Insurance Design and Pharmaceutical Innovation*

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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 document a shift in pharmaceutical R&D strategies after this policy took effect: therapeutic classes at greater risk of exclusion experienced a relative reduction in investments. This shift reduced development of drug candidates that appear more incremental: that is, those in drug classes with more pre-existing therapies and less scientifically novel research.

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Technological innovation is a major driver of rising healthcare spending, raising questions as to whether current payment systems appropriately balance incentives to innovate with cost containment. While insurance expansions have been shown to spur R&D investments, critics argue that generous coverage policies create perverse incentives for firms to develop expensive products with little incremental clinical value.[1]

As prescription drug costs rise, politicians and policymakers have increasingly called for the federal government to contain spending by limiting insurance coverage for high-cost, low-value treatments. Despite the importance of this policy debate and the widespread adoption of value-based pricing and coverage decisions outside the US, there is limited empirical evidence on how insurance design shapes incentives for 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 US generally provided coverage for all FDA-approved drugs.[2] To manage costs, plans used a combination of cost-sharing tiers and ordeal mechanisms to direct patients to less expensive drugs. However, these approaches 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 plans, dramatically shifted their policies and began excluding coverage for some drugs entirely. These exclusions applied to many newly approved drugs without generic equivalents. This practice, known as maintaining a "closed formulary," has since become standard, with 846 branded drugs excluded by at least one of the three largest PBMs as of 2020 (Xcenda 2020).

Closed formulary policies can substantially reduce the profitability of excluded drugs. When GlaxoSmithKline's blockbuster asthma inhaler, Advair, was excluded by Express Scripts in January 2014, its US sales fell by over 30% within a few months (Pollack 2014). Similarly, exclusions can reduce the expected profitability of drugs that have yet to reach

[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), Frank and Zeckhauser (2018), and Dranove et al. (2020) highlight the risk that generous drug payments may yield excessive incremental innovation.

[2]There are exceptions to this pattern, with some private insurance plans applying restrictive formularies prior to 2012. Importantly, these early formulary restrictions were set by individual plans, unlike the post-2012 restrictions we study in this paper, which were centrally negotiated by Pharmacy Benefit Managers that manage coverage for many different insurance companies with a shared formulary.

the market. The high blood pressure medication Edarbi received FDA approval in 2011 but was almost immediately excluded by CVS Caremark in 2012, suppressing demand before it could become established. By September 2013, Edarbi's manufacturer, Takeda, had sold off its US distribution rights, despite keeping these rights in other countries.

Declines in the potential profitability of drugs arising from downstream exclusion policies can potentially affect pharmaceutical firms' upstream R&D investments. For instance, since its experience with Edarbi, Takeda has not developed any further drugs for hypertension, choosing instead to focus on oncology and rare diseases, areas that have seen far fewer exclusions.

Studying how PBM policies shape pharmaceutical innovation can inform our understanding of how to design payment policies that balance 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.[3] Indeed, the largest PBM, CVS Caremark, manages benefits for 75 million Americans—more than the number of enrollees in either Medicare or Medicaid.

We identify the effect of PBM coverage decisions on upstream innovation by comparing drug development activity across therapeutic classes that vary in their risk of facing exclusions, before and after the introduction of closed formulary policies. We begin by matching hand-collected data on PBM's excluded drugs with information on the characteristics of over 100 therapeutic classes. We show that exclusions were more common in drug markets that, prior to the introduction of closed formularies, had more existing therapies and high prescription volume. Using this information, we create an index that categorizes drug markets on the basis of their ex-ante predicted exclusion risk. We then use data on drug development pipelines to track R&D investments across therapeutic classes that vary in their predicted exclusion risk.

Following the introduction of closed formularies, pharmaceutical investments fell markedly in drug classes at high risk of exclusions relative to trends in low risk classes. For a one standard deviation increase in a drug class's exclusion risk, there was an 11% decline in the number of drugs entering pre-clinical and clinical development. These declines affect

[3]Congressional Budget Office (2007) predicts that the government will not be able to negotiate lower prices with drug manufacturers unless it adopts a PBM-pioneered model of providing preferential access for specific drugs on publicly-run formularies.

drug candidates in all phases of development, but are largest among earlier stage candidates. 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. R&D declined the most in high prescription volume markets with a large number of existing therapies, as well as in classes where drug patents were based on older and less disruptive science.

Our analysis identifies a *relative* decline in R&D across drug classes at high vs. low exclusion risk, but cannot distinguish whether this comes from a total decline in innovative activity or a reallocation of R&D investment. As a result, we are limited in our ability to evaluate the full welfare implications of closed formulary policies. Our findings suggest, however, that the policies of downstream drug buyers can influence the economic returns to upstream pharmaceutical R&D. Prior to the introduction of closed formularies, pharmaceutical firms could expect their drugs to be widely covered by insurers if they become FDA approved. In this world, firms have strong incentives to develop incremental drugs aimed at large disease markets—such drugs would be likely to receive FDA approval and to generate a large base of revenues if approved. Yet with closed formularies, these incremental drugs became precisely those at greatest exclusion risk.

We build on a broad literature examining the drivers of innovation across a range of settings. A large body of evidence shows that public health insurance expansions create incentives for firms to develop new technology (Acemoglu et al. 2006; Blume-Kohout and Sood 2013; Clemens and Olsen 2021; Dranove et al. 2020; Finkelstein 2004; Krieger et al. 2017). Kyle and McGahan (2012) and Budish et al. (2015) highlight the role of patent policy in encouraging innovation, while Yin (2008) studies the role of tax credits and Clemens and Rogers (2020) focuses on public procurement incentives. Finally, public research funding has positive spillovers on private patenting (Azoulay et al. 2019; Li et al. 2017), and local agglomeration effects are an important driver of innovation (Jaffe et al. 1993) and technology diffusion (Agha and Molitor 2018; Baicker and Chandra 2010).

Our paper contributes to this literature in two ways. First, to our knowledge, this is the first study of how restricting prescription drug coverage affects pharmaceutical innovation. Theoretical work in this area highlights the tradeoff between insurance design and innovation (Garber et al. 2006; Lakdawalla and Sood 2009). Although policies that restrict prescription

drug coverage and aggressively negotiate prices are widely used in Europe and Asia, there is little empirical evidence of how these policies affect dynamic incentives for innovation. Second, while existing work focuses on the role of public sector policies, ours is the first to show that the decisions of *private* firms can have important effects on pharmaceutical innovation. Our findings suggest that insurance design choices are powerful tools that may shape the direction of pharmaceutical R&D.

1 Institutional Background

1.1 The Role of Pharmacy Benefit Managers (PBMs)

In the US, 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 insurance claims at the pharmacy: verifying the patient's coverage, obtaining payment from the insurer, and transmitting that payment to the pharmacy. 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 demand for expensive drugs. First, insurance plans assign expensive drugs to different coverage tiers, with higher patient cost-sharing. Second, prior authorization requirements imposed on select drugs require physicians to obtain advance approval from the PBM or insurer prior to coverage. Finally,

[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 the Government Accountability Office (2019) report for a more complete picture of the supply chain.

step therapy requirements allow coverage for certain expensive drugs only after the patient has tried and failed cheaper alternatives.

PBMs may also lower costs by pooling demand across multiple payers in order to negotiate bulk discounts. Given the concentration in the industry and their role in shaping patient demand, PBMs have substantial negotiating power with manufacturers. Drugmakers routinely offer large rebates in order to secure more favorable formulary positions. PBMs may return a portion of this savings to institutional payers and keep a portion for themselves.

1.2 The Introduction of Formulary Exclusions

Prior to the introduction of closed formularies, PBMs had limited success in reducing the use of expensive medications because pharmaceutical firms employed a variety of techniques to circumvent their coverage restrictions. For example, to increase the use of drugs placed in more expensive coverage tiers, pharmaceutical firms introduced "co-pay coupons" that reduced patients' out-of-pocket costs.[5] Similarly, drug sales representatives actively helped physicians' offices fill out the paperwork necessary to request a prior-authorization—in some cases by developing specialty software that would auto-fill these forms (Pinsonault 2002).[6]

Beginning with CVS in 2012, major PBMs responded by implementing closed formularies (Pollack 2014). For the first time, PBMs published lists of drugs that their standard plans would not cover at all, directing potential users to recommended alternatives.

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:

> "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).

[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 88% of prior authorization requests were approved by health plans (Scott-Levin 2001).

The success of closed formularies at curbing utilization reduces the profitability of targeted drugs. Yet, 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:

> "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'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 drugmakers can charge, regardless of whether exclusions actually take place.

1.3 Formulary Exclusions and Upstream Innovation

As illustrated above, PBMs may use the threat of exclusions to extract surplus from drug manufacturers. Manufacturers may make price concessions in order to compete for a spot on the restrictive formulary, or the mere threat of exclusion could lead to lower prices even if few drugs are actually excluded in equilibrium. In either scenario, closed formulary policies—which enable the *possibility* of exclusions—may reduce the expected revenues of drug candidates that can be credibly threatened with exclusions.

These changes in expected profitability may in turn influence pharmaceutical firms' upstream R&D decisions. Specifically, concerns about formulary coverage may lead firms to apply a higher "bar" for drugs at greater risk of facing exclusion. After the introduction of formulary exclusions, industry consultants began routinely advising pharmaceutical companies that "[m]arket access strategy should underpin decision-making throughout the entire product lifecycle, including portfolio decision-making" (Siegal and Shah 2019). Rather than simply demonstrating safety and efficacy (the standard for FDA approval), firms were also advised to conduct more ambitious clinical trials to demonstrate superiority in head-to-head comparisons with competitor's drugs (Schafer 2018; Siegal and Shah

[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).

2019).[8] Formulary considerations may reduce the number of drug candidates promoted through clinical testing both by weeding out drugs that do not meet this higher standard, and by raising the cost and complexity of clinical trial design.

2 Data

To understand the impact of exclusion policies on innovation, the key economic object we are interested in measuring is pharmaceutical firms' perceptions of exclusion risk associated with developing new drug candidates across different classes. The ideal measure would capture both the risk that the new drug is itself excluded, as well as the risk that the new drug is less profitable because it must offer large price concessions in order to avoid exclusion.

To develop our measure of exclusion risk, we link data on drug market characteristics across classes (from First Data Bank) with the incidence of formulary exclusions (from PBM documents). We then investigate the relationship between exclusion risk and drug development by linking exclusion risk to Cortellis data on R&D activity. The data underlying these analyses is summarized below.

1. **Formulary Exclusions**: We collected data on formulary exclusions, from publicly disclosed standard formulary lists published by CVS Caremark, Express Scripts, and OptumRX through 2017 (Agha et al. 2021). Together, these firms account for approximately 70% of the PBM market. Our data cover "standard" formulary exclusions: these exclusions apply to most health plans administered by a particular PBM. Insurers may elect to provide more expansive coverage by opting out of the standard formulary, but we do not have information on exclusions within these custom plans.[9]

2. **First Data Bank**: We collect data on drug markets from First Data Bank (FDB) (2018). FDB is a commercial database that contains information on each approved

[8] In a related analysis, Seabright (2013) analyzes how drug procurement may affect trial design, particularly the incentive to investigate treatment effect heterogeneity predictable by biomarkers. Cohen et al. (2021) discuss how timing considerations may impact firms' decisions to seek FDA approval.

[9] 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).

drug's ATC4 classification, pricing, and generic substitutes. We use this information to construct drug-class level predictors of exclusion risk.

3. **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 Cortellis Investigational Drugs database (Clarivate Analytics 2018). 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. Because FDA approval is prerequisite for beginning human clinical trials, Cortellis has near complete coverage of drug candidates that advance into human testing.

   Our primary outcome is the total number of drug candidates within a class that entered or advanced to any stage of development each year. Table 1 Panel A reports the summary statistics of development activity across different stages.

Throughout most of the paper, our unit of analysis is a narrowly defined drug class, following the Anatomical Therapeutic Chemical (ATC) classification system. We use an ATC4 (four-digit) level classification, which identifies chemical subgroups that share common therapeutic and pharmacological properties. Appendix Table A1 lists several examples of ATC4 designations.

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 with no generic equivalent, and to those for which we observe measures of prescription volume and price in 2011. Our primary sample has 127 ATC4 classes. Table 1 Panel B shows the summary statistics of various market characteristics for our sample of ATC4s.

3 Understanding Exclusion Risk

3.1 The Rise of Formulary Exclusions

Figure 1 Panel A illustrates the rise of drug exclusions over time and across PBMs. As described in trade press and national media (Pollack 2014; Fein 2015), CVS began with the exclusion of 38 drugs in 2012. Over the next five years, CVS oversaw a sustained expansion in the number and types of excluded drugs. 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.

Exclusions largely targeted newer branded drugs: 75% of those excluded had no molecularly equivalent generic substitute. Exclusions are concentrated in therapeutic areas with large numbers of patients. Appendix Figure A.1 plots exclusions by disease category at the drug level and shows that diabetes drugs have been the most frequently excluded. Other disease categories with high numbers of exclusions include cardiovascular, endocrine, and respiratory diseases.

PBM formulary choices affect patients' drug use. It has been widely documented that demand for drugs is elastic to out-of-pocket prices, implying that eliminating insurance coverage for excluded drugs will suppress demand (Abaluck et al. 2018; Einav et al. 2017; Choudhry et al. 2011; Tamblyn et al. 2001). In addition, several papers have shown that formulary exclusions specifically reduce utilization of targeted drugs (Chambers et al. 2016; Huskamp et al. 2003; Wang and Pauly 2005).[10] In Appendix Table A.2, we verify this in our own data by tracking how PBM exclusions affect Medicare Part D prescription volume over time. Our findings indicate that a drug's market share of claims (measured as the fraction of the drug's prescription volume relative to other drugs in the ATC4 class) falls by about 25% for each of the 3 major PBMs that exclude it.

3.2 Predictors of Formulary Exclusion Risk

Using the FDB data, we construct several potential predictors of exclusion risk for ATC4 drug classes. We measure the availability of therapeutic alternatives using the number of

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

existing branded drugs within an ATC4, the number of existing generics within the same class, and the number of finer-grained ATC7 subclasses. 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 Medicare Expenditure Panel Survey. Finally, we collect data on the price of branded and generic drugs, keeping in mind that price data do not reflect the rebates that manufacturers often pay to PBMs. All of these market characteristics are from 2011, before the introduction of exclusions in 2012.

Figure 1 Panel B plots the coefficients from bivariate logit regressions of exclusion on each drug class characteristic. Drug classes with higher prescription volume and more treatment options are more likely to experience exclusions. These patterns are consistent with contemporaneous descriptions of PBMs' exclusion strategies, which indicate that exclusions often target "me-too drugs" with multiple therapeutic substitutes (Reinke 2015), as well as drugs with many prescribed patients: "[T]here's no reason to go after trivial drugs that aren't going to drive savings" (Miller and Wehrwein 2015).[11]

Building on these insights, we estimate a single index of exclusion risk using logistic regression as follows:

$$Pr(\text{Excluded}_c|\mathbf{X}_c) = F(\alpha\mathbf{X}_c) \tag{1}$$

Excluded_c is an indicator for whether drug class c actually experiences exclusions in 2012 or 2013 and X_c is a vector of market characteristics described earlier. We take the resulting fitted values, denoted Pr(Excluded)_c, as our primary measure of exclusion risk for drug class c. Table 2 shows the results of this exercise, and Appendix Figure A.2 plots the resulting distribution of predicted exclusions.

To estimate Equation (1), we use market characteristics from 2011, prior to the introduction of closed formulary policies, in order to avoid confounding our risk measure with development responses that are endogenous to the exclusion policies we study. We discuss threats to identification further in Section 4.

For Pr(Excluded)_c to capture firms' perceptions of exclusion risk over the duration of the post-period, it must meet two conditions. First, drug classes predicted to have high exclusion risk in 2012 and 2013 should also be more likely to face exclusions in later years. Second,

[11] We find no statistically significant relationship between drug prices and exclusion risk, but because our data does not measure prices net of rebates, these correlations are difficult to interpret.

because exclusion threat can depress profitability even in the absence of actual exclusions (by forcing drugmakers to grant price concessions), our measure should capture the threat of exclusion even in classes where no drugs face early exclusions. Appendix Table A.3 provides support for both predictions. Classes at high risk of early exclusions are also more likely to see later exclusions: a one standard deviation increase in early exclusion risk correlates with a 19 percentage point increase in the likelihood that an ATC4 class experiences exclusions in later periods, from a mean of 39%. Even among drug classes that do not experience any exclusions in 2012-13, those with higher predicted exclusion risk are more likely to see exclusions in later periods: a one standard deviation increase in early exclusion risk generates a 13 percentage point increase in the likelihood of late exclusions, from a base rate of 31%.

4 The Impact of Exclusion Risk on Subsequent Drug Development

4.1 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:

$$\text{Development}_{ct} = \beta_1 \text{Pr(Excluded)}_c \times \mathbb{I}(\text{Year}_t \geq 2012) + \mathbf{X}_{ct}\gamma + \delta_c + \delta_t + \epsilon_{ct} \qquad (2)$$

In Equation (2), Development_{ct} measures the number of new drug candidates in drug class c at year t. The index Pr(Excluded)_c captures a drug class's exposure to exclusions, as defined in the previous section. The regressions control for drug class fixed effects (δ_c), year fixed effects (δ_t), and some specifications include time-varying drug market controls ($\mathbf{X}_{ct}$).

For the coefficient β_1 to represent the causal impact of formulary exclusions on drug development, the exclusion risk index Pr(Excluded)_c must satisfy a conditional exogeneity assumption. Specifically, market characteristics used to construct this index cannot predict changes in R&D investment that would have occurred even in the absence of exclusive

formularies, after conditioning on drug class fixed effects, year fixed effects, and other control variables.

While we cannot directly test this assumption, we can investigate whether these drug classes were on parallel development trends prior to the introduction of PBM formulary exclusions. In Figure 2, we report an event study graph over a 5-year pre-period to assess the plausibility of this assumption. This graph is based on a modified version of Equation (2), which replaces the single indicator variable for 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.

Even with parallel pre-trends, our identification arguments could be threatened if other changes in global drug development incentives coincided with the introduction of PBM formulary exclusions, particularly if these changes disproportionately affected drug classes at high exclusion risk. For example, changes in drug purchasing policies in international markets may have independent effects on innovation, as might changes in industry structure resulting from PBM mergers. We discuss these possibilities and interpret our findings in Section 4.3.

4.2 Main Results

Table 3 presents our main regression results. The outcome is the total number of drug candidates promoted to the next 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, a 12% reduction from a mean of 30.6 advancing candidates.[12] This estimate reflects declining development in higher-risk classes relative to trends in lower-risk classes. In Column 2, we show that our results are robust to controlling for time-varying market conditions: the number of approved branded drugs, the number of generic drugs, the mean price of branded drugs minus the mean price of generic drugs, the number of ATC7 subclasses with approved drugs, and prescription volume. Adding these controls lowers our estimated coefficient slightly from 3.6 to 3.3, which translates into an 11% decrease in annual development per standard deviation increase in

[12] 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 3, we calculate $-24.04 * 0.15 = -3.6$.

exclusion risk. In Columns 3 and 4, we consider an alternative functional form: $\log(1 + \text{Development}_{ct})$. The log-transformed outcome suggests that development activity declines by 6% for every 1 standard deviation increase in class exclusion risk. In Appendix Table A.4, we decompose this total effect by drug development stage; across all stages, from preclinical through Phase 3 trials, a one standard deviation increase in exclusion risk predicts a decline in innovation ranging from 8% to 14%. We find no significant effect of exclusions on new drug launches, although our estimate is imprecise relative to the mean frequency of launches.

One concern is that innovation in ATC4 classes at high exclusion risk 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 face exclusions and, independently, also see natural attenuation in innovative activity. Figure 2 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. In Appendix Figure A.3, we report results from various placebo policy tests to provide further evidence that our results are not driven by secular differences in innovative potential across low- and high-exclusion risk classes.

In addition, we conduct a variety of robustness checks. Our results remain statistically significant when applying a wild cluster bootstrap (see Appendix Table A.5), using alternative functional specifications such as Poisson regression or the inverse hyperbolic sine transformed outcome (see Appendix Table A.6), or testing alternative rules for attributing drug candidates to ATC4 classes (see Appendix Table A.7). Our results are also robust to a variety of approaches for assessing exclusion risk: predicting based on the count or share of excluded drugs within an ATC4 class, or simply using an indicator variable for whether a drug class had any realized exclusions in 2012-2013 (see Appendix Table A.8). Finally, we obtain similar estimates when augmenting our predictors of exclusion risk to include 2014 data on copay coupons from Van Nuys et al. (2018) (see Appendix Table A.9).

4.3 Discussion

Our results suggest that the policies of US PBMs have a meaningful impact on the drug development decisions of global firms. To contextualize this result, we consider other possible

changes in pharmaceutical markets and quantify the implications of these results for different types of drug classes.

First, the strength of formulary exclusion policies is likely related to the market power of PBMs, which increased over this period through three major mergers: CVS's acquisition of Caremark in 2007 (Harris 2007), Express Scripts' acquisition of Medco Health Solutions in 2012 (Lee 2012), and OptumRx's (owned by UnitedHealth) acquisition of Catamaran in 2015 (Mathews and Walker 2015). In each case, the acquiring PBM introduced its closed formulary 1–5 years after its acquisition. Our results should therefore be interpreted as describing the effect of exclusion policies in a setting where downstream buyers have substantial market power.

Second, while the US drug market plays an outsized role in shaping global development incentives, accounting for 40% of total pharmaceutical spending in 2018 (IQVIA 2019), policy changes in other countries may also contribute to our findings. Any changes to drug purchasing in large markets that occur around 2012 and differentially affect crowded drug classes would be particularly relevant. The European Union does not centrally control prices or coverage of prescription drugs (Rodwin 2019) and the five largest European markets collectively account for only 15% of global spending. As a result, we believe that the ongoing administration of their national formulary policies is unlikely to explain our results. The most relevant policy we have been able to identify is a series of initiatives implemented in Japan beginning in 2006 aimed at encouraging generic substitution of branded drugs. Japan is a large market for branded pharmaceuticals (second after the US[13]), representing 7% of the global spending (IQVIA 2019), and this policy may have depressed incentives for innovation in markets with generic competition. However, the implementation of these policies was gradual and began several years prior to the introduction of closed PBM formularies in the US (Kuribayashi et al. 2015).

Finally, to better describe the drug markets that experience declines in R&D investment attributable to formulary exclusions, we use our estimates to conduct a quantification exercise considering three dimensions of difference across markets: crowdedness, size, and scientific novelty. Because drug classes with these market characteristics have different predicted

[13]The second largest pharmaceutical market in general is China (11% of global spending), but branded drugs comprise a much smaller share of this market than in Japan or the US.

exclusion risk (as estimated in Table 2), our findings imply differential impacts of formulary exclusions. In Panel A of Appendix Figure A.4, we predict the largest declines in drug development for drug markets with the most existing therapies; among drug classes in the top tercile of available therapies, exclusions depress development by over 4%. In Panel B, we predict larger R&D declines for drug classes with higher prescription volume, topping out at an 8% fall in the top tercile. In Panels C and D, we apply patent-to-science linkages created by Marx and Fuegi (2020) to assess the scientific novelty of drug classes as measured by citations to recent or "disruptive" science.[14] In both cases, our calculations show that formulary exclusions lead to larger R&D reductions in less scientifically novel drug classes.

These calculations suggest that PBMs wielded the threat of formulary exclusion in a way that disproportionately reduced R&D effort for incremental treatments, with many existing substitutes and older, less novel underlying science. This analysis is suggestive: our finding of differential impact on large, crowded drug classes could reflect the possibility that competition lowered the returns to new investment in these areas. While we see no evidence of this slow-down for more crowded classes in our placebo analysis reported in Appendix Figure A.3, other long-run changes in pharmaceutical markets might affect the nature of these relationships.

5 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 insurance policies restricting prescription drug coverage affects upstream investments in pharmaceutical R&D.

Drug classes facing a one standard deviation greater risk of exclusions see an 11% decline in drug development activity relative to trends in lower risk classes, 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.

[14] Our measure of "disruptiveness" follows Funk and Owen-Smith (2017) and Wu et al. (2019), which captures the idea that a research article representing a paradigm shift will generate forward citations that will not cite the breakthrough article's backward citations.

The limitations of our current 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. The overall welfare implications of exclusive formularies will depend on their impact on aggregate pharmaceutical R&D, which is not identified by our empirical strategy. Second, it remains challenging to accurately value foregone innovation. 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. Additional research will be needed to quantify the tradeoffs associated with decreased development. Third, because we cannot directly observe drug price rebates, there is more work to be done quantifying the impact of formulary exclusions on pharmaceutical revenue.

Our analysis focuses on the first wave of PBM formulary exclusions, which largely targeted drugs in markets with many available options. In recent years, formularies have begun to exclude therapies for relatively rare and sensitive diseases, 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, possibly leading to declines in R&D in those classes as well.

Viewed from a public policy perspective, this research opens the door for insurance design to be a part of the broader toolkit that policymakers use to encourage and direct investments in innovation. Existing policy efforts to shape innovation have relied almost exclusively on directly influencing the costs and returns to R&D, through patents, tax credits, or research funding. Our results suggest that managers and policymakers can also use targeted coverage limitations and price negotiation—for example, those generated by value-based pricing—to reduce R&D efforts in areas with limited incremental clinical value.

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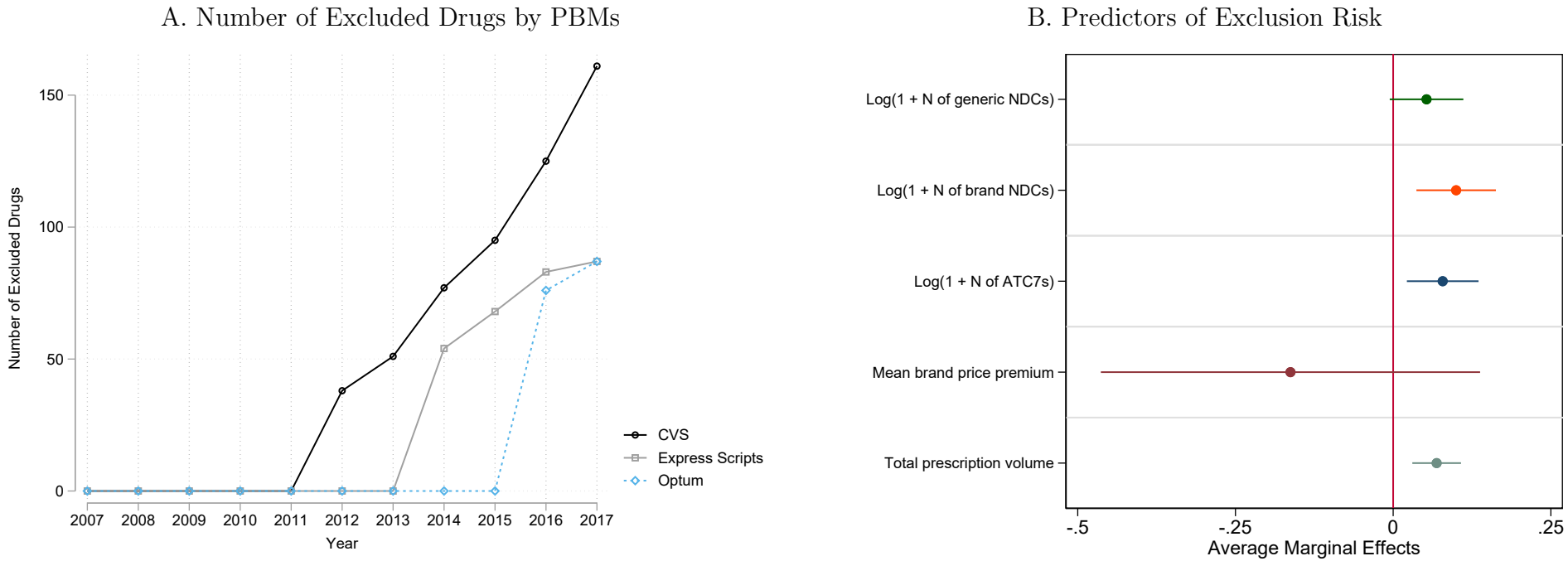
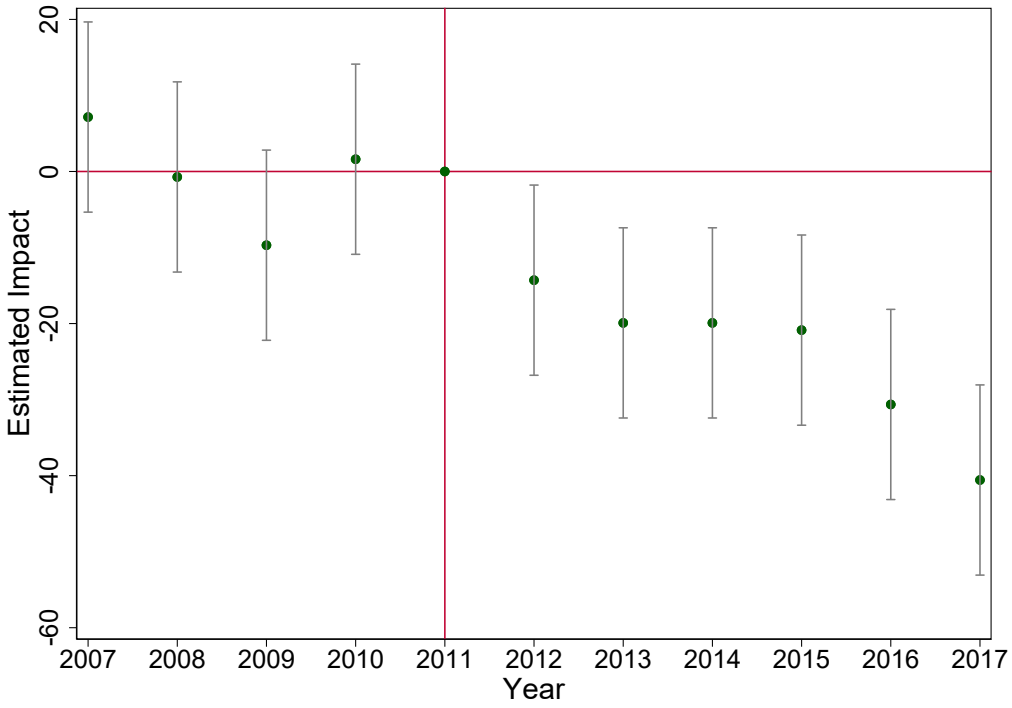
Figure 1: Trends and Predictors of Exclusion



Notes: This figure displays the trends and predictors of exclusion. In Panel A, we plot the number of drugs excluded by each of the three largest Pharmacy Benefit Managers. CVS was the first to begin excluding drugs in 2012, followed by Express Scripts in 2014 and OptumRx in 2016. In Panel B, we used the 2011 market characteristics of the ATC4 class to predict exclusion risk. The plotted average marginal effects were generated by conducting bivariate Logit 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). 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 year of 2011 Medical Expenditure Panel Survey (2017).

FIGURE 2: IMPACT OF PREDICTED EXCLUSION RISK ON NEW DRUG DEVELOPMENT: EVENT STUDY



NOTES: Figure displays coefficient estimates and 90% confidence intervals from a modified version of Equation (2). 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 ($\mathbb{I}(\text{Year} \geq 2012)$) 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 Table 2.) The regression controls for ATC4 fixed effects and year fixed effects. The sample includes 1,397 ATC4-year observations.

Table 1: Summary Statistics

(A) New Drug Development

	Mean	Std. Dev.	Median
All	30.61	42.06	13.05
Preclinical	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 2007-2017 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 total prescription volume are from the 2011 Medical Expenditure Panel Survey.

Table 2: Predicting Exclusion Risk

VARIABLES	(1) Exclusion
Log(1 + N of generic NDCs)	-0.0543**
	(0.0252)
Log(1 + N of brand NDCs)	0.0527
	(0.0415)
Log(1 + N of ATC7s)	0.0861
	(0.0532)
Mean brand price - mean generic price	-0.000695
	(0.000616)
Total prescription volume	1.37e-09**
	(6.17e-10)
Observations	127
Pseudo R2	0.241

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 listed in the table; average marginal effects are reported. 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 3: Impact of Predicted Exclusion Risk on New Drug Development

VARIABLES	(1) New Development	(2) New Development	(3) Log(1+New Dev.)	(4) Log(1+New Dev.)
Post X Pr(Exclusion)	-24.04***	-21.99***	-0.382***	-0.333***
	(5.898)	(6.575)	(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

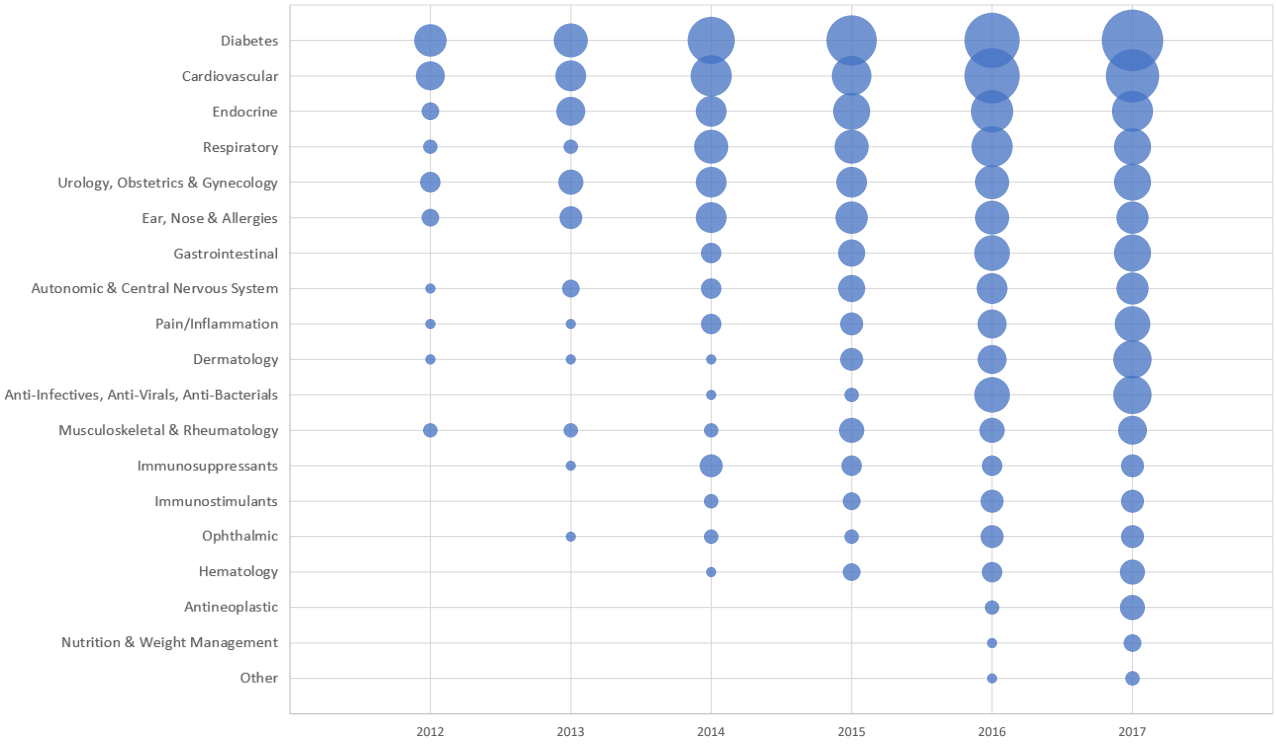
Notes: This table reports results from estimation of equation (2); each column reports a different regression specification. The unit of observation is an ATC4 drug class × year. The outcome variable "New Development" is the annual count of new development activity (across all stages). The treatment 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 Table 2.) 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: *** $p<0.01$, ** $p<0.05$, * $p<0.1$.

Online Appendix

Insurance Design and Pharmaceutical Innovation

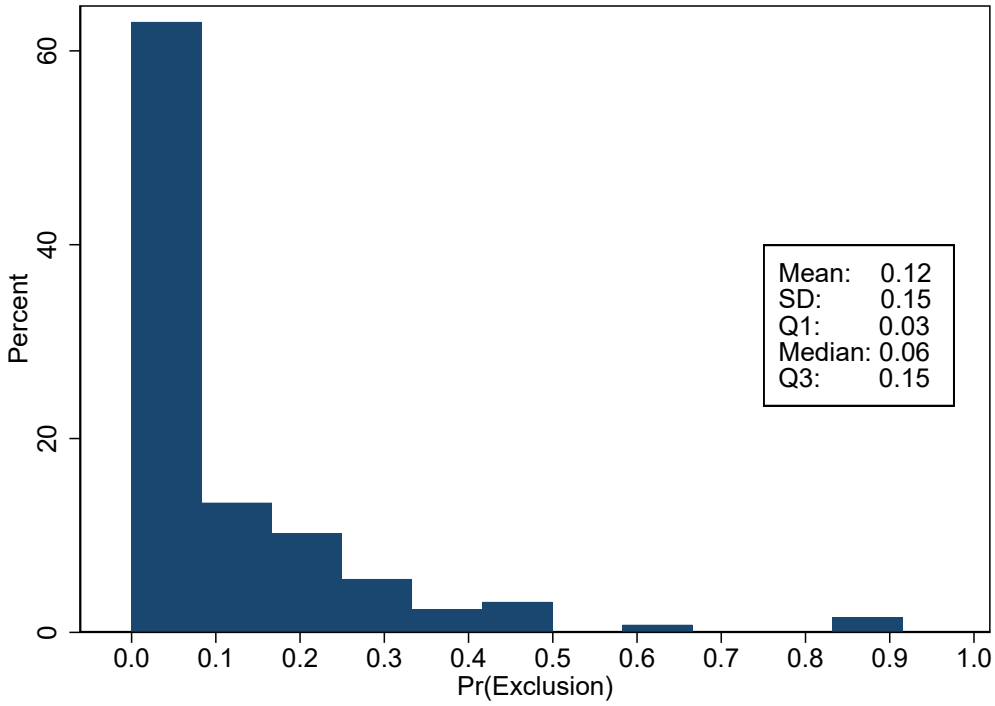
Leila Agha, Soomi Kim, Danielle Li

Figure A.1: Number of Excluded Drugs by Disease Categories



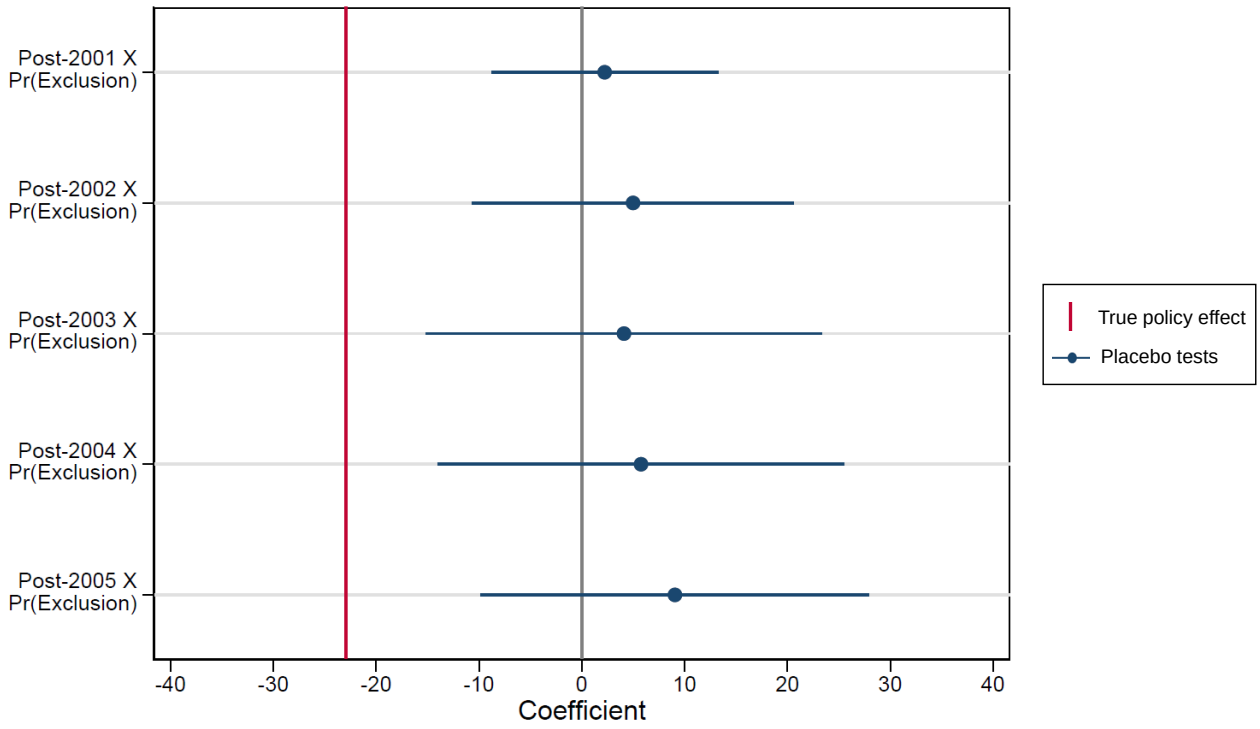
Notes: Each bubble represents a disease category in a year, and the size of the bubble reflects the number of drugs that were excluded by CVS, Express Scripts, or OptumRx in that disease category. There were a total of 300 drugs that were ever excluded from 2012-2017 by at least one of the three PBMs. Of these 300 excluded drugs, we were able to match 260 of them to the First Data Bank data, from which we obtained the ATC4 data and 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 and summarized by The Doctor-Patient Rights Project (2017).

FIGURE A.2: DISTRIBUTION OF PREDICTED EXCLUSION RISK



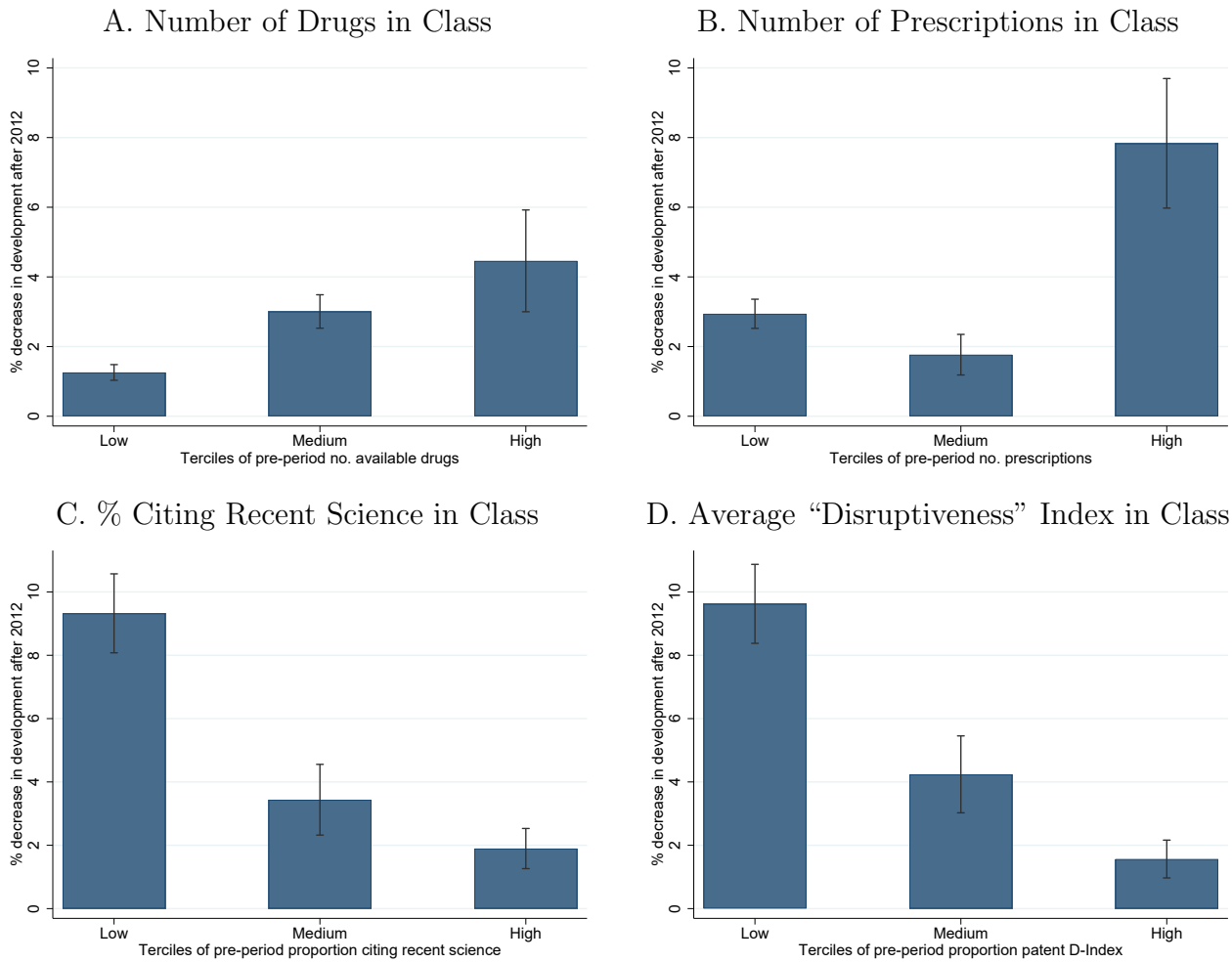
NOTES: This histogram plots the distribution of predicted exclusion risk of the 127 ATC4s in our main analyses. Summary statistics are also provided. See notes to Table 2 for details on how the exclusion risk was calculated.

Figure A.3: Placebo Test: Impact of Predicted Exclusion Risk on New Drug Development



Notes: For a more detailed discussion of this placebo analysis, see Appendix B. This coefficient plot shows the "placebo tests" of the results reported in Column 2 of Table 3. 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 2. This true policy estimate of -22.96 is statistically significant and parallels the specification in Column 2 of Table 3, but the only difference is that when constructing the exclusion risk, we dropped the price variables due to missing historical price data covering the placebo policy periods. The blue coefficients report the "placebo tests" coefficients and 95% confidence intervals, paralleling results reported in Column 2 of Table 3. First, as in the exclusion risk used in Table 3, the model to predict exclusion risk was constructed by using 2011 market characteristics to predict exclusions by 2013, but now 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 3. For instance, for the 2002 placebo policy, the pre-period was 1997-2001, the post-period was 2002-2007, and we used 2001 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.

FIGURE A.4: COUNTERFACTUAL DEVELOPMENT ACTIVITY BY PRE-PERIOD ATTRIBUTES OF DRUG CLASS: EXISTING THERAPIES, PRESCRIPTIONS, AND SCIENTIFIC NOVELTY



NOTES: This figure displays the percent decrease in annual development attributable to exclusions. Predictions are based on our estimation of equation (2), matching the specification reported in Table 3 Column 2. To measure predicted new drug candidates in the presence of exclusions, we calculate the fitted value 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. The figure shows the percent difference between predictions at the ATC4 $\times$ 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. In Panels C and D, 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 C groups drug classes by the share of pre-period patents in a drug class citing recent science as of 2011 (recent is defined as publications since 2006). Panel D 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 A.1: Examples of ATC4 Codes Defining Drug Markets

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: Prescription Volume

A. Summary Statistics, Part D Claims per Drug

	Mean	Std. Dev.	Median	Count
Claims for non-excluded drugs	178,503	932,026	3,841	3,046
Claims for excluded drugs	477,332	1,220,225	52,929	791
Market share, non-excluded drugs	0.225	0.328	0.042	3,046
Market share, excluded drugs	0.116	0.213	0.029	791

B. Impact of Exclusions on Prescription Volume

	(1)	(2)
VARIABLES	Log(Market Share)	Log(Market Share)
Number of Excluding PBMs	-0.206**	-0.293***
	(0.0823)	(0.0756)
Observations	3,699	3,475
Drug FE	YES	YES
Cohort X Year FE	YES	YES
Market Controls	NO	YES

Notes: For a more detailed discussion of this analysis, see Appendix A. Panel A 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 table compares drugs that were ever excluded to those that were never excluded during the sample period. Panel B estimates the impact of PBM formulary exclusion on the volume of Medicare Part D insurance claims. The unit of observation is a drug $\times$ year. The outcome variable is the annual market share of the index drug relative to all other drugs in the ATC4 class, described in Panel A. The key independent variable of interest is the number of PBMs excluding the drug that year. All regressions include drug fixed effects and drug age $\times$ calendar year fixed effects. (Drug age is measured as number of years elapsed since market entry.) Specification (2) includes additional controls for ATC4 class $\times$ calendar year fixed effects to account for trends in demand for different drug classes. 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 A.3: Early Exclusion Risk and Later Exclusions

VARIABLES	(1) Late Exclusion	(2) Late Exclusion
Standardized exclusion risk	0.189***	0.134**
	(0.0468)	(0.0543)
Observations	127	112
Sample	All ATC4s	ATC4s without early exclusions
Fraction with Late Exclusions	0.39	0.31

Notes: Using a logit regression, we investigate 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 3; 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, dividing by its standard deviation. 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. Average marginal effects are reported. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.

Table A.4: Impact of Predicted Exclusion Risk on New Drug Development By Stages

VARIABLES	(1) All	(2) Preclinical	(3) Phase 1	(4) Phase 2	(5) Phase 3	(6) Launch
Post X Pr(Exclusion)	-21.99***	-11.05***	-6.010***	-3.831***	-1.100**	0.220
	(6.575)	(3.405)	(2.078)	(1.350)	(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: See notes to Table 3. Each column reports a regression with a different outcome variable. Column 1 replicates the result reported in Table 3 Column 2 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.

Table A.5: Impact of Predicted Exclusion Risk on New Drug Development: Wild Cluster Bootstrap

VARIABLES	(1) New Development	(2) Log(1+New Dev.)
Post X Pr(Exclusion)	-21.99***	-0.333**
	[-37.79, -5.854]	[-.5375, -.03391]
Observations	1,397	1,397
Year FE	YES	YES
ATC FE	YES	YES
Market Controls	YES	YES

Notes: Columns 1 and 2 of this table repeat the specifications reported in Table 3 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. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1.

Table A.6: Impact of Predicted Exclusion Risk on New Drug Development: Alternative Functional Forms

VARIABLES	(1) IHS New Dev	(2) IHS New Dev	(3) Poisson New Dev	(4) Poisson New Dev
Post X Pr(Exclusion)	-0.368***	-0.317**	-0.524***	-0.455***
	(0.123)	(0.131)	(0.0834)	(0.0999)
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 results in Table 3, but with alternative functional forms. Columns 1-2 report regressions using the inverse hyperbolic sine transformation of development activity as the outcome, while Columns 3-4 report results using Poisson regressions. Standard errors are clustered at the ATC4 level for the regressions with inverse hyperbolic sine transformation, and robust standard errors are reported for the Poisson regressions. 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

	Direct Linking Approach		*Indirect Linking Approach*	
	(1)	(2)	(3)	(4)
VARIABLES	New Development	New Development	New Development	New Development
Post X Pr(Exclusion)	-20.98***	-18.60***	-4.308***	-4.460***
	(6.053)	(6.749)	(1.331)	(1.474)
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: For a more detailed discussion of ATC4 linking, see Appendix C. These results parallel the specification underlying Table 3, 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 Columns 1-2, we only count track development activity among the subset of drug candidates for which Cortellis directly reports the drug class. In Columns 3-4, we impute ATC4s from ICD9 codes for all drug candidates, rather than relying on Cortellis' reporting of drug class. 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 EXCLUSION RISK ON NEW DRUG DEVELOPMENT: ALTERNATIVE DEFINITIONS OF EXCLUSION RISK

	Predicted Count Exclusion		*Predicted Share Exclusion*		*Realized Exclusion*	
	(1)	(2)	(3)	(4)	(5)	(6)
VARIABLES	New Dev.	New Dev.	New Dev.	New Dev.	New Dev.	New Dev.
Post X Exclusion Risk	-7.867***	-7.136**	-59.12*	-56.76*	-5.824**	-4.534**
	(2.578)	(2.748)	(33.77)	(31.22)	(2.568)	(2.290)
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	NO	YES	NO	YES	NO	YES

NOTES: For a more detailed discussion of alternative measures of exclusion risk, see Appendix D. This table reports results from estimating a modified version of Equation (2), applying alternative definitions of exclusion risk. Instead of defining exclusion risk as whether an ATC4 class is predicted to have at least one drug with an exclusion as in Table 3, the exclusion risk here is defined as how many drugs are predicted to be excluded in an ATC4 class in Columns 1-2 and what share of drugs are predicted to be excluded in an ATC4 class in Columns 3-4. In Columns 5-6, rather than using continuous measures of predicted exclusion risk as our measure of treatment, we use a binary definition of treatment by looking at realized exclusions: whether at least one drug in an ATC4 class was actually on a PBM exclusion list. For further details on the regression specifications, see notes to Table 3. Standard errors are clustered at the ATC4 level. Statistical significance is indicated as: *** $p<0.01$, ** $p<0.05$, * $p<0.1$.

Table A.9: Impact of Predicted Exclusion Risk on New Drug Development: Incorporating Coupon Data

A. Predicting Exclusion Risk with Coupon Data

VARIABLES	(1) Exclusion
ATC4 class with copay coupons	0.153***
	(0.0495)
Log(1 + N of generic NDCs)	-0.0412*
	(0.0246)
Log(1 + N of brand NDCs)	0.0304
	(0.0383)
Log(1 + N of ATC7s)	0.0519
	(0.0471)
Mean brand price - mean generic price	-0.000580
	(0.000553)
Total prescription volume	1.03e-09*
	(5.94e-10)
Observations	127

B. Impact of Predicted Exclusion Risk on New Drug Development

VARIABLES	(1) New Development	(2) New Development	(3) Log(1+New Dev.)	(4) Log(1+New Dev.)
Post X Pr(Exclusion)	-18.18***	-16.59***	-0.404***	-0.383***
	(4.093)	(3.992)	(0.102)	(0.112)
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: For more details on the measurement of copay coupons see Appendix D. Panel A parallels Table 2 and Panel B parallels Table 3, but now with a measure of drug copay coupons as an additional predictor of exclusion risk. Statistical significance is indicated as: *** p<0.01, ** p<0.05, * p<0.1. .

A Impact of Exclusions on Drug Utilization in Medicare Part D

As discussed in Section 3.1, a PBM's formulary choices (coverage and prices) have been shown to have an impact on patients' drug use. To test whether these patterns hold in our setting, we investigate the link between PBM formulary exclusions and drug sales. Because sales volume is not measured by FDB, we turn to publicly available data on annual Medicare Part D claims volume by drug.[1] 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 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.

We estimate the following regression equation:

$$\text{Log(Claims)}_{dt} = \beta_1 \text{Excluded}_{dt} + \mathbf{X}_{dt} + \delta_d + \delta_t + \epsilon_{dt} \tag{3}$$

Here, Claims_{dt} refers to the fraction of Medicare Part D claims made on drug d in year t, relative to all other drugs in the ATC4 class (i.e., the drug d's market share 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 market share. 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 $\times$ calendar year fixed effects to capture time trends and drug lifecycle patterns.

Our sample consists of branded drugs that were on the market prior to the introduction of exclusions, had no generic substitutes, and 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

[1] This data is published annually by the Centers for Medicare & Medicaid Services (2018). 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.

protected class.[2] Further note that in some cases different formulations or packaging of the same drug are listed with separate drug names on formulary exclusion lists, but are reported as a single drug in the Medicare Part D data; we use the more aggregate definition of a drug for this analysis in keeping with the unit of observation in Part D.

In Appendix Table A.2, we show that each excluding PBM decreases a drug's market share by 25% ($e^{-0.293} - 1$), 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. 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).

[2]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.

B Placebo Policy Analysis

We conduct a series of placebo tests of the introduction of closed formularies. 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 reported in Table 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. These are drug classes that, at a given point in time, have a relatively large number of treatment 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. 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 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.

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 3, except that we drop price when constructing the exclusion risk due to missing historical price data covering the placebo policy periods.[3] 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 2. 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

[3]The true estimated policy effect of -22.96 is statistically significant and very similar to the estimate of -21.99 reported in Table 3.

period from 1997-2007. We end the placebo tests with the 2006 placebo policy change, because its 5-year post-period ends in 2011, the last year of our true policy pre-period.

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 -22.96, the placebo estimates range from 2.2 to 9.1, and none are statistically significant.

C 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.[4] Since this results in a drug being matched (indirectly via ICD9) to many ATC4s, we assigned the likelihood of an ATC4 matching to a drug based on the probabilistic match scores from Filzmoser et al. (2009), such that the assigned weights sum to 1 for each drug.

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

[4]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.

D Alternative Measures of Exposure to Exclusion Risk

Our analysis is based on differentiating drug classes at varying risk of formulary exclusion. In our primary analysis, we use 2011 ATC4 market level characteristics to predict exclusion risk, defined as whether an ATC4 class is predicted to have at least one drug with an exclusion by 2013. In this section, we describe several alternative approaches.

Alternative functional forms

Appendix Table A.8 tests alternative functional forms for predicting exclusion risk. Columns 1-2 use 2011 ATC4 market characteristics to predict the *count* of excluded drugs in a class by 2013, while columns 3-4 use 2011 ATC4 market characteristics to predict the *share* of excluded drugs in a class by 2013. Like our main measure of exclusion risk, both of these alternatives provide continuous measures of predicted exclusion risk, and thus have the benefit of capturing variation in the *threat* of exclusions—in drug classes that are similar to the initially targeted set but that did not experience early exclusions. Columns 5-6 present results using a binary definition of *realized* exclusions (whether at least one drug in an ATC4 class was on a PBM exclusion list by 2013) and show a similar pattern of results as our main analysis. All of these approaches find that new drug development is declining in exclusion risk. Scaling each of the coefficients in Appendix Table A.8 by the standard deviation of the relevant exclusion risk measure, we predict a similar magnitude reduction in drug development in each specification: 2.7 (column 2), 1.7 (column 4), and 1.5 (column 6).

Copay coupons

Contemporaneous industry reports describe drugs with copay coupons as a major target of PBM formulary exclusions (Foulkes 2015). This motivates an additional analysis using copay coupons as a predictor of exclusion risk. We use copay data from Van Nuys et al. (2018), which are available in the year 2014 and for the top 200 drugs (by sales volume). Because this coupon data comes from the post-period, after the introduction of PBMs' closed formularies, we do not include it in our baseline measure of exclusion risk. We incorporate copay coupons into our prediction of exclusion risk as an additional robustness check. As

reported in the logit regression in Panel A of Appendix Table A.9, drug classes targeted with copay coupons have a large and statistically significant increase in exclusion risk, even after conditioning on the other measured market characteristics. Using this augmented measure of exclusion risk, we repeat our analysis testing how exclusion risk predicts changes in development activity after 2012. Results reported in Panel B of Appendix Table A.9 continue to find that drug classes at higher risk of exclusion experience a relative reduction in exclusion risk after 2012; a one standard deviation increase in exclusion risk predicts 3.0 fewer promoted drugs per ATC4 class-year.

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