Variation in US Private Health Plans' Coverage of Orphan Drugs

James D. Chambers, PhD; Ari D. Panzer, BS; David D. Kim, PhD; Nikoletta M. Margaretos, BA; and Peter J. Neumann, ScD

Orphan drugs (ie, drugs indicated for rare diseases) pose a singular challenge for health plans. Although they target small patient populations, their high costs, rising numbers, and strong backing by patient groups force plans to confront ever-more-delicate decisions about how to provide access, even in the face of sometimes highly uncertain evidence.[1,2] The challenge is intensifying: From 1997 to 2017, spending on orphan drugs grew from 4% to 10% of total prescription drug spending, with spending on orphan drugs totaling $43 billion in 2017.[3] An estimated 25 million to 30 million Americans live with an orphan disease.[4]

Eighty-seven percent of orphan drug spending is made up of specialty drugs, which are typically complex large-molecule drugs that require special administration, monitoring, and handling, although high-priced small-molecule drugs are also often considered specialty drugs.[3] Specialty drugs are also used to treat a range of nonorphan conditions, including rheumatoid arthritis, hepatitis C, Crohn disease, and multiple sclerosis.

Research has demonstrated that health plans sometimes restrict patient access to orphan drugs. Results of one study found that private plans apply restrictions in roughly a quarter of orphan drug coverage decisions.[5] Another study reported that Medicare and private plans often place orphan drugs on the highest co-payment tier of their formularies.[6]

However, the circumstances under which plans restrict access to orphan drugs have not been reported. It is unclear, for example, whether plans are more likely to restrict orphan drugs with larger budget impacts. Knowledge of these circumstances would help patients, providers, and policy makers better understand the coverage decisions affecting access. We analyzed a database of private health plan coverage decisions to (1) compare coverage of orphan and nonorphan drugs, (2) examine variation in orphan drug coverage across the largest US private plans, and (3) evaluate factors influencing orphan drug coverage decision making.

ABSTRACT

OBJECTIVES: To compare coverage of orphan and nonorphan drugs, to examine variation in orphan drug coverage across the largest US private plans, and to evaluate factors influencing coverage decisions.

STUDY DESIGN: Database and regression analyses.

METHODS: We analyzed a data set of private health plan coverage decisions for specialty drugs (N = 5000) in 3 ways. First, we compared the frequency with which plans applied restrictions in their decisions for orphan and nonorphan drugs. Second, we examined variation in the frequency with which 17 of the largest 20 private plans applied coverage restrictions for orphan drugs. Third, we used multivariate regression to examine factors associated with restricted orphan drug coverage.

RESULTS: Health plans are less likely to restrict orphan drugs compared with nonorphan drugs. Of orphan drug decisions (n = 2168), plans did not apply coverage restrictions in 70% of cases, applied restrictions in 29%, and did not cover in 1%. In contrast, of nonorphan drug decisions (n = 2832), plans did not apply coverage restrictions in 53% of cases, applied restrictions in 41%, and did not cover in 6%. The frequency of restrictions for orphan drugs varied from 11% to 65% across plans. The attributes of orphan drugs that were more likely to be associated with restrictions than others included drugs for noncancer diseases, drugs with alternatives, self-administered drugs, drugs indicated for diseases with a higher prevalence, and drugs with higher annual costs (all *P* <.05).

CONCLUSIONS: Health plans restrict access to orphan drugs approximately one-third of the time, and restrictions vary considerably across plans. Plans more often add restrictions for orphan drugs that are indicated for diseases with a higher prevalence and that have higher annual costs.

METHODS

Data

We identified orphan drug coverage decisions using the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) database. SPEC includes publicly available specialty drug coverage decisions issued by 17 of the 20 largest US private health plans. SPEC includes coverage decisions relevant to the included plans' commercial lines of business. Of the 3 largest plans excluded from SPEC, 1 does not make its coverage decisions publicly available and 2 focus exclusively on Medicare or Medicaid populations.

SPEC includes information on health plans' specialty drug coverage decisions and the supporting evidence that they cite. SPEC details drug-level information, including the number of years since a drug's FDA approval and whether a drug is indicated for a pediatric population. Roughly half (51%) of drugs in SPEC are physician-administered and covered through the plans' medical benefit. The remaining drugs are self-administered drugs, which plans cover through their pharmacy benefit.

We define a coverage restriction as a health plan decision to reduce the size of the eligible patient population compared with the population described in the FDA label. We further classify restrictions into categories: (1) patient subgroup (requirement for patients to meet certain clinical criteria, such as disease severity), (2) step therapy protocol (requirement for patients to first fail an alternative treatment before gaining access to a drug), (3) prescriber restriction (requirement for a certain type of physician—for example, a rheumatologist—to prescribe the drug), (4) combination therapy (requirement for a drug to be used concomitantly with another medication), and (5) other.

SPEC includes 204 drugs. Because a drug can be indicated for multiple diseases, the database includes 409 unique drug–indication pairs (186 orphan drug–indication pairs; 223 nonorphan drug–indication pairs). For example, because ruxolitinib is indicated for myelofibrosis and polycythemia vera (both orphan diseases), it appears twice in the database. SPEC includes 5000 coverage decisions (2168 for orphan drugs; 2832 for nonorphan drugs) across the 17 health plans. Included decisions are current as of March 2018.
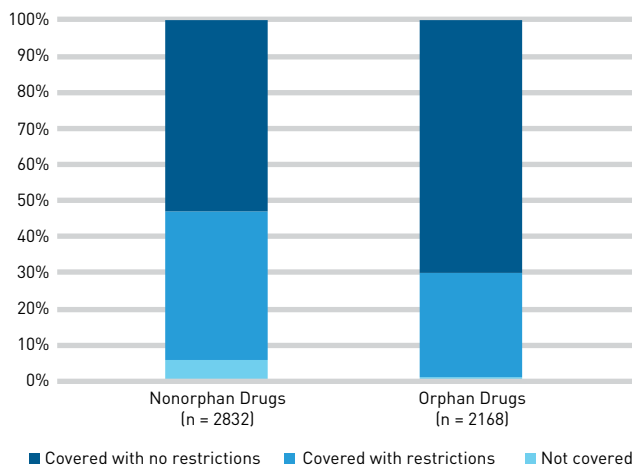
Variables

Dependent variable. The dependent variable is dichotomous (yes/no) and describes whether the health plan's coverage decision restricted patients' access to a drug beyond the drug's FDA label. "No restrictions" means a plan covered the drug consistent with its label. Coverage restrictions included decisions in which the plan did not cover the drug or the plan applied some restriction (for example, by step therapy protocol).

Independent variables. We include 10 independent variables that we selected either because they have been previously shown to be

TAKEAWAY POINTS

▸ Private US health plans less often apply restrictions in their coverage decisions for orphan drugs than in their coverage decisions for nonorphan drugs (30% vs 47% of the time, respectively).

▸ Health plans vary in the frequency with which they apply restrictions in their orphan drug coverage decisions.

▸ Private US health plans more often add orphan drug coverage restrictions (eg, patient subgroup restrictions, step therapy protocols) for drugs for diseases other than cancer, drugs with alternatives, self-administered drugs, drugs indicated for diseases with a higher prevalence, and drugs with higher annual costs.
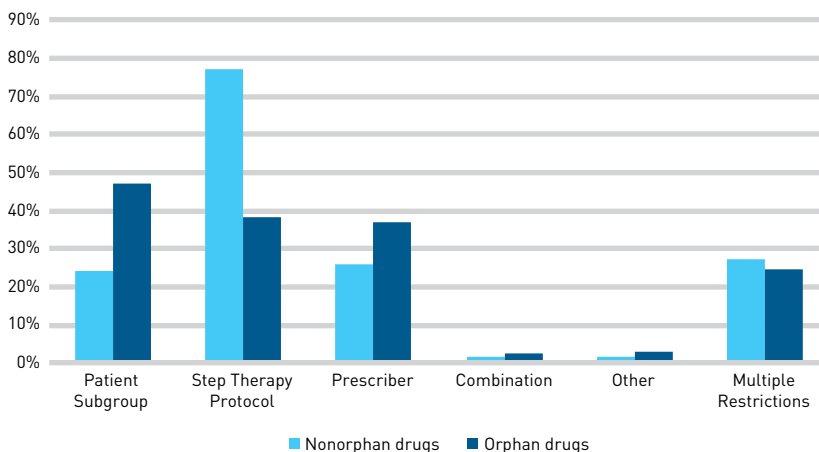
associated with restricted drug coverage[5] or because we consider them likely to be associated with coverage restrictions. *Cancer treatment* is a dichotomous variable capturing whether a drug is indicated to treat cancer. *Available alternative* is a dichotomous variable capturing whether a drug has any therapeutic alternatives (ie, whether the FDA has approved another drug for the same indication). *Pediatric population* is a dichotomous variable accounting for whether a drug is indicated for pediatric or adolescent patients. Examples include nusinersen for spinal muscular atrophy and velaglucerase alfa for Gaucher disease type 1. *Years since approval* is a continuous variable accounting for the number of years since a drug's FDA approval. When a drug is approved for multiple orphan indications, we consider the approval date for each indication separately. For example, tocilizumab was approved to treat polyarticular juvenile idiopathic arthritis in 2013 and approved for cytokine release syndrome in 2017; thus, the time since FDA approval differs for these indications. *Safety* is a dichotomous variable describing whether the drug has been flagged by the FDA for a safety concern (specifically, a black box safety warning or implementation of a Risk Evaluation and Mitigation Strategy program).[7] *FDA expedited approval* is a dichotomous variable accounting for whether the FDA included the drug in one of its expedited approval programs, including priority review, fast track, accelerated approval, or breakthrough therapy.[8] *Self-administered* is a dichotomous variable capturing whether the drug is self- or physician-administered. We categorize tablets, capsules, and subcutaneously self-injected drugs as being self-administered, and drugs injected or infused in inpatient or outpatient settings as being physician-administered. *Nonorphan indication* is a dichotomous variable accounting for situations in which an orphan drug is also indicated for a nonorphan indication. For instance, adalimumab is approved for orphan indications (eg, pediatric Crohn disease) and nonorphan indications (eg, rheumatoid arthritis). *Disease prevalence* is a categorical variable accounting for the prevalence of the indicated disorder. We obtained estimates of US disease prevalence from a review of the medical literature and the websites of national clinical organizations. To construct the variable, we divided observations into quartiles based on prevalence magnitudes. *Annual cost* is a categorical variable capturing the yearly per-patient drug cost (and dividing observations into quartiles). We estimated these costs using dosing information from the drug's label and the Federal Supply Schedule (FSS) price (federal purchaser price

FIGURE 1. Health Plan Coverage of Nonorphan and Orphan Drugs

the average effect of an independent variable on coverage across health plans while accounting for differences among them. We report associations between independent variables and coverage restrictiveness using odds ratios, which describe how much larger or smaller the odds of restricted coverage are for an independent variable (eg, drugs with alternatives compared with drugs with no alternatives). We considered *P* values <.05 to be statistically significant. We performed analyses using Stata SE version 13 (StataCorp LP; College Station, Texas).

RESULTS

Comparing Orphan and Nonorphan Drug Coverage

The vast majority of orphan drug coverage decisions (2146 of 2168 decisions; 99%) provide at least some coverage: 70% of decisions provide coverage without restrictions, 29% add restrictions, and 1% provide no coverage. By comparison, among nonorphan drug coverage decisions in SPEC (n = 2832), 53% provide coverage without restrictions, 41% add restrictions, and 6% provide no coverage (**Figure 1**).

In orphan drug restrictions, plans most commonly limit coverage by patient subgroup restrictions (47% of restricted decisions). In contrast, for nonorphan drug restrictions, plans most commonly apply step therapy protocols (77% of restricted decisions) (**Figure 2**).

Variation in Orphan Drug Coverage

The degree to which plans restricted orphan drug coverage decisions varied across health plans, ranging from 11% to 65% (**Figure 3**).
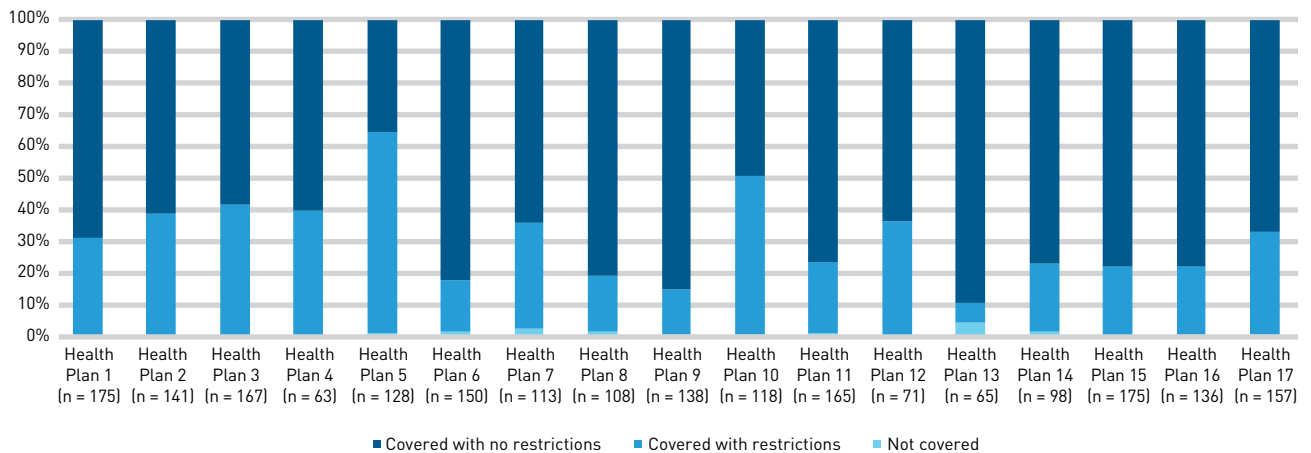
Factors Associated With Restricted Orphan Drug Coverage

Health plans are more likely to restrict coverage of orphan drugs indicated for noncancer diseases, for drugs having available alternatives, for self-administered drugs, and for more recently approved products. Plans are also more likely to restrict orphan drugs with higher annual costs and drugs indicated for higher-prevalence diseases (**Table**). All findings are significant (*P* <.05).

DISCUSSION

Health plans cover orphan drugs more generously than nonorphan drugs: 70% versus 53% of coverage decisions do not include coverage restrictions, respectively. Still, the roughly one-third of orphan drug coverage decisions with restrictions are notable and have not been previously reported.

Plans most often restrict coverage of orphan drugs by applying patient subgroup restrictions. For example, one plan restricts coverage of omalizumab for chronic idiopathic urticaria by requiring that patients be symptomatic for

based on a drug's average sales price inclusive of rebates).[9] If the FSS drug price was unavailable, we relied on alternative sources, including the CMS Average Sales Price (a product's average sales price as submitted to CMS) and the IBM Micromedex RED BOOK (a proprietary source of drug pricing).[10,11]

Analysis

We analyzed the data in 3 ways. First, we compared the frequency with which plans applied coverage restrictions for nonorphan and orphan drugs. Second, we evaluated variation in orphan drug coverage across health plans. Third, we developed a multilevel, random-effect, logistic regression model to estimate the relationship between the independent variables and the likelihood of restrictive orphan drug coverage. We used a multilevel model to estimate

FIGURE 2. Percentage of Restricted Coverage Decisions in Which Health Plans Applied Different Types of Restrictions

FIGURE 3. Health Plan Coverage of Orphan Drugs[a]

■ Covered with no restrictions ■ Covered with restrictions ■ Not covered

[a]Each n is the number of orphan drug coverage decisions issued by the health plan.

at least 6 weeks before they are granted access to the treatment. In another example, a plan restricts coverage of rilonacept for cryopyrin-associated periodic syndromes by requiring that patients' disease causes functional impairment that results in limitations of activities of daily living.

We found considerable variation in orphan drug coverage across plans. This finding has important implications and suggests that a patient's insurance company can impact their access to orphan drugs. Reasons for this variation are unclear but may reflect differences in contracting arrangements or in the rebates that plans negotiate, as well as the fact that plans tailor decisions according to their particular patient populations, local practice patterns, and budgetary realities.

Various factors are associated with the restrictiveness of orphan drug coverage. Health plans less often apply restrictions in their coverage decisions for orphan drugs indicated for cancer than for orphan drugs indicated for noncancer diseases, a finding that may indicate that health plans award cancer treatments a special status.[12] Health plans more often restrict coverage for more recently approved orphan drugs, possibly because such drugs have a less mature evidence base and because plans have less experience managing them. Health plans tend to restrict coverage of self-administered more than physician-administered orphan drugs, suggesting that plans manage pharmacy benefit drugs more aggressively than medical benefit drugs. Plans more often restrict coverage of drugs with a therapeutic alternative, likely due to the fact that plans provide more generous access to drugs representing patients' sole therapeutic option.

Although by definition orphan drugs are indicated for small populations (the FDA assigns orphan status to drugs indicated for diseases affecting fewer than 200,000 individuals[13]), drugs indicated for the most prevalent orphan diseases are more than twice as likely to be restricted as drugs indicated for the least prevalent orphan

diseases. Health plans' sensitivity to disease rarity suggests their attentiveness to drugs' budget impact. This sensitivity may also explain the fact that drugs with the highest estimated annual costs are roughly twice as likely to be restricted as drugs with the lowest estimated annual costs. These findings are consistent with previous research that found that health plans were more likely to restrict specialty drugs (orphan and nonorphan specialty drugs) with higher annual costs and greater budget impacts.[5] Concerns over the overall costs of orphan drugs seem likely to intensify (58% of all drugs approved by the FDA in 2018 were orphan drugs, for example).[14]

This research provides a window into the struggles that plans face in light of an ever-increasing number of orphan drugs. Historically, plans have been able to absorb the costs of the few available orphan drugs. However, the growing number of orphan drugs and their larger budget impact likely mean that health plans will more often apply coverage restrictions to orphan drugs in the future. It is important for the medical community to understand that orphan drugs are not exempt from drug utilization management strategies.

Limitations

Our study has a number of limitations. First, because the drug prices that plans negotiate with product manufacturers are not publicly disclosed, we rely on alternative sources of drug prices, not the actual prices paid by health plans. Second, our findings may not generalize to decisions made by other private health plans or by Medicare and Medicaid. Also, because we focus exclusively on orphan drugs for which plans have issued a coverage decision, our findings may not generalize to drugs that plans cover through formularies. Third, we do not account for patient cost sharing or other possible benefit design features. Fourth, there may be unobserved confounders influencing plan decision making. For instance, we do not control for the quality of the evidence that plans cite in their orphan drug coverage decisions. Because the

TABLE. Effect of Independent Variables on the Likelihood That Orphan Drug Coverage Decisions Will Be Restrictive (n = 2168 observations)

Independent Variable (% of observations)	Multivariate Analysis	
	Odds Ratio	95% CI
Cancer treatment		
No (62%)	Reference	
Yes (38%)	0.162**	0.118-0.223
Available alternative		
No (30%)	Reference	
Yes (70%)	1.79**	1.382-2.321
Pediatric population		
No (76%)	Reference	
Yes (24%)	0.947	0.718-1.249
Years since approval[a] (mean [SD] = 10.178 [7.690])	0.946**	0.932-0.961
Safety		
No (55%)	Reference	
Yes (45%)	0.906	0.711-1.153
FDA expedited approval		
No (43%)	Reference	
Yes (57%)	1.207	0.947-1.539
Self-administered		
No (56%)	Reference	
Yes (44%)	1.482**	1.181-1.861
Nonorphan indication		
No (66%)	Reference	
Yes (34%)	0.871	0.655-1.159
Disease prevalence (range)		
First quartile (54-4343)	Reference	
Second quartile (4886-19,542)	1.400*	1.027-1.908
Third quartile (21,640-76,974)	1.504*	1.049-2.156
Fourth quartile (80,000-200,000)	2.277**	1.632-3.177
Annual cost (range)		
First quartile ($499-$18,480)	Reference	
Second quartile ($19,056-$84,671)	1.209	0.899-1.625
Third quartile ($85,006-$171,893)	0.801	0.559-1.146
Fourth quartile ($175,271-$905,556)	1.878**	1.279-2.758

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

[a]Years since approval is a continuous variable; therefore, the mean and SD are presented.

FDA often bases orphan drug approvals on clinical studies with less rigorous study designs (eg, lack of control arms and small sample sizes), health plans are faced with uncertain evidence upon which to base their decisions.[15,16]

CONCLUSIONS

The largest US private health plans restrict access to orphan drugs in approximately one-third of coverage decisions. Plans most often restrict coverage by requiring patients to meet certain clinical criteria, such as experiencing symptoms that result in limitation of activities of daily living. Plans vary in the frequency with which they apply coverage restrictions to their orphan drug coverage decisions. Plans more often add restrictions to drugs for diseases other than cancer, drugs with alternatives, self-administered drugs, drugs indicated for diseases with a higher prevalence, and drugs with higher annual costs. ∎

REFERENCES

1. Handfield R, Feldstein J. Insurance companies' perspectives on the orphan drug pipeline. *Am Health Drug Benefits.* 2013;6(9):589-598.
2. Hyde R, Dobrovolny D. Orphan drug pricing and payer management in the United States: are we approaching the tipping point? *Am Health Drug Benefits.* 2010;3(1):15-23.
3. Orphan drugs in the United States: growth trends in rare disease treatments. IQVIA website. iqvia.com/-/media/iqvia/pdfs/institute-reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.pdf?_=1544648528329. Published October 2018. Accessed March 12, 2019.
4. FAQs about rare diseases. National Institutes of Health National Center for Advancing Translational Sciences website. rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases. Updated November 30, 2017. Accessed March 12, 2019.
5. Chambers JD, Kim DD, Pope EF, Graff JS, Wilkinson CL, Neumann PJ. Specialty drug coverage varies across US commercial health plans. *Health Aff (Millwood).* 2018;37(7):1041-1047. doi: 10.1377/hlthaff.2017.1553.
6. Cohen JP, Awatin JG. Patient access to orphan drugs. *Expert Opin Orphan Drugs.* 2017;5(12):923-932. doi: 10.1080/21678707.2017.1402676.
7. Approved Risk Evaluation and Mitigation Strategies (REMS). FDA website. accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed March 12, 2019.
8. Guidance for industry: expedited programs for serious conditions—drugs and biologics. FDA website. fda.gov/media/86377/download. Published May 2014. Accessed March 12, 2019.
9. Office of Procurement, Acquisition and Logistics (OPAL). US Department of Veterans Affairs website. va.gov/opal/nac/fss/pharmPrices.asp. Updated August 6, 2019. Accessed August 29, 2019.
10. July 2018 ASP pricing file [zip file]. CMS website. cms.gov/apps/ama/license.asp?file=/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/Downloads/2018-July-ASP-Pricing-File.zip. Updated May 29, 2019. Accessed August 29, 2019.
11. IBM Micromedex RED BOOK. IBM website. ibm.com/us-en/marketplace/micromedex-red-book. Accessed August 29, 2019.
12. Neumann PJ, Bliss SK, Chambers JD. Therapies for advanced cancers pose a special challenge for health technology assessment organizations in many countries. *Health Aff (Millwood).* 2012;31(4):700-708. doi: 10.1377/hlthaff.2011.1309.
13. Orphan Drug Act, PL 97-414, 96 § 2049 (1983).
14. Advancing health through innovation: 2018 new drug therapy approvals. FDA website. fda.gov/media/120357/download. Published January 2019. Accessed March 12, 2019.
15. Mitsumoto J, Dorsey ER, Beck CA, Kieburtz K, Griggs RC. Pivotal studies of orphan drugs approved for neurological diseases. *Ann Neurol.* 2009;66(2):184-190. doi: 10.1002/ana.21676.
16. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. *JAMA.* 2011;305(22):2320-2326. doi: 10.1001/jama.2011.769.

Visit **ajmc.com/link/4262** to download PDF