

Predictors of Orphan Drug Coverage Restrictions in Medicare Part D

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The growing number of very expensive orphan drugs entering the market and the pressure to contain drug spending have raised insurers' concern about orphan drug costs.¹⁻³ Multiple authors argue that insurers' concern about orphan costs is not warranted and their restrictions on benefit design are unjustified.¹⁻³ This is because, unlike other high-priced drugs, orphan drugs are meant to treat diseases that are far less common and, theoretically, pose a smaller budgetary impact on insurers.¹ Whereas specialty drugs accounted for 29% of total drug expenditure among commercial plans in 2013, orphan drugs made up only 9%.¹ However, orphan drugs are often treated with the same level of scrutiny as high-priced specialty drugs. Although they are commonly included on plan formularies, orphan drugs are typically subjected to the most restrictive forms of utilization controls and the highest cost-sharing tiers.^{4,5} It is unclear what factors health plans take into consideration in their orphan drug benefit design: Do they consider the scarcity of choice for patients with rare diseases or the price elasticity of demand among orphan drug users?

In total, rare diseases affect between 25 million and 30 million Americans. Only 5% of the approximately 7000 rare diseases have available treatments, the most common treatment modality being drugs.⁴ As of 2016, 449 orphan drugs were approved in the United States.⁶ Even when an orphan drug for a rare disease is available, the ease and affordability of accessing it present a further challenge for patients.⁷ In addition to the high price of orphan drugs, patients are confronted with utilization controls typically associated with orphan drugs.⁶ Examples are prior authorization (PA), quantity limits (QLs), and placement on the highest cost-sharing or "specialty" tiers of formularies.^{4,5,8} PA requires the enrollee to obtain the insurer's permission before a drug can be purchased. QLs limit how many prescriptions an enrollee can fill. Step therapy requires the enrollee to try the preferred (hypothetically most cost-effective) treatment option before purchasing a costlier one. Which tier the drug is placed on determines its coinsurance rate.⁹ Across commercial and Medicare plans, orphan drugs are typically placed in the specialty tier, where the patient pays up to 40% of the drug's full price. Because many orphan drugs cost

ABSTRACT

OBJECTIVES: It is unclear on what basis Medicare drug plans impose coverage restrictions on orphan drugs. This study aims to investigate the factors associated with utilization controls in Medicare fee-for-service Part D formularies.

STUDY DESIGN: Cross-sectional analysis.

METHODS: We used multivariate logistic regression to assess the association between orphan drug characteristics and use of formulary utilization controls in 2016. We controlled for number of beneficiaries per drug, exclusivity expiration, and the number of plans and beneficiaries per formulary. We conducted sensitivity analyses using fixed and random effects.

RESULTS: On average, 85% of orphan drugs on a formulary were placed on its highest cost-sharing tier and 76% were subject to prior authorization (PA). Orphan drugs with annual costs of \$50,000 or more had twice the odds of having PA requirements compared with less expensive ones. Relative to orphan drugs with a single indication, drugs with multiple indications were more likely to have restrictions. Less effective drugs had 1.5 times the odds of highest tier placement relative to more effective drugs. The presence of black box warnings and patient assistance programs were associated with more restricted access. Orphan drugs with generics were less likely to undergo restrictions than those without generics (all $P < .05$).

CONCLUSIONS: Plans are making evidence-based decisions by rewarding more clinically effective and safer orphan drugs. They are penalizing drugs with multiple indications. Surprisingly, plans place fewer restrictions on orphan drugs that have a generic equivalent, which may further discourage generic entry into the orphan space, where competition is already sparse.

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TAKEAWAY POINTS

- ▶ Most orphan drugs covered in Medicare Part D are subject to utilization controls. Eighty-five percent are placed on the highest tier of a formulary, and 76% undergo prior authorization.
- ▶ Drug cost is not the only characteristic Medicare plans consider. They place more restrictions on orphan drugs with black box warnings and patient assistance programs than those without.
- ▶ They place fewer restrictions on orphan drugs that are more clinically effective, that have only a single indication, and that underwent expedited FDA review. They also favor orphan drugs with generic substitutes, likely due to negotiated rebates.

TABLE 1. Manually Collected Variables and Corresponding Data Sources

Variable	Data source
<ul style="list-style-type: none"> • Number of orphan indications • Exclusivity expiry • Black box warning • Expedited review • Number of years since first FDA approval 	<ul style="list-style-type: none"> • FDA Orphan Drug Database
Total number of indications	<ul style="list-style-type: none"> • FDA label repository (from Drugs@FDA) • Center for Biologic Evaluation and Research webpage
Therapeutic (ie, generic or branded generic equivalent)*	<ul style="list-style-type: none"> • Drugs@FDA • Purple Book
Patient assistance program	<ul style="list-style-type: none"> • Medicare.gov Patient Assistance Programs site
Efficacy	<ul style="list-style-type: none"> • Micromedex
Patent expiry (not included in analysis)	<ul style="list-style-type: none"> • Orange Book

*For therapeutic equivalent, we searched for presence of “therapeutic equivalent” for products in the Drugs@FDA database and for “biosimilarity or interchangeability evaluations” for biologics in the Purple Book.

more than \$100,000 per year, it is very likely that out-of-pocket expenditures for a patient taking an orphan drug will exceed \$40,000 per year.¹⁰

Previous work has found that the imposition of utilization controls varies widely across orphan drugs, from 6% for albendazole (Albenza) to 75% for tetrabenazine (Xenazine).⁴ It is unclear, however, what determines such variations. Clinical considerations have been ranked as the most important factor.² Others were expected cost, number of patients, availability of treatment options, and disease prevalence. The growing importance of patient assistance programs (PAPs) in facilitating access to orphan drugs has also been recognized.² Among commercial plans, previous studies found that lower cost, lower disease prevalence, a longer time since FDA approval, and a lack of substitutes predicted less restrictive coverage.^{11,12} Black box safety warnings have been found to be correlated with more restrictions on drugs in Medicare formularies.^{13,14}

We aimed to characterize the formulary restrictions on orphan drugs specifically in the Medicare Part D program. We assessed the association between orphan drug characteristics, as informed by earlier studies, and the odds of being subject to PA and highest tier placement on the formulary. The independent variables of interest are whether the drug had a generic equivalent; whether

the drug had a single orphan, multiple orphan, or multiple nonorphan indications; the drug's level of efficacy; the presence of a black box warning; whether the drug underwent expedited FDA review; the number of years since FDA approval; and the presence of a PAP for that drug.

METHODS

Using the FDA Orphan Drug Database, we identified 413 orphan drugs that had “designated and approved” indications with marketing approval dates between the beginning of 1982 and the end of 2015. To identify which orphan drugs were used by Medicare beneficiaries, orphan drugs were matched to the Medicare Part D Spending Dashboard of 2016 using brand name as a unique identifier. A total of 206 orphan drugs matched. The unmatched remainder (n = 207) were investigated by examining a 10% random sample of those drugs. The majority of orphan drugs not found in Medicare Part D had an intravenous route (71%) and would therefore most likely be covered under Medicare Part B instead of D. Three drugs (14%) were discontinued. Two drugs (10%) had no trade name, and 1 drug (5%) was indicated for a pediatric population use and would be uncommonly used by Medicare beneficiaries (eAppendix A

[eAppendices available at ajmc.com]).

Drug characteristics were extracted from the sources outlined in Table 1. Eight drugs were not found in Drugs@FDA; 1 was discontinued and therefore dropped from the sample, and 7 were biological products. The corresponding information of the 7 biologics was abstracted via the Center for Biologic Evaluation and Research website.

The identified orphan drugs (n = 205) were merged with Medicare formulary data using the Public Use Files of 2016. The final sample consisted of 193 orphan drugs represented by 390 National Drug Codes (NDCs). Average annual cost was extracted from the Medicare Part D Prescription Drug Event file of 2016.

The independent variables of interest were defined as follows:

1. Orphan drug type (categorical: “true-single,” “true-multiple,” “partial”): an orphan drug was categorized as “true” if it had only approved orphan indications on its FDA label and “partial” if it had additional nonorphan indications, following Divino et al.¹ The “true” category was further broken down into single indication and multiple indications. The last available label prior to 2016 was retrieved from Drugs@FDA and compared against the approved orphan indications stated in the FDA Orphan Drug

TABLE 2. Efficacy Classification in IBM Micromedex

Class	Rating	Description
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective.
Class IIa	Evidence favors efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

TABLE 3. Description of Medicare Prescription Drug Plan Formularies (n=65)

	Total (N=31,824 NDC-formulary combinations)	Mean (SD)	Range
Plans	988	15.4 (18.1)	1-79
Drug (trade name)	193	139.5 (14.4)	107-193
Drug (NDC)	390	271.4 (29.9)	209-387
Count of beneficiaries	19,091,750	298,308 (687,409)	0-3,474,203
Percentage of drugs per formulary in protected class (NDC)	146	42.5% (2.6%)	36.3%-47.5%
Percentage of drugs covered in all formularies (NDC)	-	34.4%	-

NDC, National Drug Code.

- Database. Off-label use was considered out of scope, and new uses over time were not taken into account because this was a cross-sectional study.
- Generic equivalent (binary): identifies whether the orphan drug has a generic (or branded generic) equivalent based on FDA reporting of “therapeutic equivalence” in the Drugs@FDA database.
 - Presence of foundation-funded PAP (binary): identifies whether there was a PAP listed for the orphan drug on the Medicare website¹⁵ at the time of data extraction. The website lists programs available by drug name, along with the sponsoring drug company or foundation name, eligibility criteria, and benefit assistance details. Information on drug name and sponsor name were extracted into an Excel sheet, and we differentiated between drug company and foundation programs. Medicare beneficiaries cannot qualify for PAPs funded by pharmaceutical manufacturers as per the Anti-Kickback Statute.¹⁶
 - Level of efficacy (categorical: “effective,” “evidence favors efficacy,” “evidence is inconclusive,” “ineffective”): extracted from IBM Micromedex, which is an evidence-based clinical resource to support informed treatment decisions that has been adopted by 5000 hospitals and health care institutions in 83 countries.¹⁷ Micromedex determines efficacy rating based on factors such as the size of the study, statistical power, end points, study design, confounders, and results. For drugs with multiple indications or efficacy ratings assigned to the same indication, the indication with the highest efficacy was considered. **Table 2** indicates the description of each efficacy category.
 - Black box warning (binary): identifies if a boxed safety warning appears on a drug’s FDA label to call attention to serious or life-threatening risks.¹⁸
 - Expedited review (binary): identifies whether the drug underwent a standard or an expedited FDA review mechanism such as fast track, breakthrough therapy, accelerated approval, or priority review.
 - Years since first FDA approval (continuous): identifies the number of years since initial approval of the drug in the United States.

The sample included the universe of FDA-approved orphan drugs in all 65 Medicare stand-alone formularies in 2016. The unit of analysis was the formulary-NDC combination. We used 2 logistic regression models to predict (1) a PA requirement compared with no PA requirement and (2) highest tier placement relative to lower tier placement. The 7 independent variables of interest listed previously were included.

In all models, expired exclusivity status of the drug, number of beneficiaries per drug, and number of plans and beneficiaries per formulary were included in the model as potential confounders, and standard errors were clustered by formulary. In predicting PA, we also controlled for average annual cost (categorical variable: “less than \$50,000,” “equal to or greater than \$50,000”). The original cost variable was recoded because logit transformed LOWESS plots between cost and PA revealed a distinctive cutoff point around the median of \$50,000 (**eAppendix B**).

We conducted 4 sensitivity analyses. We repeated the analysis using a mixed effects logistic regression to predict the odds of PA including a formulary random effect and, separately, a model that included a formulary fixed effect. We ran the fixed and random effects models with and without including formulary characteristics (number of plans and beneficiaries) as covariates and clustering the standard errors by formulary.

TABLE 4. Description of Utilization Controls

	Total (of 390)	Mean (SD) percentage	Range (%)
Percentage of drugs on the highest tier of corresponding formulary	313	84.4 (8.4)	28.2-89.6
Percentage of drugs per formulary with prior authorization	330	75.6 (10.8)	51.9-87.9
Percentage of drugs per formulary with quantity limits	241	32.6 (19.1)	0.0-74.0
Percentage of drugs per formulary with step therapy	31	0.34 (1.0)	0.0-6.5
Percentage of drugs per formulary with any of the above restrictions	355	91.8 (4.3)	68.8-96.3

^aExtreme numbers correspond to outlier formulary ID16522 used by contractor Meridian Health Plan of Michigan, Inc, covering only 2570 enrollees and used by only 1 plan, Advantage-Plus Meridian.

TABLE 5. Multivariate Logistic Regression Models Predicting Prior Authorization and Highest Tier^a

Dependent variable	Prior authorization		Highest tier	
	Odds ratio	95% CI	Odds ratio	95% CI
Observations	13,568		13,568	
Independent variables	Odds ratio	95% CI	Odds ratio	95% CI
Has generic equivalent: no (reference)				
Has generic equivalent: yes	0.286***	0.249-0.327	0.227***	0.182-0.285
Orphan type: 1, true with single indication (reference)				
Orphan type: 2, true with multiple indications	1.86***	1.69-2.03	4.61***	2.98-7.13
Orphan type: 3, partial	1.54***	1.29-1.84	1.01	0.828-1.24
Recoded efficacy: 1, effective (reference)				
Recoded efficacy: 2, evidence favors efficacy or evidence is inconclusive	0.991	0.915-1.07	1.53***	1.32-1.78
Black box warning: no (reference)				
Black box warning: yes	1.28***	1.14-1.45	0.983	0.856-1.13
Expedited approval: no (reference)				
Expedited approval: yes	0.835***	0.729-0.958	0.644***	0.550-0.753
Foundation-funded patient assistance program: no (reference)				
Foundation-funded patient assistance program: yes	1.21**	1.00-1.46	5.52***	4.41-6.91
Expired exclusivity: no (reference)				
Expired exclusivity: yes	0.904	0.772-1.060	0.699***	0.579-0.844
Years since first FDA approval	0.951***	0.946-0.956	0.938***	0.931-0.946
Average annual cost: 1, < \$50,000 (reference)				
Average annual cost: 2, ≥ \$50,000	1.70***	1.46-1.99	-	-
Number of beneficiaries per NDC	1.00***	1.00-1.00	1.00***	1.00-1.00
Number of plans per formulary	1.01	0.993-1.02	1.01**	1.00-1.02
Number of beneficiaries per formulary	1.00	1.00-1.00	1.00*	1.00-1.00
Constant	4.95***	3.84-6.38	10.70***	7.03-16.20

*P < .1; **P < .05; ***P < .01.

^aStandard errors are clustered by formulary.

RESULTS

A total of 193 orphan drugs were represented across all 65 Medicare stand-alone formularies (Table 3). There were 390 unique NDC codes for orphan drugs in the Medicare formularies. On average, a formulary included 271 (SD = 30) NDCs. On average, 43% of NDCs on a formulary belonged to a protected class (defined as any of Medicare’s 6 protected classes: antidepressants, antipsychotics, anticonvulsants, immunosuppressants for treatment of transplant rejection, antiretrovirals, and antineoplastics). Thirty-four percent of the orphan drugs were included in all formularies, and most of these were drugs for treating cancer.

Ninety-two percent of orphan drugs had some type of coverage restriction. On average, the highest tier on which orphan drugs were placed per formulary was tier 5 and the second highest was tier 4 (Table 4). Specifically, 84% were placed on the highest tier of the corresponding formulary, 76% had PA requirements, 33% had QLs, and only 0.34% had a step therapy requirement.

Of 390 drugs, 32% cost \$50,000 or more per year. The proportion with expired exclusivity was 49%, and the mean (SD) number of years since first US approval was 16.5 (11.3). Forty-four percent of the orphan drugs were “true” orphans having only a single indication, 21% were “true” orphans with multiple indications, and 35% were “partial” orphans. The majority (67%) of the orphan drugs had no generic (or branded generic) equivalent. Most (61%) orphan drugs were associated with a foundation-funded PAP. More than half of orphan drugs in the sample (59%) were classified as “effective”; approximately 40%, “evidence favors efficacy”; and fewer than 1%, “evidence is inconclusive.” Accordingly, the last 2 categories were combined as 1 in the regression analyses. Approximately 43% had a black box warning, and 56% underwent expedited review at the FDA.

Controlling for potential confounders, the presence of a generic equivalent was associated with lower odds of both having PA and highest tier placement (Table 5). Similarly, a greater number of years since FDA approval was associated with lower odds of PA and highest tier placement. Because the use of QLs and step therapy was infrequent in these formularies, we do not report on these outcomes. Compared

with true orphan drugs with a single indication, “true-multiple” orphans had significantly higher odds of having PA and highest tier placement; results for “partial” orphans were significant for PA. Orphan drugs classified as less effective were more likely to have highest tier placement compared with the most effective orphan drugs, and orphan drugs with black box warnings were more likely to have PA than those without. Expedited review was associated with lower odds of PA and highest tier placement. Orphan drugs with a PAP had higher odds of PA and highest tier placement than their counterparts without a PAP. Orphan drugs that cost \$50,000 per year or more had 1.704 times the odds of having PA than those that cost less than \$50,000 per year.

Four sensitivity analyses were run to predict the odds of any utilization control. Results remained robust with negligible differences in coefficients and CI values across the models ([eAppendix C](#)).

DISCUSSION

This study investigated the factors associated with insurance plans’ decisions to impose utilization controls on orphan drugs. Most orphan drugs covered in Medicare Part D undergo coverage restrictions. Eighty-five percent are placed on the highest tier of a formulary and 76% undergo PA. Only 34% were covered in all formularies, and 43% belonged to a protected class. This signals that orphan drugs without substitutes may not always be covered and patients needing those drugs may not find their prescribed medicines in their plan’s formulary.

Annual cost was a strong predictor of PA. The positive relationship between cost and restrictions is consistent with previous evidence.^{11,12} However, other factors also played a significant role in predicting the outcome.

Researchers and policy makers have had great concern lately around questionable practices that many consider “abuses” of the Orphan Drug Act, such as applying for numerous orphan indications to extend a product’s market exclusivity (also known as stacking of indications) and differentiating subgroups of patients, such as patients with breast cancer aged 40 to 50 years from those aged 50 to 60 years (also known as salami-slicing).¹⁹ In this study, plans appear to take into consideration the drug’s number of indications in their benefit design. Even after controlling for the number of beneficiaries per drug, a greater number of indications was associated with greater odds of restrictions. Orphan drugs with multiple orphan or nonorphan indications are significantly more likely to undergo PA compared with those with single indications. These results are consistent with recent analyses of specialty and orphan drug restrictions in commercial plans.^{11,12}

Orphan drugs with generics had lower odds of undergoing PA or highest tier placement than those without generics. This surprising finding suggests that the branded version may be preferred over the generic on Medicare Part D formularies, possibly because of higher expected rebates from the branded manufacturer. Alternatively, there might be less of a need for utilization management in

this setting given that orphan products with generics were less expensive than those without generics. This phenomenon is in line with the findings of a recent study showing that most (72%) Medicare formularies offered better tier placement to the branded over the generic product for at least 1 product across a wide pool of multisource drugs.²⁰ This is also consistent with the findings of another study that found that Medicare beneficiaries pay less out of pocket for branded than generic medications because of manufacturer discounts provided while in the Part D coverage gap.²¹ However, our result contradicts the findings of previous studies that found that the lack of substitutes was associated with fewer restrictions across commercial plans.^{11,12}

PAPs had a strong relationship with highest tier placement and a significant but smaller positive association with PA; this corresponds to the tendency of PAPs to focus on alleviating cost sharing rather than PA restrictions.

Plans seem to consider clinical value and safety in their orphan drug benefit design. Less effective drugs were significantly more likely to be placed on the highest tier, and orphan drugs with black box warnings were more likely to require PA. This is in line with the findings of a previous study in which participants ranked clinical considerations as the No. 1 factor affecting orphan drug benefit design² and Medicare analyses that showed a negative relationship between black box warnings and unrestricted orphan drug coverage.^{13,14}

Although previous research did not detect a significant relationship between expedited review and restrictions among commercial plans,¹² our results showed that, in Medicare, expedited review was correlated with significantly lower odds of PA and highest tier placement, possibly due to the necessity and urgency associated with an expedited approval pathway.

Limitations

This study has several limitations. Although the share of beneficiaries enrolled in Medicare Advantage (MA) plans is increasing over time, we restricted the sample to stand-alone plans because of the inherent differences in the incentive structure that MA and stand-alone plans face. MA plans are responsible for the downstream costs associated with drug adherence, such as hospitalization or emergency department visits, whereas stand-alone plans are not.⁹ Also, because this study was cross-sectional in nature, we do not claim causality, but we have enough evidence to highlight significant characteristics that could explain variability in coverage restrictions. Furthermore, data limitations did not allow us to investigate what criteria PA requirements entailed; some PA requirements could be more restrictive than others. A PA could simply require an attestation that the beneficiary has a particular diagnosis (ie, is only an administrative burden to the physician), or it could require patients to meet stringent clinical criteria, such as symptoms of particular severity and longevity. We have only considered the presence of a generic substitute, which could misrepresent the effect of generic availability on the outcome if other therapeutically interchangeable

products or alternative treatments for the orphan disease exist; however, this is unlikely because most orphan drugs do not have alternatives. We interpret the absence of an orphan drug from a stand-alone plan's formulary as a noncoverage decision, but it should be noted that the patient might still be able to access the drug either through a formulary exception or through Part B.

CONCLUSIONS

In this study, we set out to understand on what basis Medicare Part D plans place coverage restrictions on orphan drugs, such as PA and placement on the highest cost-sharing tier. Drug cost was not the only strong predictor of PA. Plans are making evidence-based decisions by rewarding more clinically effective drugs and those without black box warnings. They are penalizing orphan drugs with multiple indications and PAPS.

Surprisingly, plans place fewer restrictions on orphan drugs that have a generic equivalent. Incentivizing brand over generic use may further discourage generic entry into the orphan space, where competition is already sparse and prices are persistently high. Future research should attempt to identify which factors promote or block generic competition for orphan drugs. ■

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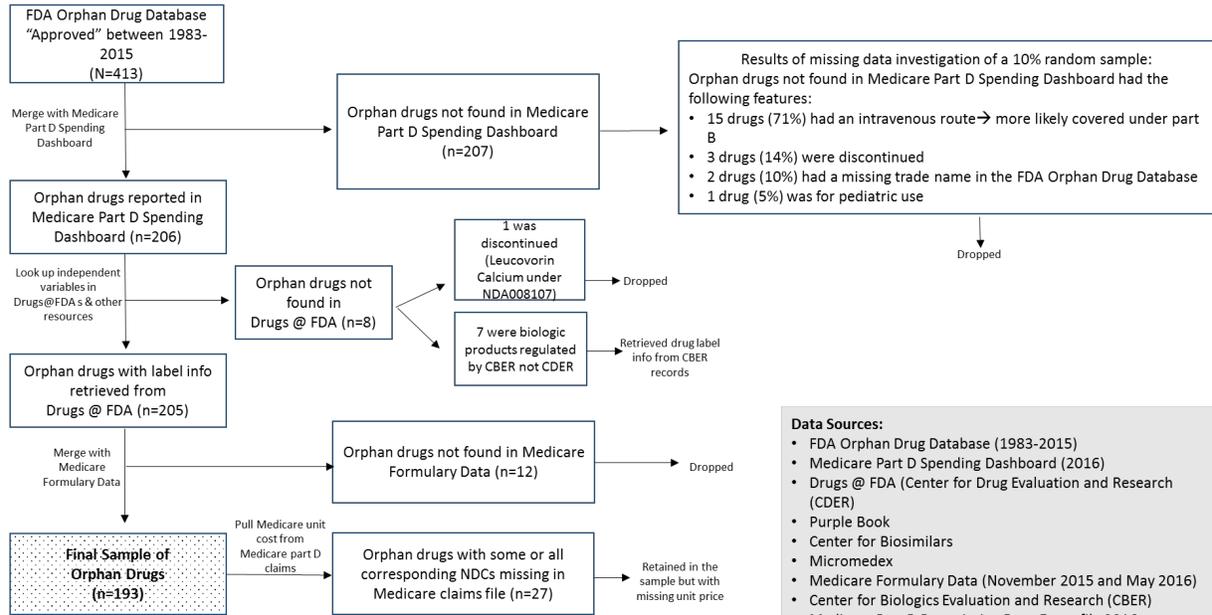
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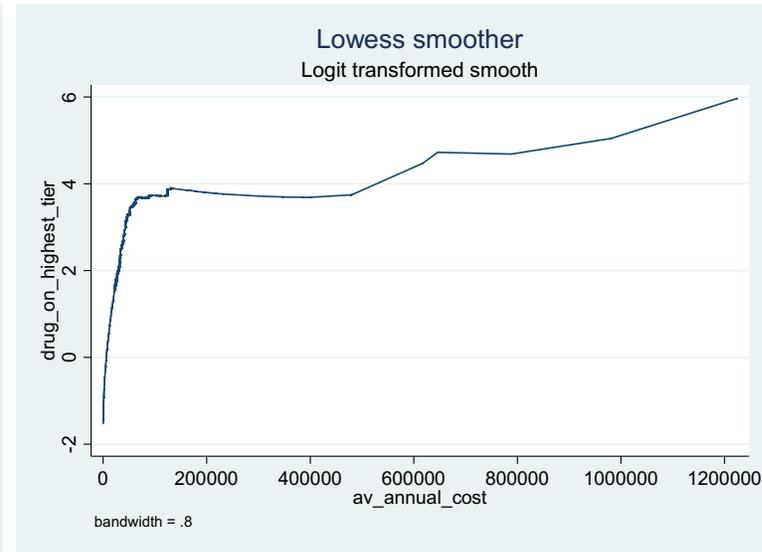
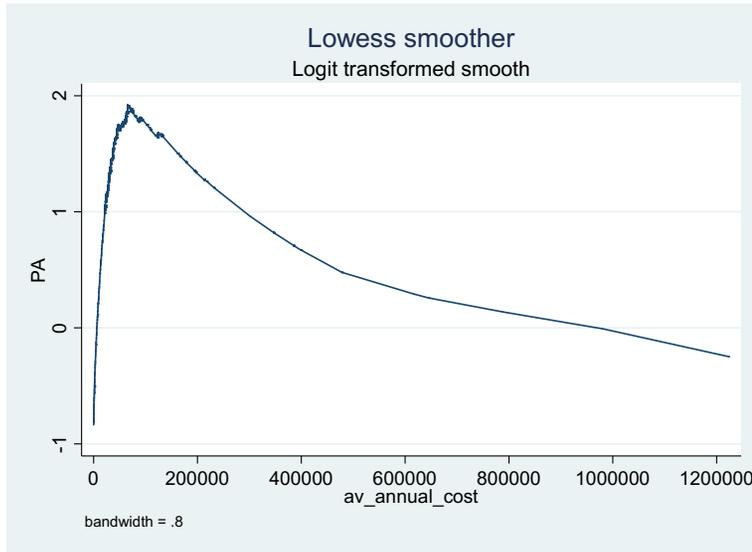
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eAppendix A. Data Preparation



eAppendix B. Logit Transformed Lowess Smoother for Prior Authorization and Highest Tier Placement vs. Average Annual Cost as a Continuous Variable



eAppendix C. Sensitivity Analysis Using Multivariate Logistic Regression Models Predicting Prior Authorization

Model	A	B	C	D	E
	Main model	Adding random effect for formulary	Model B without formulary characteristics	Adding fixed effect for formulary to main model	Model D without formulary characteristics
Observations	13,568	13,568	13,568	13,568	13,568
Number of groups	--	61	61	--	--
Independent variable	odds ratio	odds ratio	odds ratio	odds ratio	odds ratio
Has generic equivalent=No (Reference)					
Has generic equivalent=Yes	0.286*** (0.0197)	0.254*** (0.0130)	0.254*** (0.0130)	0.252*** (0.0185)	0.252*** (0.0129)
Orphan type=1 "True with single indication" (Reference)					
Orphan type=2 "True with multiple indications"	1.855*** (0.0875)	1.999*** (0.135)	1.998*** (0.135)	2.011*** (0.115)	2.011*** (0.136)
Orphan type=3 "Partial"	1.542*** (0.141)	1.645*** (0.115)	1.644*** (0.115)	1.654*** (0.176)	1.654*** (0.116)
Recoded efficacy=1 "Effective" (Reference)					
Recoded efficacy=2 "Evidence favors efficacy" or "Evidence is inconclusive"	0.991 (0.0400)	1.005 (0.0564)	1.005 (0.0564)	1.006 (0.0448)	1.006 (0.0566)
Blackbox warning=No (Reference)					
Blackbox warning=Yes	1.284*** (0.0803)	1.331*** (0.0688)	1.331*** (0.0688)	1.334*** (0.0883)	1.334*** (0.0692)
Expedited approval=No (Reference)					
Expedited approval=Yes	0.835*** (0.0582)	0.819*** (0.0411)	0.819*** (0.0411)	0.818*** (0.0629)	0.818*** (0.0411)
Foundation-funded Patient Assistance Program=No (Reference)					

Foundation-funded Patient Assistance Program=Yes	1.207**	1.203***	1.203***	1.203*	1.203***
	(0.116)	(0.0630)	(0.0630)	(0.128)	(0.0632)
Expired exclusivity=No (Reference)					
Expired exclusivity=Yes	0.904	0.917	0.916	0.918	0.918
	(0.0733)	(0.0518)	(0.0518)	(0.0789)	(0.0520)
Years since first FDA approval	0.951***	0.946***	0.946***	0.946***	0.946***
	(0.00271)	(0.00241)	(0.00241)	(0.00300)	(0.00242)
Average annual cost=1 "Less than \$50,000" (Reference)					
Average annual cost=2 "Equal to or greater than \$50,000"	1.704***	1.765***	1.765***	1.771***	1.771***
	(0.135)	(0.103)	(0.103)	(0.153)	(0.103)
Number of beneficiaries per NDC	1.000***	1.000***	1.000***	1.000***	1.000***
	(8.48e-06)	(8.02e-06)	(8.02e-06)	(9.09e-06)	(8.03e-06)
Number of plans per formulary	1.006	1.005	--	0.959***	--
	(0.00647)	(0.00647)		(0.00139)	
Number of beneficiaries per formulary	1.000	1.000	--	1.000***	--
	(1.35e-07)	(1.67e-07)		(7.80e-07)	
Constant	4.950***	5.902***	6.716***	6.005***	12.76***
	(0.641)	(0.830)	(0.829)	(0.655)	(2.856)
Variance		0.663***	0.691***		
		(0.0650)	(0.0673)		

*** p<0.01, ** p<0.05, * p<0.1

Standard errors are clustered by formulary. Fixed effects are not displayed in table.