of even the highest tier drugs is roughly 30-40%, subsidizing patient costs still netted pharmaceutical firms substantial revenues via the insurer contribution (Claxton et al. 2011).

[6]One audit study found that over 88% of prior authorizations were approved by health plans (Scott-Levin 2000).

"It is only through exclusion where we can prevent manufacturer subversion of a formulary strategy with co-pay coupons. As shown, an exclusion formulary will have more than a 95% preferred drug use versus 55% preferred share in tiered formularies." (Foulkes 2015)

Express Scripts reported a similar experience with its own exclusions:

"We had a significant market share shift; nearly 70% in volume moved away from the non-covered drugs into covered drugs...and that percentage has continued to increase ever since then....And has it worked? It has worked really well." (Myers 2014)

A natural question is why PBM formulary exclusions were introduced in 2012. While we do not have direct evidence regarding CVS's deliberations, industry analysts have pointed to a variety of potential factors. The steady rise of copay coupons since 2007, previously documented by Dafny et al. (2017), eroded PBMs' ability to manage drug demand via their traditional tiering. In addition, growing PBM market concentration strengthened PBMs' bargaining power, while consolidated pharmacy networks improved PBMs' ability to communicate and implement formulary restrictions (Miller and Wehrwein 2015). A key concern is whether these same trends that led to the introduction of exclusion policies may have directly contributed to declining innovation in drug classes at high risk of exclusion. We investigate this possibility in Section 5.2 by looking for the presence of differential pre-trends and conducting placebo experiments.

2 Formulary Exclusions and Upstream Innovation

The adoption of closed formularies can substantially affect the expected profitability of new drugs. As in the case of Advair, a drug's profits can be eroded if it is actually excluded, but, perhaps more importantly, the *threat* of facing exclusion can also reduce prices even if a drug is never excluded in practice. Stephen Miller, the Chief Medical Officer of Express Scripts, describes using the threat of exclusion in price negotiations with pharmaceutical manufacturers:

"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).[7]

Consistent with the market dynamics described by Garthwaite and Morton (2017), a credible threat of exclusions reduces the net price that drug makers can charge.

Because exclusions impact anticipated profits, the introduction of closed formularies changed the set of factors that pharmaceutical executives considered during the drug development process. Rather than focusing primarily on FDA approvals, industry consultants began routinely advising pharmaceutical companies that now "[m]arket access strategy should underpin decision-making throughout the entire product lifecycle, including portfolio decision-making" (Siegal and Shah 2019). These concerns about formulary coverage may lead firms to apply a higher "bar" for drugs that risk facing exclusions: rather than simply demonstrating safety and efficacy (the standard for FDA approval), firms were also advised to conduct additional clinical trials to demonstrate superiority in head-to-head comparisons with competitor's drugs.[8] Formulary considerations may reduce investment both by weeding out drugs that do not meet this higher standard, and by raising the cost and complexity of clinical trial design.

In Appendix A, we formalize this intuition by developing a simple model of how drug exclusion policies impact firms' R&D decisions. In this model, a potential pharmaceutical entrant faces a choice: invest in developing a drug for a "new" drug class (where no incumbent treatments exist) or invest in developing a drug for an "old" class (where an incumbent therapy is available). In the absence of exclusions, PBMs 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

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[7]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).

[8]To provide evidence of superiority, a firm may choose to pursue more costly and ambitious clinical trials in order to provide stronger evidence of efficacy relative to existing treatments. For example, the firm may decide to directly compare a drug candidate to incumbent drugs to establish superiority in class, rather than simply focusing on efficacy relative to a placebo (Schafer ; Siegal and Shah 2019).

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 investment 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.

We note that the welfare implications of this change in drug development incentives are theoretically ambiguous. First, losses to pharmaceutical firms can be cast as gains to 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 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. We discuss additional issues related to welfare in Section 6.

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.[9] Our data cover "standard" formulary exclusions: these exclusions apply to most health plans administered by a

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[9]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). Finally, OptumRx began publishing formulary exclusions in 2016, when its market share was 22% (Fein 2017).

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.[10] 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.[11] 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.[12] Most Medicare Part D plan sponsors contract with PBMs for rebate negotiation and benefit management (Government Accountability Office 2019), and many Part D plans feature closed formularies (Hoadley et al. 2011), making Medicare Part D a suitable

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[10]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).

[11]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.

[12]This data is published annually by the Center for Medicare and Medicaid Studies. We accessed it online at `https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/Historical_Data`, in November 2019.

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.[13] 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 insulin analogue (ATC4 A10A), a non-insulin blood glucose lowering drug (A10B), or other

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[13]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.

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 2011 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 Understanding Exclusion Risk

4.1 Exclusions over Time

Figure 1 illustrates the rise of drug exclusions over time and across PBMs. CVS was the first major PBM to implement a closed formulary, starting with the exclusion of 38 drugs in 2012. Over the next six years, CVS oversaw a sustained expansion in the number of types of drugs it added to its exclusion lists. 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.

We find that exclusions largely targeted newer branded drugs: 75% of those excluded in our data had no molecularly equivalent generic substitute. Exclusions also targeted therapeutic areas with large numbers of patients. For example, Figure 2 plots exclusions by disease category at the drug level and shows that, 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.

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 choices (coverage and prices) have been shown to have a clear impact on patients' drug use. A large body of work has documented that patient demand for drugs is elastic to out-of-pocket prices, suggesting that eliminating insurance coverage for excluded drugs will suppress demand.[14] In addition, several papers have shown that formulary exclusions specifically reduce the utilization of targeted drugs (Chambers et al. 2016; Huskamp et al. 2003; Wang and Pauly 2005).[15].

To test whether these patterns hold in our setting, we investigate the link between PBM formulary exclusions and drug sales, using data on Medicare Part D prescription drug claims from 2012-2017. We estimate the following regression equation:

$$\text{Log(Claims)}_{dt} = \beta_1 \text{Excluded}_{dt} + \mathbf{X}_{dt} + \delta_d + \delta_t + \epsilon_{dt} \tag{1}$$

Here, Claims_{dt} refers to the number of Medicare Part D claims made on drug d in year t. Because the distribution of Part D claims per drug is highly right-skewed (see Appendix Table A.2), we report our results in terms of the natural log of the drug's claim count. The key variable of interest is Excluded_{dt}, how many of the three main PBMs were excluding the drug in a given year. We include drug fixed effects in all specifications so that our effect is identified from within-drug changes in formulary exclusion status. We also include drug age × calendar year fixed effects to capture time trends and drug lifecycle patterns.

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[14]For example, the following papers find evidence of negative price elasticities for drugs, as a function of insurance cost-sharing: Abaluck et al. (2018), Einav et al. (2017), Choudhry et al. (2011), Thiebaud et al. (2008), Tamblyn et al. (2001).

[15]While CVS was the first to implement a standardized national closed formulary in 2012, the two older papers cited above provide evidence from smaller scale exclusions by individual insurance plans. These earlier formulary coverage decisions affect many fewer patients than the national PBM formularies we study here, but are likely to have similar effects on the drug choices of enrolled patients.

Our sample consists of drugs that were on the market prior to the introduction of exclusions, and which have at least 11 annual Part D claims. 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.[16]

In Table 2, we show that each excluding PBM decreases a drug's prescription volume by 24% ($e^{-0.274} - 1$), relative to comparable drugs that did not experience an exclusion. Column 2 shows that our results are robust to including additional controls for time-varying demand for the drug class, captured with ATC4 X calendar year fixed effects. In Columns 3 and 4, we obtain a similar result when focusing on market share rather than prescription volume: each excluding PBM reduces a drug's market share by 20%. We note that this analysis does not allow us to measure prescription drug sales that are not claimed in Medicare Part D; if formulary exclusions lead 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.

The effects we measure capture the combined effect of reduced prescriptions for the focal drug, as well as possible reallocation toward non-excluded drugs in its category. These findings show that exclusions had a major impact on shifting sales and market share across competitor drugs, beyond what PBMs previously accomplished for these drugs with traditional demand management tools such as tiering, prior authorization, or step therapy. Moreover, our magnitudes are consistent with anecdotal case by case reporting: for example, after its exclusion by Express Scripts, sales of the asthma inhaler Advair fell 30% while sales for its non-excluded competitor Symbicort increased 20% over the same period (Pollack 2014).

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.

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[16]The protected classes are antidepressants, antipsychotics, anticonvulsants, antineoplastic agents, antiretroviral agents, and immunosupressants. Of the 181 excluded drugs prescribed in Part D, only 20 fall into these classes.

4.3 Predictors of Formulary Exclusion Risk

Having provided evidence that exclusions harm revenues, we next examine the factors that predict exclusion risk. Because drug exclusions steadily expanded after their introduction in 2012, we focus on using a drug class's pre-period market characteristics to predict early exclusions, those that occurred in 2012 and 2013. In our data, 12% of ATC4 drug classes experienced early exclusions.

Predictors of Drug-Level Exclusion

Using data from FDB described in Section 3, we begin by constructing several potential predictors of exclusion risk for 127 ACT4 drug classes. The availability of therapeutic alternatives is measured by 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). To account for the expected size of the patient population, we use the 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 manufactures often pay to PBMs. All of these market characteristics are from 2011, before the introduction of first exclusions in 2012.

Figure 3 plots the coefficients of bivariate linear regressions of exclusion on each drug class characteristic. 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 contemporaneous descriptions of PBMs' exclusion strategies, which indicate that formulary exclusions often target "me-too drugs" with multiple therapeutic substitutes (Reinke 2015), as well as 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.

Class-Level Exclusions Risk

We use the market characteristics described in the previous section to construct each drug class's risk of facing exclusions, measured at the ATC4 level. To do so, we fit a logistic regression predicting whether a drug class experience exclusions in 2012 or 2013 as a function of all of the ATC4 market characteristics described in the previous section (measured as of 2011). This regression is described below, where $F(\cdot)$ denotes the cumulative logistic distribution function.

$$Pr(\text{Excluded}_c) = F(\mathbf{X}_c \gamma) \tag{2}$$

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.2 plots the resulting distribution of predicted exclusions.

We test whether our measure of exclusion risk has empirical validity by asking whether exclusion risk fit from 2012 and 2013 exclusion lists is also predictive of 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 early exclusion risk correlates with a 17 percentage point increase in the likelihood that an ATC4 class experiences exclusions in later periods. 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.

Next, we consider the subset of ATC4s that see no exclusions during the first wave of exclusions in 2012 and 2013. This set—which includes almost 90% of our sample ATC4s—includes some drug classes that were truly at low risk of facing exclusions, as well as drug classes that were in fact at high risk, but which were able to avoid early exclusions perhaps by offering higher rebates. Because formulary exclusions can decrease expected profitability both directly through exclusions as well as indirectly by forcing firms to charge lower prices (e.g. give higher rebates) to avoid exclusions, it is important for our measure of exclusion risk to capture drug classes that see no exclusions during 2012-2013, but which were still subject to increased negotiation pressures. In Table 3 Column 2, we show that our measure of predicted exclusion risk is significantly correlated with future exclusions

even in classes with no early exclusions: a 1 standard deviation increase in early exclusion risk generates a 15 percentage point increase in the likelihood of late exclusions, from a base rate of 31%.

5 The Impact of Exclusion Risk on Subsequent Drug Development

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:

$$\text{Development}_{ct} = \beta_1 \text{Pr(Excluded)}_c \times \mathbb{I}(\text{Year}_t \geq 2012) + \mathbf{X}_{ct}\gamma + \delta_c + \delta_t + \epsilon_{ct} \qquad (3)$$

In Equation (3), 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(Excluded)_c, described in our discussion of Equation (2). 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 (δ_c), year fixed effects (δ_t), and time-varying drug market controls ($\mathbf{X}_{ct}$).

To interpret our primary coefficient of interest, β_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 (3), which replaces the single indicator variable for being in the post period ($\mathbb{I}(\text{Year}_t \geq 2012)$) with a vector of indicator variables for each year before and after the introduction of PBM exclusion lists in 2012.

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5.2   Main Results

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.[17] This estimate represents a relative decline in higher-risk classes, relative to trends in lower-risk classes. 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, the number of ATC7 subclasses (which indicate specific chemical substances) with approved drugs, and prescription volume. 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% for every 1 standard deviation increase in class exclusion risk, as reported in columns 3 and 4.

Assessing Pre-Period Trends

One potential concern for interpreting these findings is that innovation in ATC4 classes at high risk of exclusion may have been evolving on different trends, for reasons other than the introduction of formulary exclusions. For example, drug classes with many existing treatment options may be both more likely to be excluded and, independently, also see natural attenuation in innovative activity.

To assess this possibility, we first show that there are no discernible pre-trends in development that vary by exclusion likelihood, in the years leading up to the introduction of formulary exclusions. Figure 4 plots our results in an event study framework, illustrating that there appears to be little difference in drug development across drug classes at high vs. low risk of exclusions prior to 2011. These trends suggest that high exclusion classes were not experiencing declining investment over the pre-period; to the extent that either

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[17]As reported in Appendix Figure A.2, the standard deviation of the probability the class faces exclusions is 0.15. Using the coefficient reported in Table 4, we calculate $-24.03 * 0.15 = -3.6$.

demand or innovative potential was changing across drug classes in our pre-period, those changes do not appear to have cut along our predicted exclusion categories. Rather, development activity begins to diverge in 2012, and these differences grow until 2017, the last full year of our sample.

Next, we conduct a series of placebo tests. If our measure of exclusion risk captures aspects of a drug class—crowdedness for instance—that are predictive of declining R&D independent of formulary exclusions, then we would expect drug classes with high exclusion risk (measured in earlier pre-period years) to see innovation fall in response to pre-period placebo exclusion policies. To test this, we use our coefficient estimates $\hat{\gamma}$ estimated from Equation (2) to identify drug classes that appear at risk of exclusion based on their market characteristics as of each year in 2001-2005. That is, we look for drug classes that, in earlier years, shared the same mix of treatment options and prescription volumes that would have put them at high risk of exclusions in 2011. As can be seen from Figure 3, these are drug classes that, at a given point in time, have a relatively large number of branded and generic options, as well as high prescription volume. If our results were driven by trends unrelated to exclusions, we should see R&D in these classes fall in the years following our assessment of their exclusion risk.

Appendix Figure A.3 plots out results for five different tests, corresponding to a placebo policy change in each of the years 2002 through 2006. The blue horizontal lines plot the placebo policy estimates and 95% confidence interval, while the vertical red line highlights the true estimated policy effect. These estimates mirror the specification in column 2 of Table 4, except that we drop price when constructing the exclusion risk due to missing historical price data covering the placebo policy periods.[18] For example, the 2002 placebo policy estimates a positive $\hat{\beta}$ coefficient of 2.2 on predicted exclusion risk interacted with a post period indicator from Equation 3. For this placebo policy, the post period begins in 2002; exclusion risk is measured using 2001 market characteristics; and we use a corresponding 11-year sample period from 1997-2007. Similarly, the coefficient on the 2003 placebo refers to risk measured in 2002, and a sample period of 1998-2008. We end the placebo tests with the 2006 placebo policy change, because its 5 year post period ends in 2011, the last year of

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[18]The true estimated policy effect of -22.9 is statistically significant and very similar to the estimate of -22.0 reported in Table 4.

our true policy pre-period.[19] Appendix Figure A.3 suggests drug classes with similar features to those eventually targeted with exclusions did not experience declining investment over the pre-period; compared to the statistically significant true policy estimate of -22.9, the placebo estimates range from 2.2 to 9.1, and none are statistically significant.

Stages of Development

Having established evidence of a decline in overall development, Table 5 decomposes this 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.4. 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 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.

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[19]It is worth noting that there were other changes in prescription drug markets over this early pre-period, such as the introduction of Medicare Part D in 2006. While Medicare Part D did affect drug development investments, there is no evidence to suggest that it differentially impacted drug classes on based on their exclusion risk. To make sure that our results are not driven by this change, we study a variety of placebo test timing.

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 Additional 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 Table A.6 and Appendix Figure A.5 present 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 Table A.7 and Appendix Figure A.6 show that our results are similar whether 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.[20]

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 $\Pr(\text{Excluded})_c \times \mathbb{I}(\text{Year}_t \geq 2012)$ equal to zero for all observations. We use these 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.

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[20]The 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.

Availability of Existing Therapies and 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 5 Panel A compares predicted drug development activity under the observed exclusion policies to the counterfactual activity that would 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 5 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 6 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 7, 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 Wu et al. (2019) 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 7 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 away from large markets (in terms of available therapies and prescription volume) and away from common disease classes treating chronic conditions such as heart diseases and diabetes. 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.

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 (3), we isolate the *relative* change in development activity in drug categories at high exclusion risk, compared to the changes in low-risk 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 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.[21]

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 6% decline in drug development activity following the introduction of closed formulary policies. These declines in development activity occur at each stage of the 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,

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[21]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.

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.

This analysis studies the first wave of PBM formulary exclusions, but the implications may evolve with ongoing changes to exclusion strategies. For example, in recent years, formulary exclusions have begun to target therapies for relatively rare and sensitive diseases for the first time, including HIV, hemophilia and certain cancers (The Doctor-Patient Rights Project 2017; Maas 2018). Drug classes that appeared low-risk in our analysis based on early exclusion patterns may become higher-risk as exclusions expand, leading to more widespread

reductions in drug development. Additional research will be needed to quantify the tradeoffs associated with decreased development in these therapeutic areas.

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FIGURE 1: NUMBER OF EXCLUDED DRUGS BY PBMS
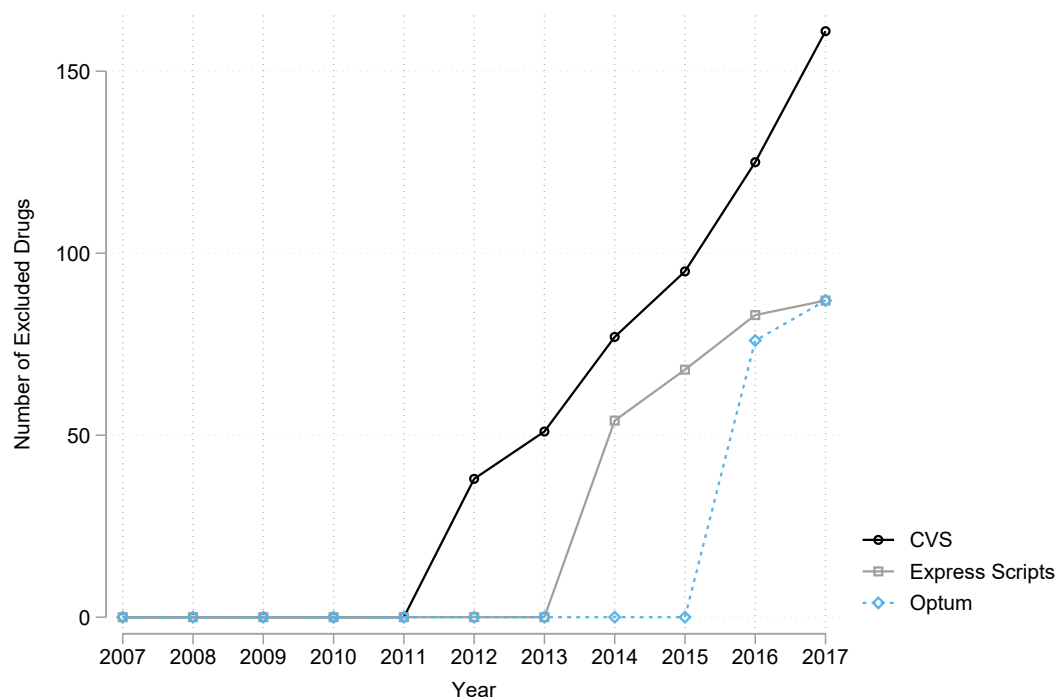
NOTES: This figure plots the number of drugs excluded by each of the three Pharmacy Benefit Managers. CVS was the first to begin excluding drugs in 2012, followed by Express Scripts in 2014 and OptumRx in 2016.
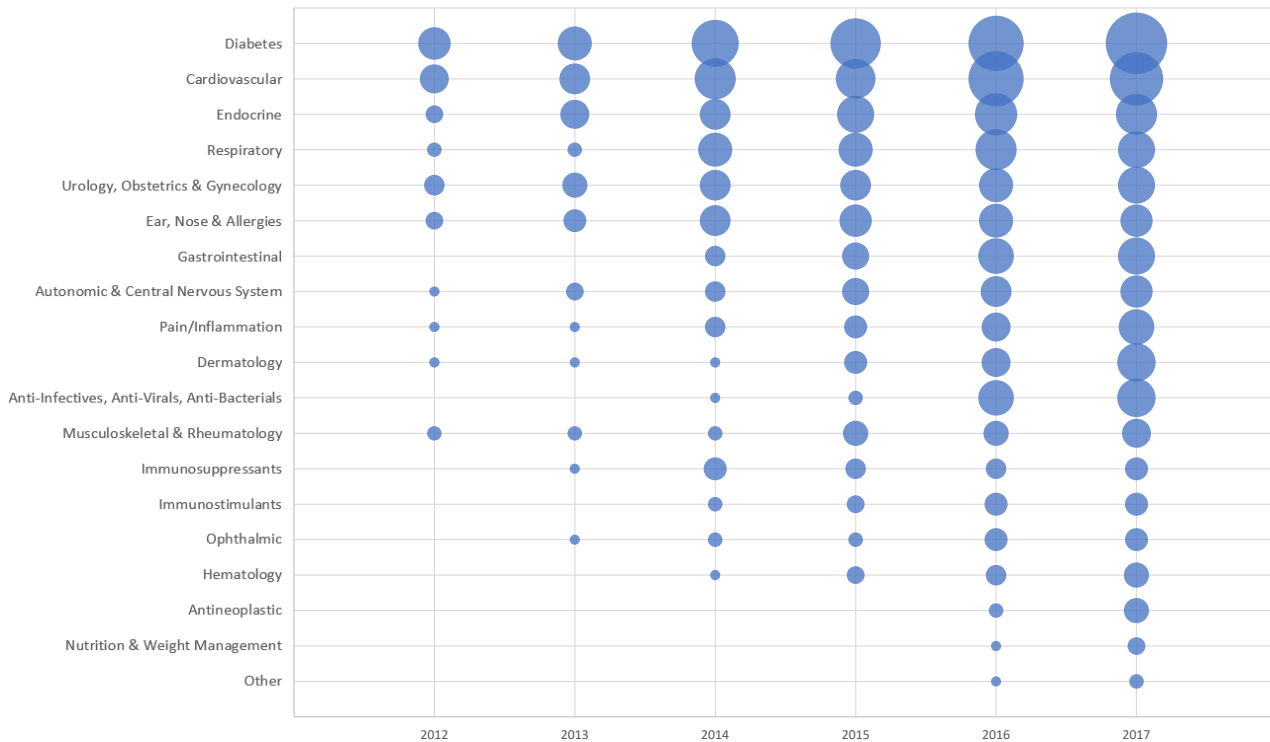
NOTES: Each bubble represents a disease category in a year, and the size of the bubble reflects the number of drugs that were excluded by CVS, Express Scripts, or OptumRx in that disease category. There were a total of 300 drugs that were ever excluded from 2012-2017 by at least one of the three PBMs. 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.
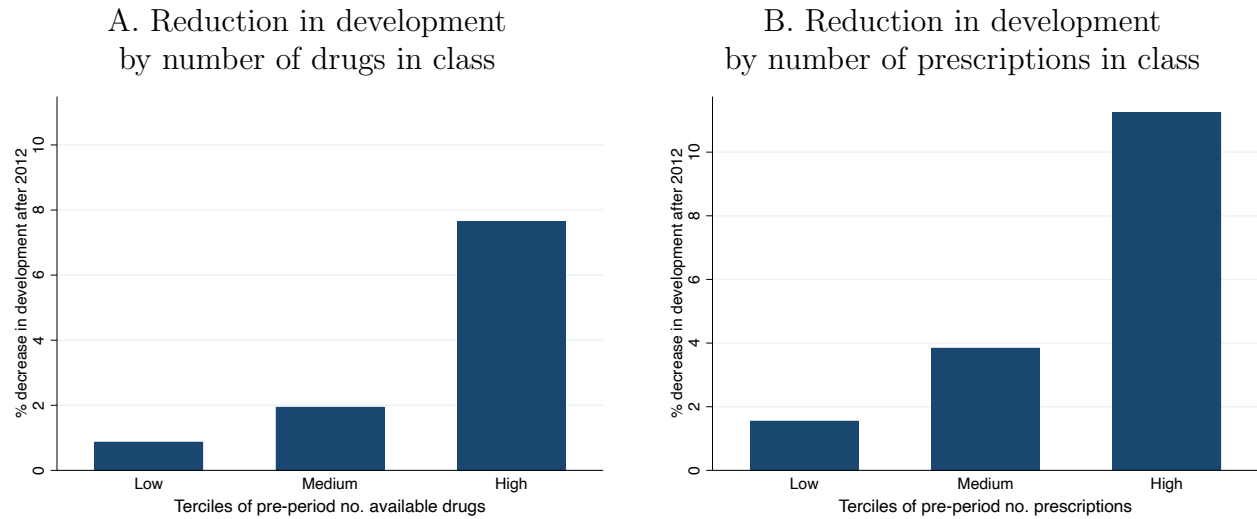
FIGURE 3: PREDICTORS OF EXCLUSION RISK
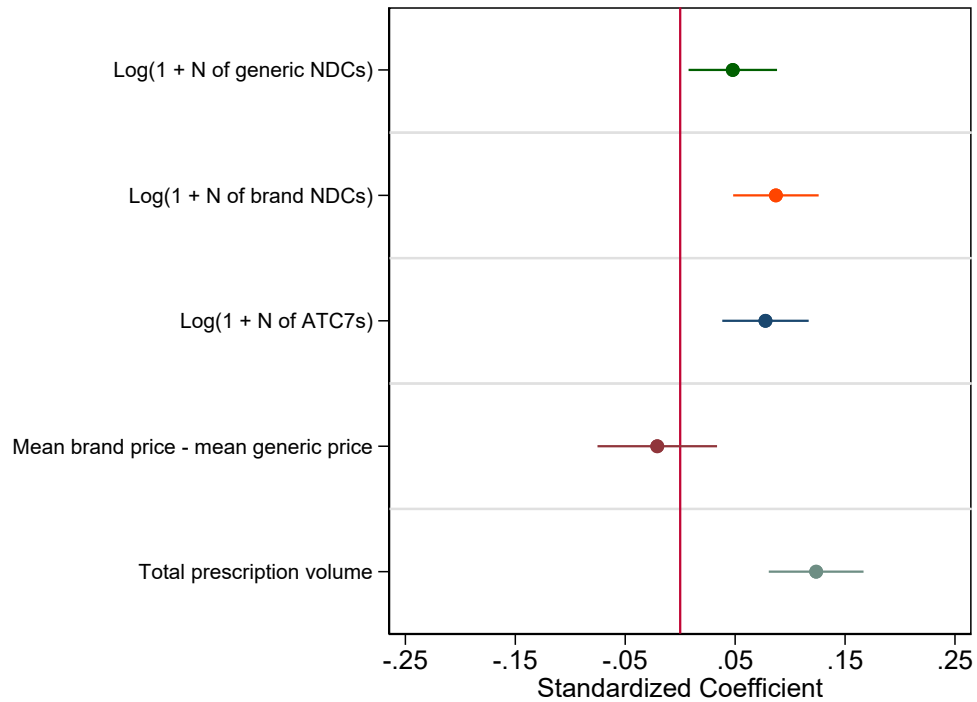
NOTES: We used the 2011 market characteristics of the ATC4 class to predict exclusion risk. The plotted coefficients were generated by conducting bivariate linear regressions of whether an ATC4 class had at least one drug excluded in 2012 or 2013 on each characteristic of the ATC4 class. Independent 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.
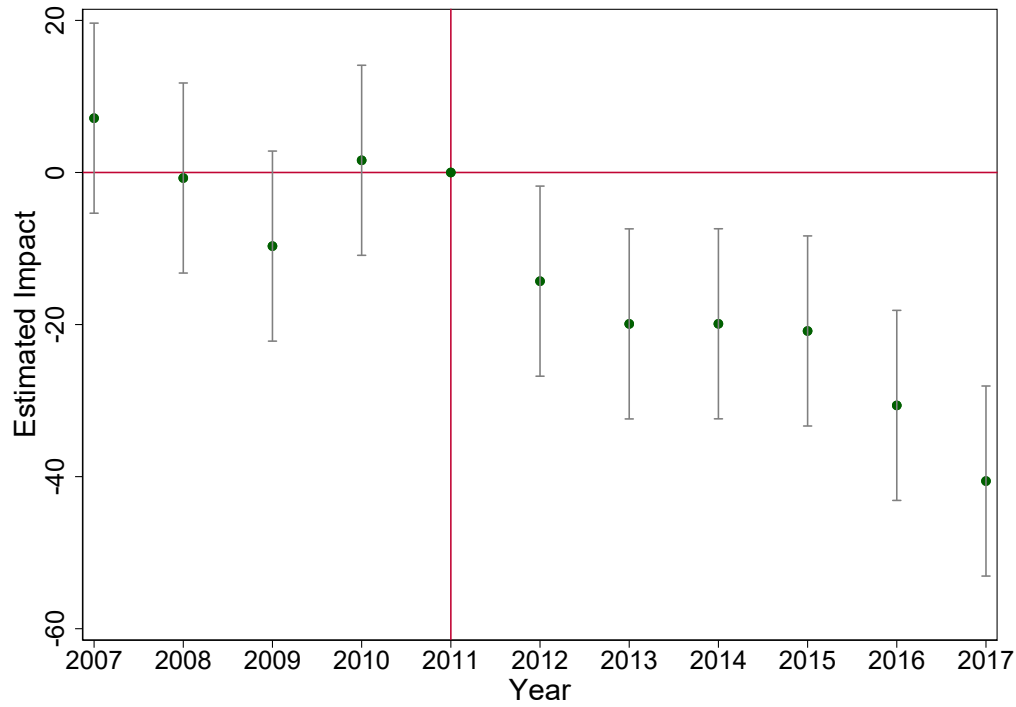
NOTES: Figure displays coefficient estimates and 90% confidence intervals from a modified version of Equation (3). The outcome variable is the annual count of new development activity (across all stages). To generate the event study graph, we replace the single post-period indicator variable ($\mathbb{I}$(Year $\geq$ 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.

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 (3); 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.
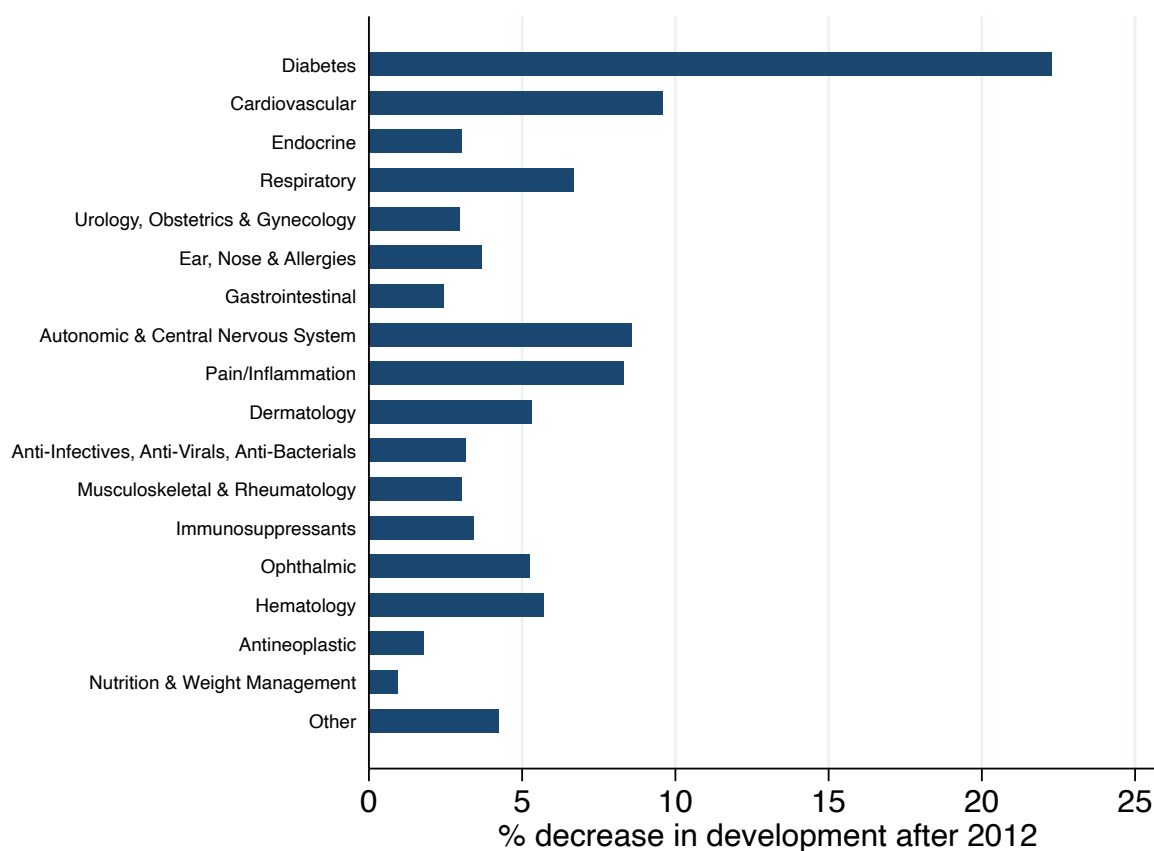
NOTES: This figure plots the predicted percent decline in drug development activity attributable to formulary exclusions, by disease class. Predictions are based on our estimation of equation (3); we match the specification reported in Table 4 column 4. We manually matched each ATC4 to a disease category; this disease taxonomy was adapted from the disease categories provided by the PBMs in their exclusion lists.

A. % Citing Recent Science

B. Average "Disruptiveness" Index
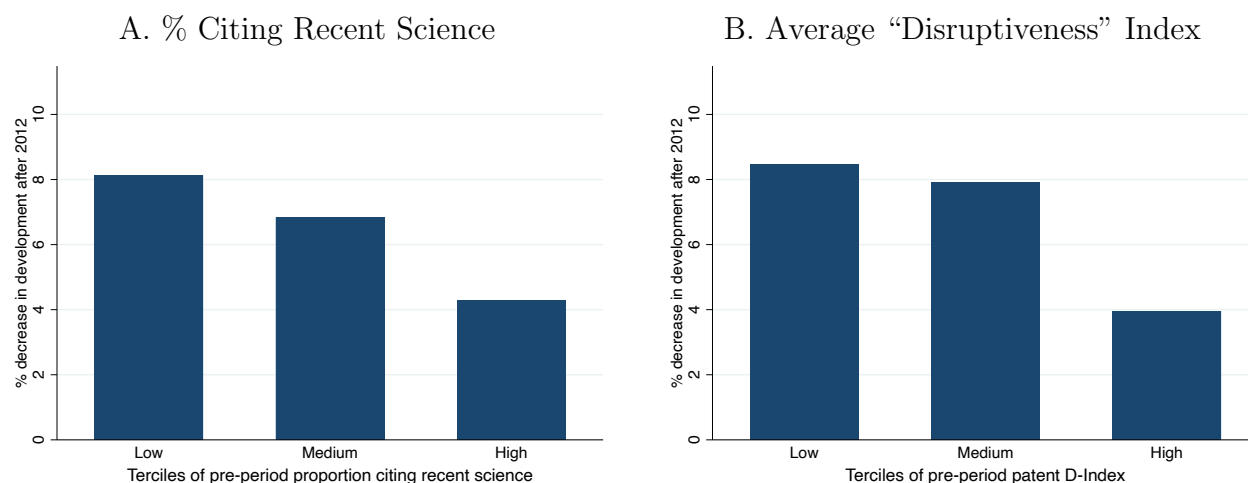
NOTES: This figure displays the percent decrease in annual development attributable to exclusions. Drug classes are divided into terciles according to attributes of patents associated with drug development activity over the pre-period, averaged from 2007-2011. Panel A groups drug classes by the share 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

	Mean	Std. Dev.	Median
All	30.61	42.06	13.05
Preclincal	17.39	26.13	6.64
Phase 1	6.54	8.84	3.07
Phase 2	4.57	6.04	2.17
Phase 3	2.11	3.04	1.04
Launch	1.02	1.63	0.31

(B) ATC4 Characteristics

ATC4 market characteristics in 2011	ATC4s with early exclusions	ATC4s without early exclusions
Mean N of generic NDCs	767.9	310.3
Mean N of brand NDCs	268	106.8
Mean N of ATC7s within ATC4	14.60	8.518
Mean brand price - mean generic price	5.822	55.98
Mean total prescription volume (millions)	70.46	17.63
Number of ATC4s	15	112

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

	(1) Log(Claims)	(2) Log(Claims)	(3) Log(Mkt. Share)	(4) Log(Mkt. Share)
Number of Excluding PBMs	-0.274***	-0.319***	-0.220***	-0.319***
	(0.0638)	(0.0733)	(0.0809)	(0.0733)
Observations	4,626	4,391	4,626	4,391
Drug FE	YES	YES	YES	YES
Cohort X Year FE	YES	YES	YES	YES
Market Controls	NO	YES	NO	YES

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

	(1) Late Exclusion	(2) Late Exclusion
Pr(Exclusion)	0.167***	0.150**
	(0.0413)	(0.0624)
Observations	127	112
Sample	All ATC4s	ATC4s without early exclusions
Fraction with Late Exclusions	0.39	0.31

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: *** $p<0.01$, ** $p<0.05$, * $p<0.1$.

|	(1) New Development	(2) New Development	(3) Log(1+New Dev.)	(4) Log(1+New Dev.)
Post X Pr(Exclusion)	-24.03***	-21.98***	-0.382***	-0.333***
	(5.894)	(6.571)	(0.108)	(0.115)
Observations	1,397	1,397	1,397	1,397
Year FE	YES	YES	YES	YES
ATC FE	YES	YES	YES	YES
Market Controls	NO	YES	NO	YES

NOTES: This table reports results from estimation of equation (3); 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

	(1) Log(1+All)	(2) Log(1+Preclinical)	(3) Log(1+Phase1)	(4) Log(1+Phase2)	(5) Log(1+Phase3)	(6) Log(1+Launch)
Post X Pr(Exclusion)	-0.333***	-0.449***	-0.331***	-0.310***	-0.259**	0.113
	(0.115)	(0.101)	(0.103)	(0.106)	(0.101)	(0.138)
Observations	1,397	1,397	1,397	1,397	1,397	1,397
Year FE	YES	YES	YES	YES	YES	YES
ATC FE	YES	YES	YES	YES	YES	YES
Market Controls	YES	YES	YES	YES	YES	YES
N of Drug Candidates Mean	30.61	17.39	6.54	4.57	2.11	1.02

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 affect 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: *** $p<0.01$, ** $p<0.05$, * $p<0.1$.
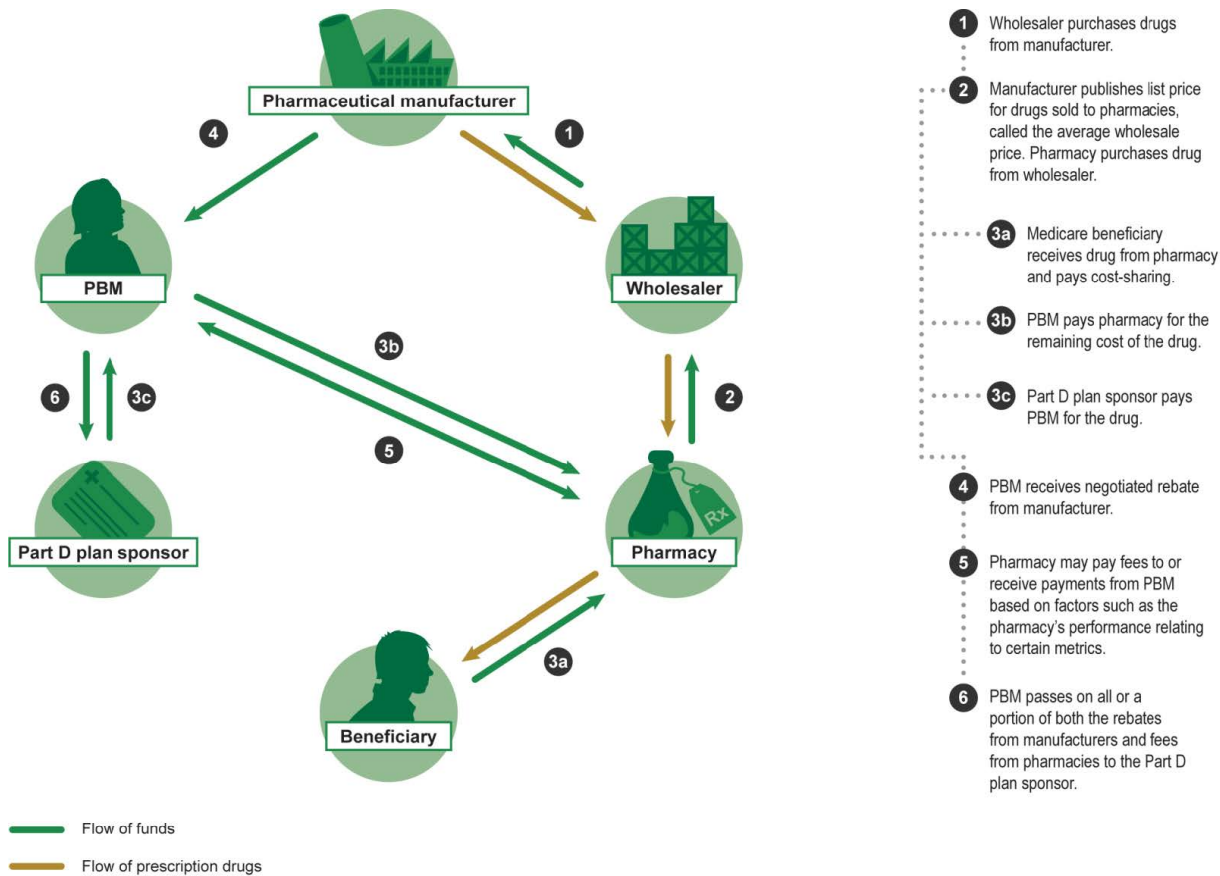
NOTES: Illustration of the flow funds and prescription drugs for a prescription drug purchase covered by a Medicare Part D Insurance plan. Other private insurance plans using PBMs have similar flow of funds. Figure credit to Government Accountability Office (2019).

FIGURE A.2: DISTRIBUTION OF PREDICTED EXCLUSION RISK
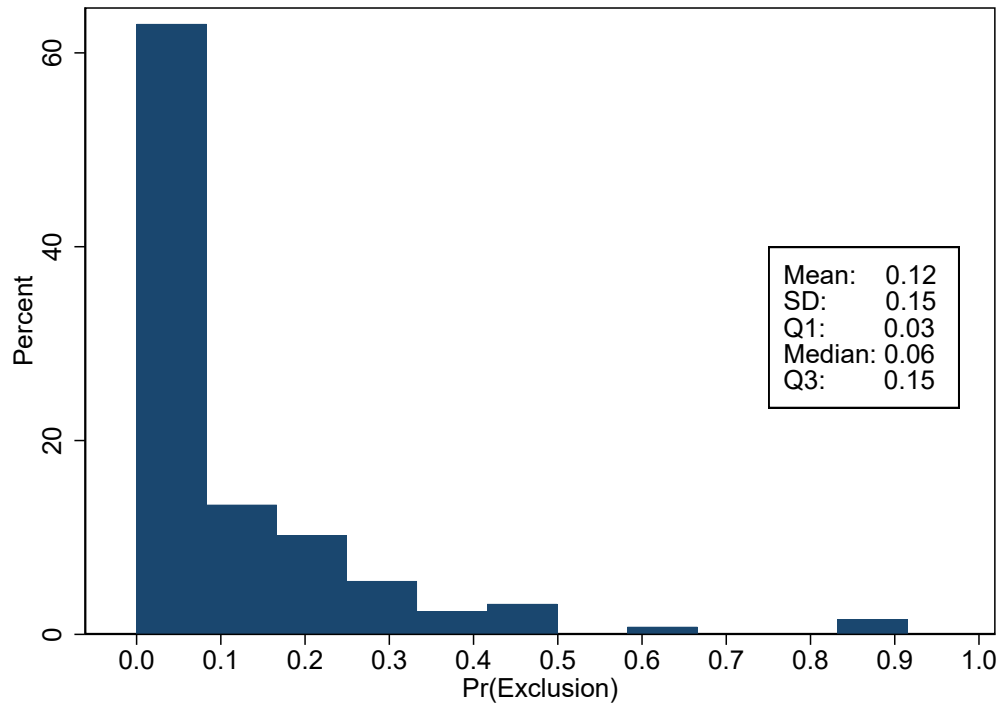
NOTES: This histogram plots the distribution of predicted exclusion risk of the 127 ATC4s in our main analyses. Summary statistics are also provided. See notes to Appendix Table A.4 for details on how the exclusion risk was calculated.

FIGURE A.3: PLACEBO TEST: IMPACT OF PREDICTED EXCLUSION RISK ON NEW DRUG DEVELOPMENT
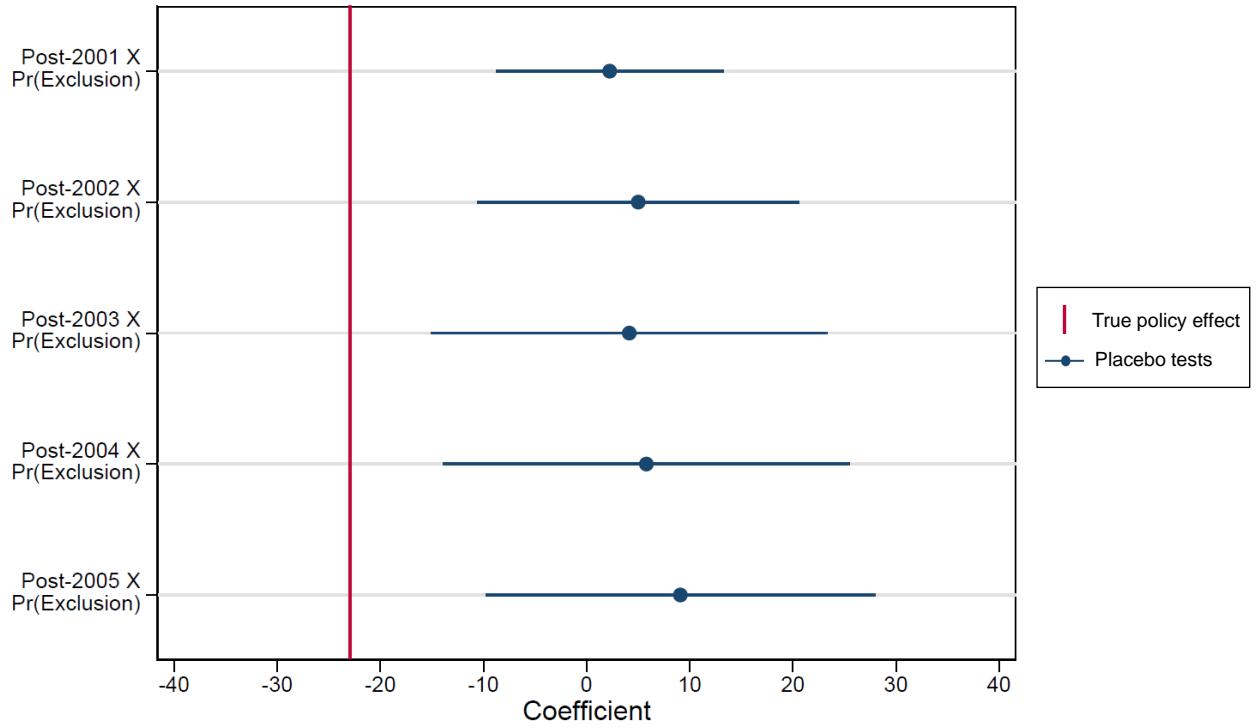
NOTES: This coefficient plot shows the "placebo tests" of the results reported in column 2 of Table 4. The red line indicates the baseline, true policy estimate; it reports β_1, the coefficient on predicted exclusion risk interacted with a post period indicator from Equation 3. This true policy estimate of -22.9 is statistically significant and parallels the specification in column 2 of Table 4, but the only difference is that when constructing the exclusion risk, we dropped the price variables. The blue coefficients report the "placebo tests" of the results reported in columns 2 of Table 4. First, as in the exclusion risk used in Table 4, exclusion risk was constructed by using the same 2011 market characteristics (but dropping price variables) to predict exclusions by 2013 using Equation (2), but here we applied the coefficients from this regression to 2001, 2002, 2003, 2004, or 2005 market characteristics to construct new versions of the exclusion risk. Second, the pre-period and post-periods were adjusted depending on the placebo policy year, such that we use the same number of pre- and post-period years as Table 4. For instance, for the 2002 placebo policy, the pre-period was 1997-2001 and the post-period was 2002-2007, and we used 2001 market characteristics to construct the exclusion risk. For the 2006 placebo policy, the pre-period was 2001-2005 and the post-period was 2006-2011, and we used 2005 market characteristics to construct the exclusion risk. Due to lack of market characteristics data in the earlier period of the data, 3 ATC4s were dropped from the sample for 2006 and 2005 placebo policies, 4 ATC4s for 2004 placebo policy, and 5 ATC4s for 2003 and 2002 placebo policies. None of the placebo estimates were statistically significant.

50

FIGURE A.4: IMPACT OF PREDICTED EXCLUSION RISK ON NEW DRUG
DEVELOPMENT: EVENT STUDY BY STAGES

A. PRE-CLINICAL

B. PHASE 1

C. PHASE 2
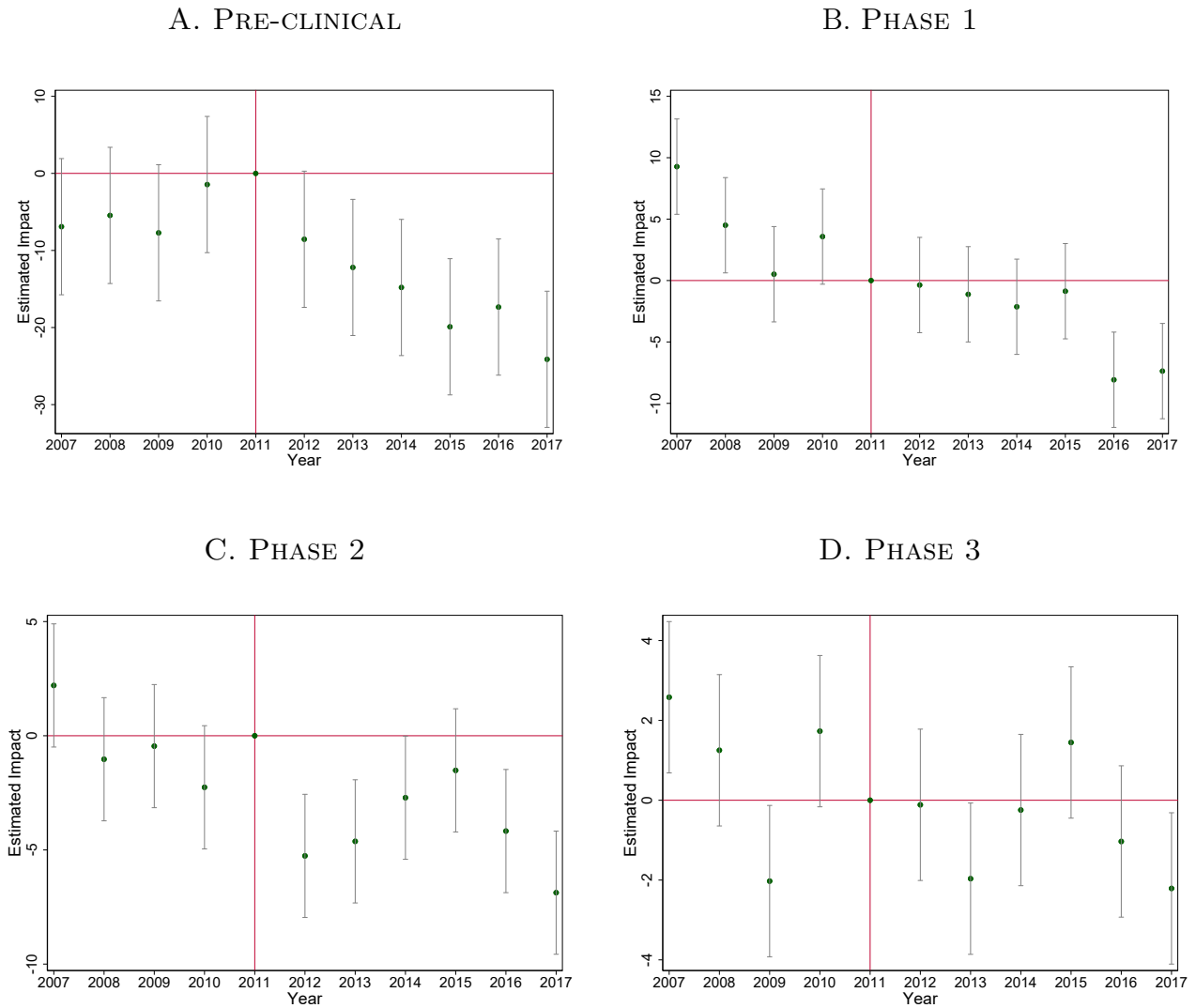
D. PHASE 3

NOTES: See notes to Figure 4. 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.
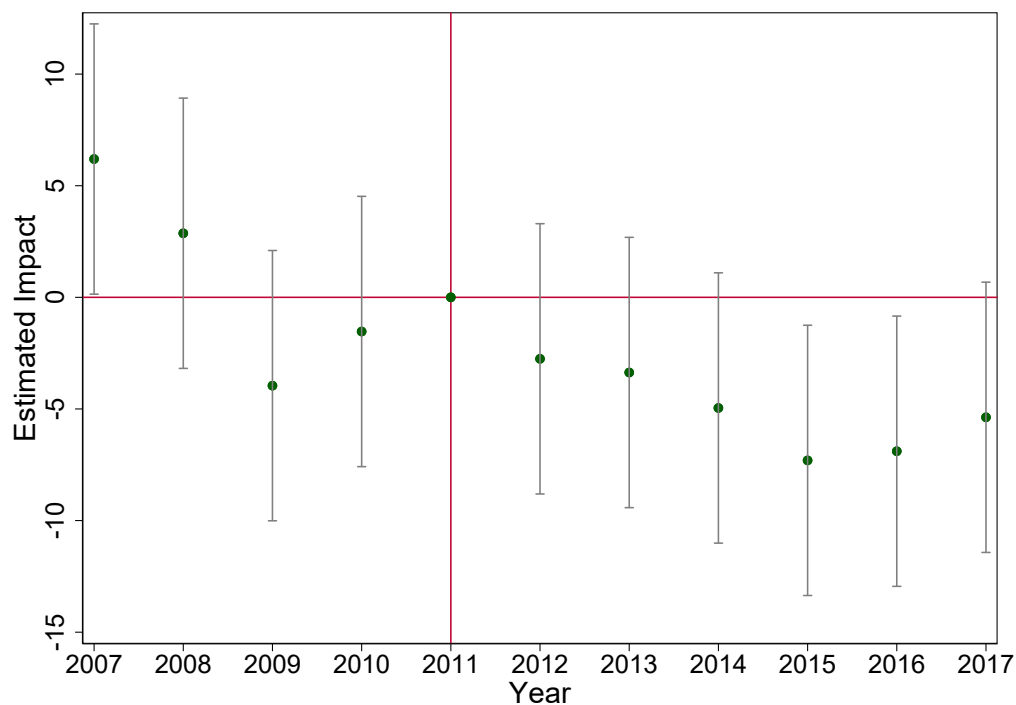
NOTES: These results parallel the specification underlying Figure 4, but with a new definition of exclusion exposure. Instead of defining exclusion risk as a continuous measure predicted using the 2011 market characteristics, the exclusion risk here is a binary variable that equals one if any drug in the ATC4 class was on a PBM exclusion list in 2012 or 2013. The sample includes 1,397 ATC4-year observations.

(A) DIRECTLY LINKED APPROACH ONLY

(B) INDIRECT LINKING APPROACH ONLY

NOTES: These results parallel the specification underlying Figure 4, 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.

A10 Diabetes drugs
A10A Insulins and analogues
A10B Blood glucose lowering drugs, excluding insulins
A10X Other drugs used in diabetes
C07 Beta blocking drugs
C07A Beta blocking agents
C07B Beta blocking agents and thiazides
C07C Beta blocking agents and other diuretics
C07D Beta blocking agents, thiazides and other diuretics
C07E Beta blocking agents and vasodilators
C07F Beta blocking agents, other combinations

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

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

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 durign 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

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

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

	(1) Exclusion
Log(1 + N of generic NDCs)	-0.674**
	(0.317)
Log(1 + N of brand NDCs)	0.656
	(0.511)
Log(1 + N of ATC7s)	1.069
	(0.665)
Mean brand price - mean generic price	-0.00862
	(0.00761)
Total prescription volume	1.70e-08**
	(8.16e-09)
Observations	128

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, LEVELS

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

NOTES: This table parallels the results reported in Table 5 but using non-logged outcomes. Each column explore 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 A.6: IMPACT OF EXCLUSIONS ON NEW DRUG DEVELOPMENT

	(1) New Development	(2) New Development	(3) Log(1+New Dev.)	(4) Log(1+New Dev.)
Post X Excluded Class	-5.824**	-4.534**	-0.161*	-0.137
	(2.568)	(2.290)	(0.0838)	(0.0891)
Observations	1,397	1,397	1,397	1,397
Year FE	YES	YES	YES	YES
ATC FE	YES	YES	YES	YES
Market Controls	NO	YES	NO	YES

NOTES: This table reports results from estimating a modified version of equation (3). 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

	(1) New Dev.	(2) New Dev.	(3) Log(1+New Dev.)	(4) Log(1+New Dev.)
Post X Pr(Exclusion)	-20.98***	-18.59***	-0.370***	-0.269*
	(6.048)	(6.745)	(0.132)	(0.146)
Observations	1,397	1,397	1,397	1,397
Year FE	YES	YES	YES	YES
ATC FE	YES	YES	YES	YES
Market Controls	NO	YES	NO	YES

(B) INDIRECT LINKING APPROACH ONLY

	(1) New Dev.	(2) New Dev.	(3) Log(1+New Dev.)	(4) Log(1+New Dev.)
Post X Pr(Exclusion)	-4.301***	-4.454***	-0.229***	-0.246***
	(1.329)	(1.473)	(0.0836)	(0.0877)
Observations	1,397	1,397	1,397	1,397
Year FE	YES	YES	YES	YES
ATC FE	YES	YES	YES	YES
Market Controls	NO	YES	NO	YES

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

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

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 ϕ^o; for class n this probability is given by ϕ^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.[22]

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[22]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 $\Pi_{e,o}^{open}$ 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:

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

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 λp 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 $b > d$.

$$
\begin{aligned}
q_{e,o}^{open} &= a - b\lambda p_{e,o}^{open} + d\lambda p_{i,o}^{open} \\
q_{i,o}^{open} &= a - b\lambda p_{i,o}^{open} + d\lambda p_{e,o}^{open}
\end{aligned}
$$

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:

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

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

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 $2b - d > 0$.*

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

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

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

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

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

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 λp. 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:

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

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

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 α in the following section. If the entrant is excluded, then it no longer pays the

$(1 - \alpha)$ revenue share to the PBM.

$$\max_{p_{e,o}^{excluded}} \left(p_{e,o}^{excluded} - m\right) \left(a - bp_{e,o}^{excluded} + d\lambda p_{i,o}^{included}\right)$$

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

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.*

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

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.[23] 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

---

[23]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 λ 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 α 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:

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

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

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 αpq. 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:*

$$\Pi_{e,o}^{excluded} = \Pi_{i,o}^{included} \ and \ \Pi_{e,o}^{excluded} > \Pi_{e,o}^{open} \tag{4}$$

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.[24]

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

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

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

---

[24]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 α, and the difference in profitability between the included and excluded drug is also increasing in α. 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:

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

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

$$\Pi_{e,o}^{open} > \frac{\phi_n}{\phi_o} \Pi_{e,n}. \tag{5}$$

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 ϕ_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:

$$\Pi_{e,o}^{excluded} > \frac{\phi_n}{\phi_o} \Pi_{e,n}. \tag{6}$$

The criterion differs from the no-exclusion condition given in Equation (5) only in the lefthand side, which had a $\Pi_{e,o}^{excluded}$ instead of $\Pi_{e,o}^{open}$. As shown above profits are higher when there is an open formulary so that $\Pi_{e,o}^{open} > \Pi_{e,o}^{excluded}$. 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.[25] 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 and Appendix Figure A.6, our results are similar regardless of the linking method used.

---

[25]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.