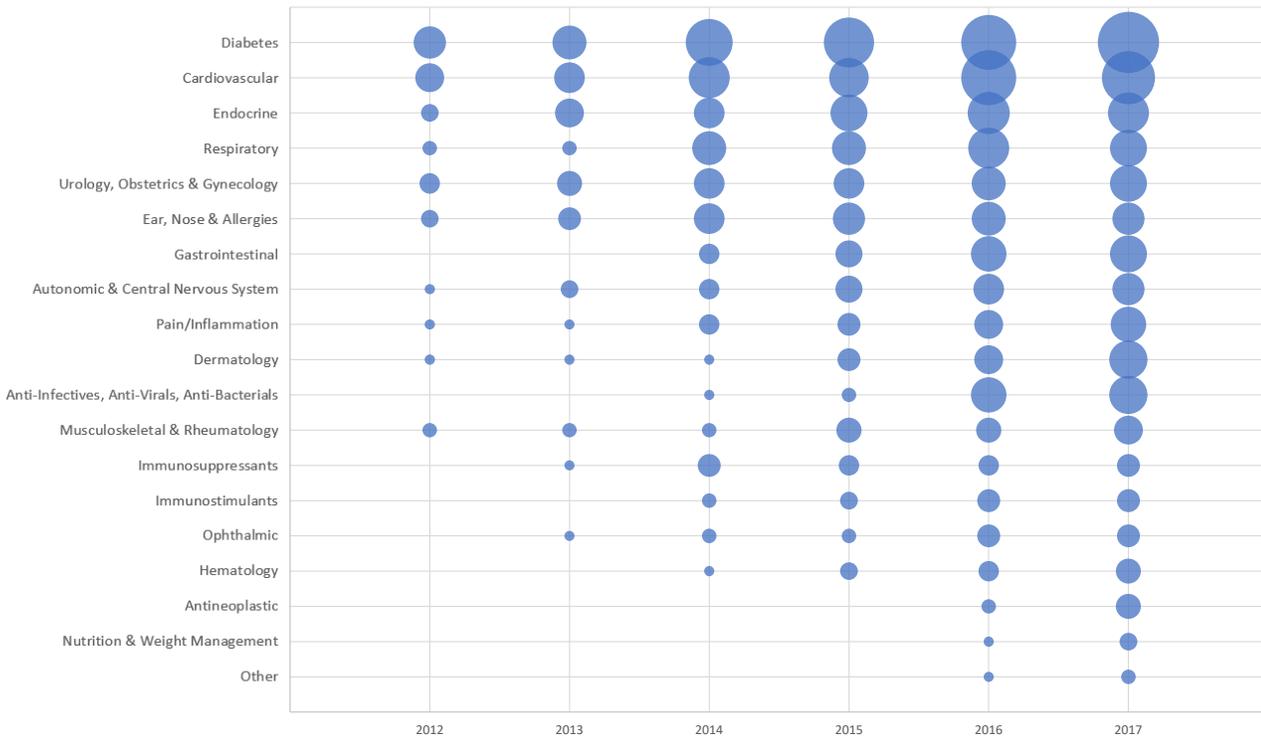


Online Appendix

Insurance Design and Pharmaceutical Innovation

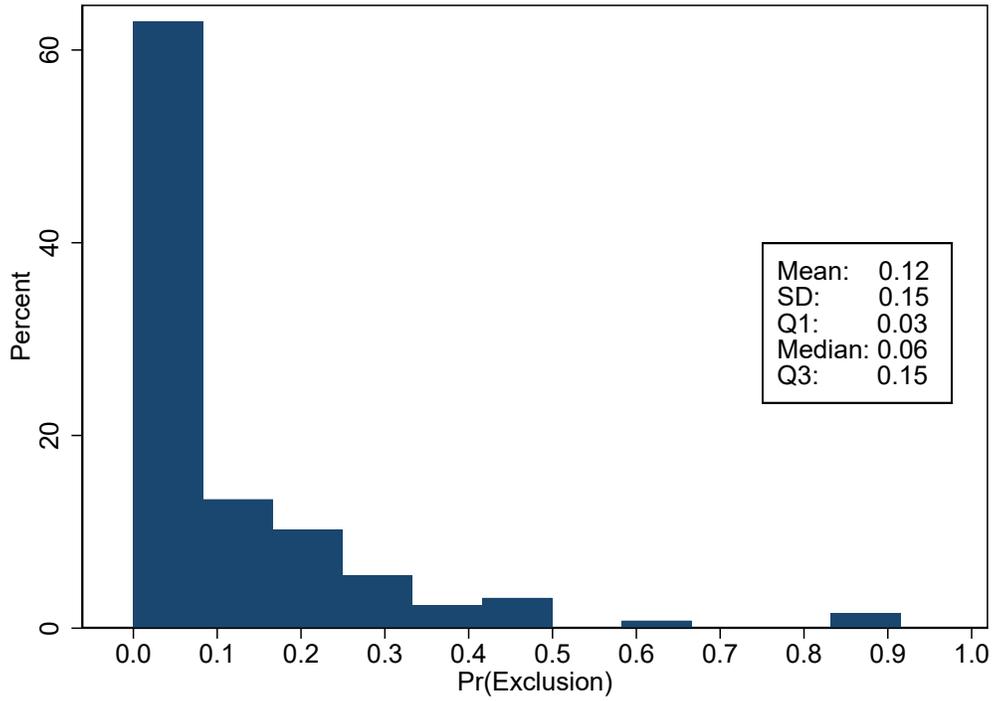
Leila Agha, Soomi Kim, Danielle Li

FIGURE A.1: NUMBER OF EXCLUDED DRUGS BY DISEASE CATEGORIES



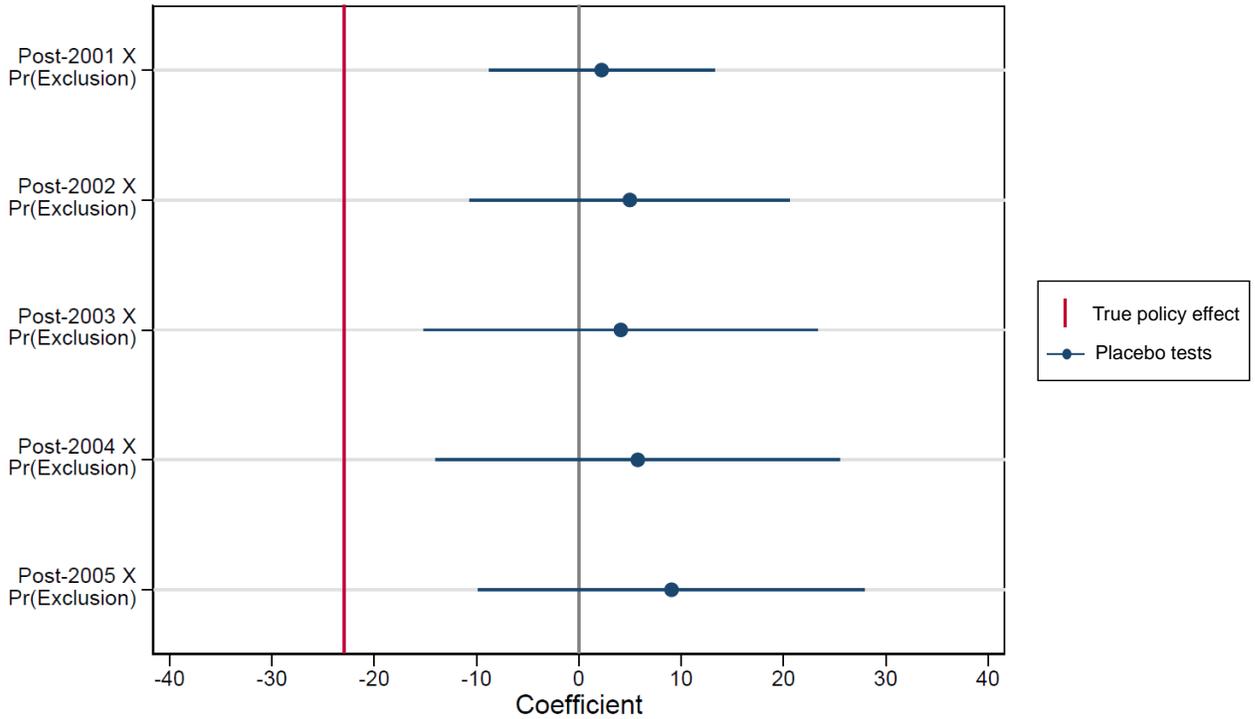
NOTES: Each bubble represents a disease category in a year, and the size of the bubble reflects the number of drugs that were excluded by CVS, Express Scripts, or OptumRx in that disease category. There were a total of 300 drugs that were ever excluded from 2012-2017 by at least one of the three PBMs. 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



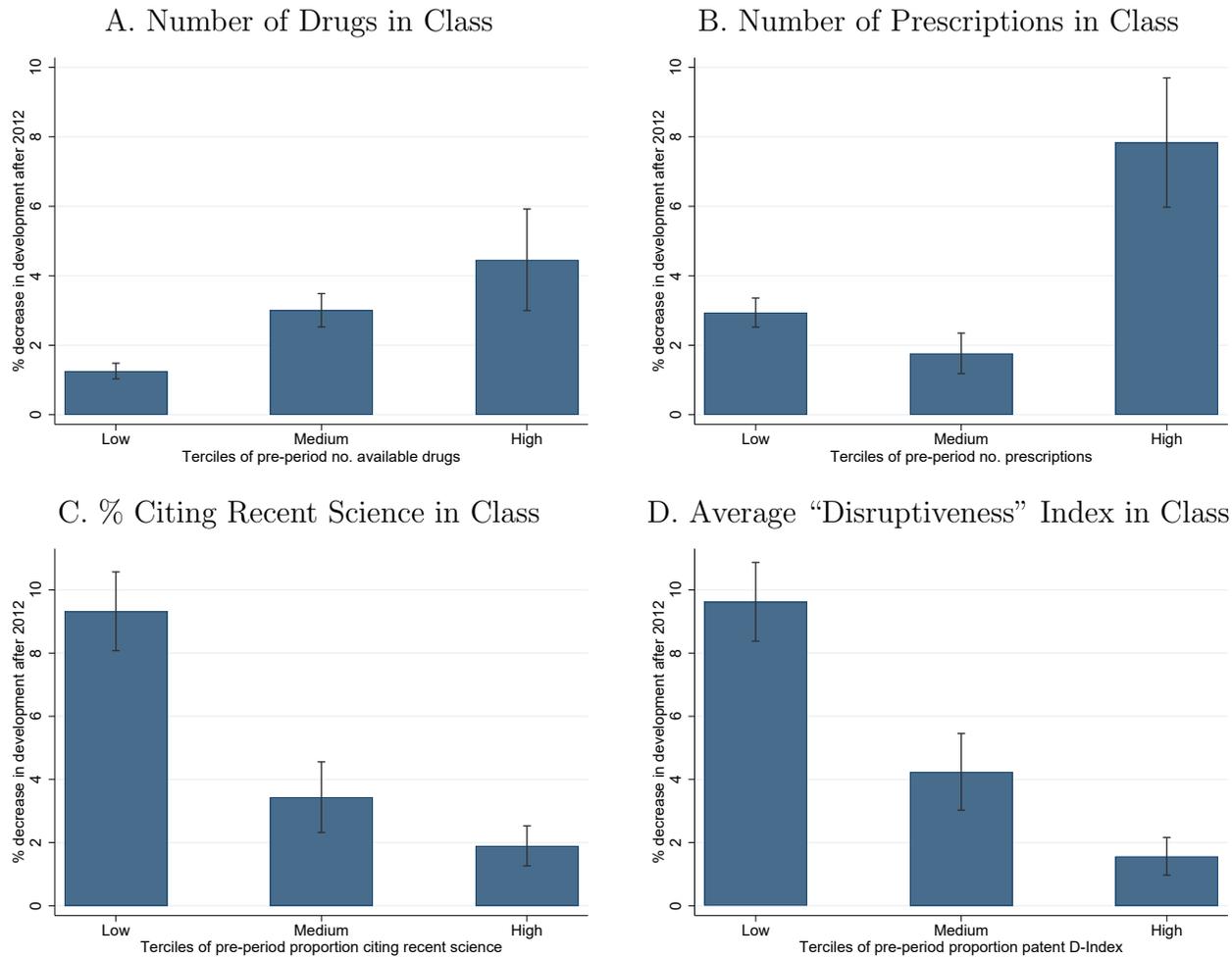
NOTES: This histogram plots the distribution of predicted exclusion risk of the 127 ATC4s in our main analyses. Summary statistics are also provided. See notes to Table ?? for details on how the exclusion risk was calculated.

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 ???. 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 ???. This true policy estimate of -22.96 is statistically significant and parallels the specification in Column 2 of Table ???, 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 ???. First, as in the exclusion risk used in Table ??, 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 ???. 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 (??), matching the specification reported in Table ?? 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 $\text{ATC4} \times \text{year}$ 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

VARIABLES	(1) Log(Market Share)	(2) Log(Market Share)
Number of Excluding PBMs	-0.206** (0.0823)	-0.293*** (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*** (0.0468)	0.134** (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 ??; 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*** (6.575)	-11.05*** (3.405)	-6.010*** (2.078)	-3.831*** (1.350)	-1.100** (0.422)	0.220 (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 ???. Each column reports a regression with a different outcome variable. Column 1 replicates the result reported in Table ?? 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*** [-37.79, -5.854]	-0.333** [-.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 ?? 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*** (0.123)	-0.317** (0.131)	-0.524*** (0.0834)	-0.455*** (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 ??, 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

VARIABLES	<i>Direct Linking Approach</i>		<i>Indirect Linking Approach</i>	
	(1) New Development	(2) New Development	(3) New Development	(4) New Development
Post X Pr(Exclusion)	-20.98*** (6.053)	-18.60*** (6.749)	-4.308*** (1.331)	-4.460*** (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 ??, 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

VARIABLES	<i>Predicted Count Exclusion</i>	<i>Predicted Share Exclusion</i>	<i>Realized Exclusion</i>			
	(1) New Dev.	(2) New Dev.	(3) New Dev.	(4) New Dev.	(5) New Dev.	(6) New Dev.
Post X Exclusion Risk	-7.867*** (2.578)	-7.136** (2.748)	-59.12* (33.77)	-56.76* (31.22)	-5.824** (2.568)	-4.534** (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 (??), 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 ??, 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 ??. 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*** (4.093)	-16.59*** (3.992)	-0.404*** (0.102)	-0.383*** (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 ?? and Panel B parallels Table ??, 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 ??, 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:

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

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 protected class.² Further note that in some cases different formulations or packaging of the

¹This 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.

²The protected classes are antidepressants, antipsychotics, anticonvulsants, antineoplastic agents, antiretroviral agents, and immunosuppressants. Of the 181 excluded drugs prescribed in Part D, only 20 fall into these classes.

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).

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 ?? 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 ??, 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 ?. 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. 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.

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

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.

⁴Filzmoser 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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