Commercial health plans use of patient subgroup restrictions: An analysis of orphan and US Food and Drug Administration–expedited programs

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Plain language summary

Health plans may manage patients' eligibility for a drug by requiring that the patients meet certain clinical criteria (eg, symptoms that indicate disease severity or being within a specified age range). These are known as patient subgroup restrictions. Plans imposed patient subgroup restrictions in roughly one-fifth of orphan drug coverage policies and in roughly one-fifth of US Food and Drug Administration–expedited drug policies. Patient subgroup restrictions were typically consistent with the data the US Food and Drug Administration reviewed to grant approval.

Implications for managed care pharmacy

US commercial health plans impose patient subgroup restrictions in their drug coverage policies with different frequencies, indicating that a patient's plan can greatly influence their access to care. Patient subgroup restrictions often used the same clinical measures as included in drugs' pivotal clinical trials. However, patient subgroup restrictions were inconsistent with the pivotal trial's eligibility criteria roughly one-fifth of the time, raising questions about how health plans developed those criteria.

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ABSTRACT

BACKGROUND: Health plans apply utilization management criteria to guide their enrollees' access to prescription drugs. Patient subgroup restrictions (ie, clinical prerequisites for drug coverage) are a form of utilization management that have not been thoroughly investigated.

OBJECTIVE: To examine the frequency with which large US commercial health plans impose patient subgroup restrictions beyond the US Food and Drug Administration (FDA) label in their coverage policies for orphan drugs and for drugs included in 1 or more FDA-expedited programs. To determine how consistently these patient subgroup restrictions align with eligibility criteria specified in each drug's pivotal clinical trial(s).

METHODS: The Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) database was used, which includes coverage policies issued by 17 large US commercial health plans. SPEC contained 3,786 orphan drug policies and 4,027 FDA-expedited drug policies (current as of December 2020). SPEC data on plans' patient subgroup restrictions were assessed for the first objective. Each patient subgroup restriction was benchmarked against the corresponding eligibility criteria for a drug's pivotal clinical trial(s) for the second objective. To do so, the "Clinical Studies" section of the drug's FDA label was reviewed or, if necessary, the published manuscript describing the drug's pivotal trial(s). Patient subgroup restrictions were categorized as follows: (1) "consistent," the restriction and trial eligibility criterion are equivalent; (2) "same measure, more stringent," the restriction and trial eligibility criteria depend on the same measure, but the plan coverage is more restrictive; (3) "same measure, less stringent," the restriction and trial eligibility criteria depend on the same measure, but the plan coverage is less restrictive; and (4) "not consistent," the restriction and trial eligibility criteria depend on different measures.

RESULTS: Health plans imposed patient subgroup restrictions in 20.2% of orphan drug policies (frequency varied by health plan, 11.7%-36.6%), and in 21.8% of FDA-expedited drug policies (frequency varied by health plan, 11.1%-47.9%). Of the 936 patient subgroup restrictions in orphan drug policies, 60.3% were categorized as consistent; 7.3% as same measure, more stringent; 12.0% as same measure, less stringent; and 20.5% as not consistent. Of the 1,070 patient subgroup restrictions in FDA-expedited drug policies, 57.5% were categorized as consistent; 6.7%

as same measure, more stringent; 16.0% as same measure, less stringent; and 19.8% as not consistent.

CONCLUSIONS: Patient subgroup restrictions for orphan drugs and FDA-expedited programs varied substantially across health plans, potentially resulting in inconsistent access to a given therapy across the approved patient population. Patient subgroup restrictions tend to be consistent with eligibility criteria specified in pivotal clinical trials.

Health plans use utilization management (UM) criteria in their drug coverage policies to guide enrollee access to safe, effective, and cost-effective care while controlling costs.[1] Coverage policies reflect a plan's interpretation about medically necessary care, which can differ from a drug's US Food and Drug Administration (FDA)–approved indication. Health plans' drug coverage criteria are sometimes more generous than the FDA's approved label, but often they are more stringent.[2] Because onerous UM criteria may delay or restrict patient access to needed therapies,[3] physicians and patients should be able to discern how a coverage policy was decided.

Researchers have evaluated health plans' use of various forms of UM criteria, including step therapy protocols,[4] formulary tiering,[5] quantity limits,[6,7] and prescriber requirements.[8] This research has found the application of UM criteria to be inconsistent across plans for the same drugs.

The literature has not thoroughly investigated how often or how consistently plans apply UM patient subgroup restrictions, ie, clinical prerequisites for drug coverage. These restrictions, including restrictions beyond the FDA label, can include requirements that a patient's symptoms must be of a certain severity or the patient must be of a certain age before the patient can gain access to a medication. Nor has the literature explored how often plan-imposed clinical criteria are grounded in clinical evidence.

This study focused on 2 drug categories that often address unmet clinical needs: (1) orphan drugs and (2) drugs included in at least 1 FDA-expedited program. The FDA can grant a drug *orphan designation* if it treats a disease affecting fewer than 200,000 patients in the United States[9] or if the drug's development cost would exceed its potential profits.[10] Orphan drug designation can extend market exclusivity by up to 7 years and confer user fee exceptions and tax credits for clinical trials.[11] The FDA can utilize 1 or more of 4 expedited programs (priority review, fast track designation, accelerated approval, or breakthrough therapy) if drugs meet certain threshold criteria.[12] Eligibility requirements and benefits for these programs vary (see Supplementary Table 1, available in online article), but they all aim to accelerate patient access to treatments for serious conditions.

This study examined the use of patient subgroup restrictions in coverage policies for orphan drugs and drugs included in 1 or more FDA-expedited programs.

Methods

Two questions were investigated: (1) how frequently do plans impose patient subgroup restrictions beyond the FDA-approved label and (2) how consistently do plan-imposed patient subgroup restrictions align with eligibility criteria specified in each drug's pivotal clinical trial(s)?

DATA

The Tufts Medical Center Specialty Drug and Evidence and Coverage (SPEC) database was used, which includes information on specialty drug coverage policies issued by 17 of the largest US commercial health plans, ranked by covered lives (see Supplementary Exhibit 1 for included plans). Included coverage data were current as of December 2020. When the FDA approves a drug for multiple indications, SPEC includes information on each drug-indication pair separately. For example, because the FDA approved canakinumab for 2 indications (periodic fever syndromes and systemic juvenile idiopathic arthritis), this drug is featured twice in SPEC.

SPEC benchmarks coverage policies against the drug's FDA-approved indications, categorizing any restrictions beyond the approved indication as follows: (1) patient subgroup restrictions (ie, clinical prerequisites for drug coverage), (2) step therapy protocols (eg, requirements that patients first try and fail an alternative treatment before gaining access to a drug), (3) prescriber requirements (eg, the requirement that a specialist prescribe the treatment), or (4) any other restrictions. For each plan's policy for a given drug-indication pair, multiple restrictions may be applied.

ANALYSIS 1: FREQUENCY OF PLAN-IMPOSED SUBGROUP RESTRICTIONS

The frequency that plan coverage policies imposed patient subgroup restrictions for orphan vs nonorphan drugs and for drugs that have utilized at least 1 FDA-expedited program vs those that have not (ie, approved through standard processes) were compared using chi-square tests. The frequency with which plans impose patient subgroup restrictions was compared with the frequency with which they impose other types of restrictions, such as step therapy protocols, by expressing them as percentages.

TABLE 1 Coverage Restrictions Beyond Labeled Indication by FDA Drug Classification

FDA drug classification		Total decisions, n	Decisions with a specific type of restriction, n (%)				
			Any restriction	Prescriber requirements	Patient subgroup restrictions	Step therapy protocol	Other restrictions
Orphan	Yes	3,786	1,716 (45.3)	845 (22.3)	764 (20.2)	649 (17.1)	66 (1.7)
	No	4,797	2,492 (51.9)	992 (20.7)	560 (11.7)	1,801 (37.5)	63 (1.3)
FDA-expedited program	Yes	4,027	1,771 (44.0)	884 (22.0)	876 (21.8)	624 (15.5)	65 (1.6)
	No	4,556	2,437 (53.5)	953 (20.9)	448 (9.8)	1,826 (40.1)	64 (1.4)

Orphan and FDA-expedited program categories are not mutually exclusive, ie, a drug may be an orphan drug and included in an FDA-expedited program. A health plan may have included multiple restriction types in a coverage decision.
FDA = US Food and Drug Administration.

ANALYSIS 2: ALIGNMENT OF COVERAGE RESTRICTIONS AND PIVOTAL TRIAL ELIGIBILITY CRITERIA

For orphan drugs and drugs included in at least 1 FDA-expedited program whose policies had patient subgroup restrictions beyond the FDA label, each patient subgroup restriction was benchmarked against the corresponding patient eligibility criteria for a drug's pivotal clinical trial(s) (ie, the studies supporting the drug's FDA approval). Information for this comparison came from the "Clinical Studies" section of the drug's FDA label. If this information was judged to be insufficient, the published manuscript describing the drug's pivotal trial(s) was reviewed. Based on this review, each patient subgroup restriction was classified into 1 of 4 categories:

1. *Consistent*: the coverage restrictions and trial eligibility criteria are equivalent.
2. *Same measure, more stringent*: the coverage restrictions and trial eligibility criteria depend on the same measure, but the plan coverage is more restrictive.
   a. For example, the trial and coverage policy both impose requirements based on the number of hereditary angioedema attacks per month, but the trial required participants to have at least 1 attack per month, whereas the coverage policy requires at least 2 such monthly attacks.
3. *Same measure, less stringent*: the coverage restrictions and trial eligibility depend on the same measure, but the plan coverage is less restrictive.
   a. For example, the trial and coverage policy both impose requirements based on Eastern Cooperative Oncology Group performance status, but the trial required participants to have a score of 0-1, whereas the coverage policy requires an Eastern Cooperative Oncology Group performance status of 0-2.
4. *Not consistent*: the coverage restrictions and trial eligibility depend on different measures, ruling out their direct comparison.

SENSITIVITY ANALYSIS

An additional assessment considered whether the results depended on the year of a drug's FDA approval. This was explored by stratifying drug-indication pairs into 2 groups: (1) those approved during the 3-year period prior to the conduct of this analysis (January 2017 through December 2020) or (2) those approved earlier. A chi-square test was performed to examine the association between the year of FDA approval and coverage restriction consistency with the drug's pivotal trial eligibility criteria.

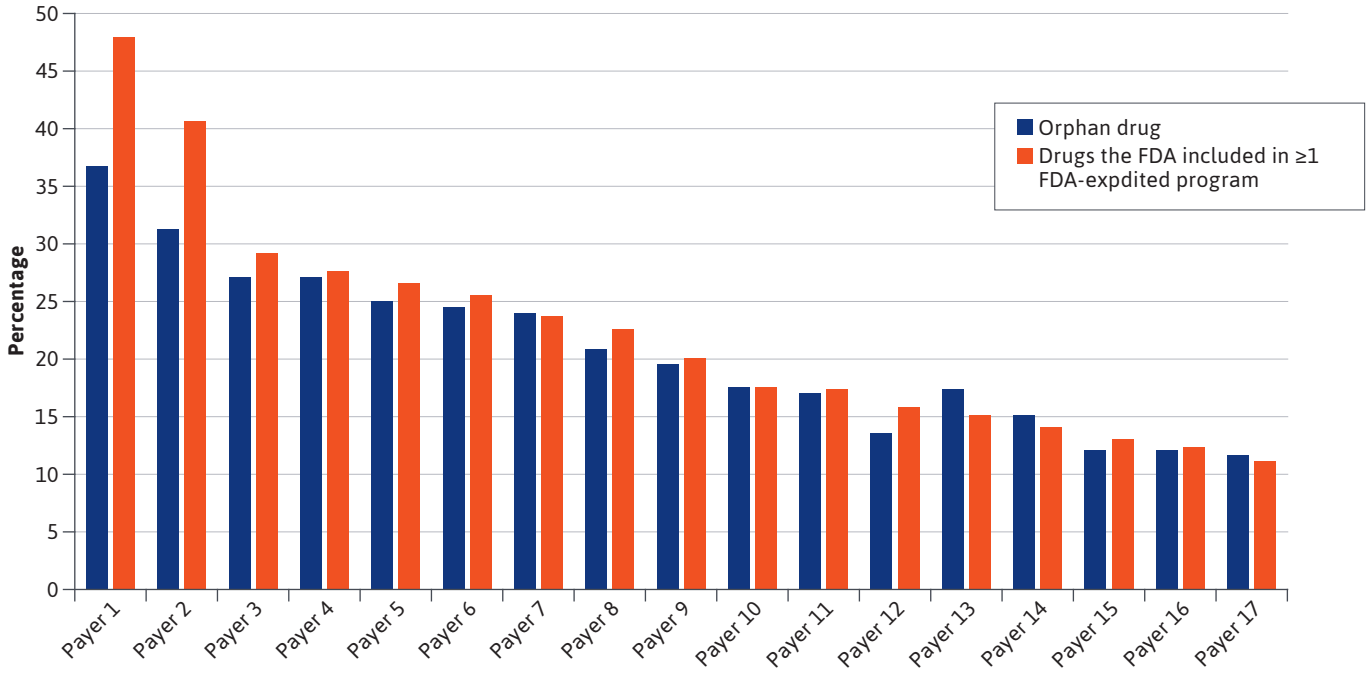
Results

As of December 2020, SPEC contained information on 311 specialty drugs. For this analysis, SPEC included 8,583 coverage policies corresponding to 646 drug-indication pairs, including 290 orphan drug-indication pairs and 308 drug-indication pairs that the FDA included in at least 1 FDA-expedited program. A total of 195 drug-indication pairs in the sample both had an orphan designation and were in at least 1 FDA-expedited program. These 195 drug-indication pairs were included in the analyses of orphan drugs and the analyses of drugs included in at least 1 FDA-expedited program.

ANALYSIS 1: FREQUENCY OF PLAN-IMPOSED SUBGROUP RESTRICTIONS BEYOND THE FDA LABEL

For orphan and FDA-expedited drugs, coverage policies imposed prescriber requirements most often, followed by patient subgroup restrictions and step therapy protocols (Table 1). Coverage policies imposed patient subgroup

FIGURE 1 Percentage of Coverage Policies in Which Health Plans Imposed Patient Subgroup Restrictions



FDA=US Food and Drug Administration.

restrictions more often for orphan drugs than for nonorphan drugs ($P<0.01$) (Table 1). Coverage policies imposed patient subgroup restrictions more often for FDA-expedited drugs than for nonexpedited drugs ($P<0.01$) (Table 1).

Plans varied with respect to how frequently their coverage policies imposed patient subgroup restrictions. For the 290 orphan drug-indication pairs, the proportion of coverage policies imposing patient subgroup restrictions ranged from 11.7% to 36.6% (blue bars in Figure 1); for the 308 FDA-expedited drug-indication pairs, this proportion ranged from 11.1% to 47.9% (orange bars in Figure 1).

Among orphan drug-indication pairs, 392 of 3,786 coverage decisions (10.4%) imposed patient subgroup restrictions but no other restrictions, whereas another 372 of 3,786 coverage decisions (9.8%) imposed both patient subgroup restrictions and at least 1 other type of restriction. Among FDA-expedited drug-indication pairs, 460 of 4,027 coverage decisions (11.4%) imposed patient subgroup restrictions but no other restrictions, whereas another 416 of 4,027 coverage decisions (10.3%) imposed both patient subgroup restrictions and at least 1 other type of restriction.

Decisions for accelerated approval drug-indication pairs were less likely to include restrictions than other FDA-expedited drug-indication pairs, including fewer patient subgroup restrictions (Table 2). Fast-track–designated drugs were most likely to have any restrictions, whereas breakthrough designation drugs were most likely to have patient subgroup restrictions.

ANALYSIS 2: ALIGNMENT OF COVERAGE RESTRICTIONS AND PIVOTAL TRIAL ELIGIBILITY CRITERIA

Of the 764 orphan drug-indication pair coverage policies with patient subgroup restrictions, plans imposed 936 restrictions (reflecting that some policies included multiple restrictions). After categorizing relative to the FDA pivotal trial, 564 (60.3%) were deemed as consistent; 68 (7.3%) as same measure, more stringent; 112 (12.0%) as same measure, less stringent; and 192 (20.5%) as not consistent (Figure 2).

Of the 876 FDA-expedited drug-indication pair coverage policies with patient subgroup restrictions, plans imposed 1,070 restrictions: 615 (57.5%) were categorized as consistent with the FDA pivotal trial; 72 (6.7%) as same

TABLE 2 Coverage Restrictions for FDA-Expedited Drugs by Type of FDA-Expedited Program

Type of FDA-expedited program	Total decisions, n	Decisions with a specific type of restriction, n (%)				
		Any restrictions	Prescriber requirements	Patient subgroup restrictions	Step therapy protocol	Other restrictions
Accelerated approval	1,046	347 (33.2)	183 (17.5)	161 (15.4)	69 (6.6)	22 (2.1)
Breakthrough designation	1,594	713 (44.7)	386 (24.2)	424 (26.6)	183 (11.5)	34 (2.1)
Fast track designation	1,163	572 (49.2)	313 (26.9)	283 (24.3)	195 (16.8)	26 (2.2)
Priority review	3,429	1,526 (44.5)	766 (22.3)	766 (22.3)	550 (16.0)	46 (1.3)

A drug may have been included in more than 1 FDA-expedited program. A health plan may have included multiple restriction types in a coverage decision.
FDA = US Food and Drug Administration.

measure, more stringent; 171 (16.0%) as same measure, less stringent; and 212 (19.8%) as not consistent (Figure 2). Findings depended on which FDA-expedited programs a drug qualified for. Restrictions were consistent with the trial least often for accelerated approval drugs and most often for priority review drugs (Figure 2).

SENSITIVITY ANALYSIS

Patient subgroup restrictions were more often consistent with pivotal trial eligibility criteria for drug-indication pairs that were FDA approved during the 3 years prior to this analysis than for drug-indication pairs that were FDA approved less recently (61.4% vs 53.6%; $P < 0.01$).

Discussion

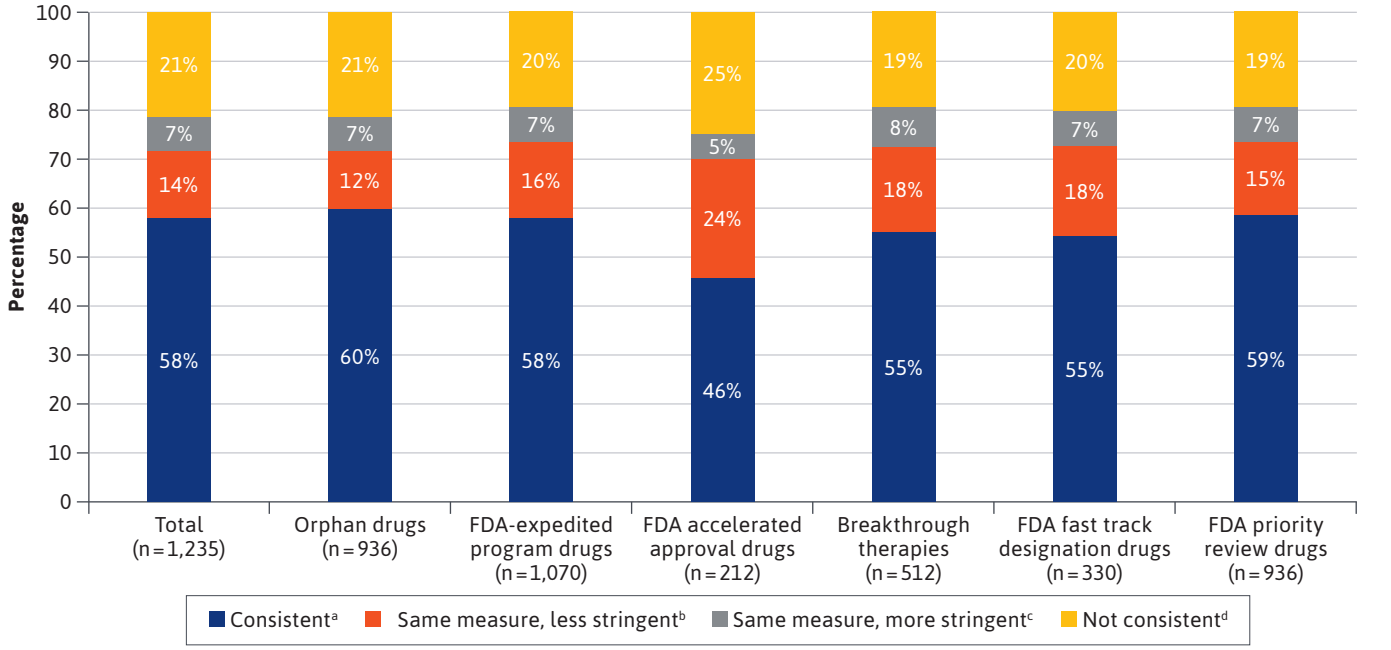
The findings of this study suggest that plans often cover drugs more narrowly than the FDA's approved indication, potentially preventing access to therapies for some patients for whom the therapies are indicated. Although patient subgroup restrictions may be reasonable and appropriate if there is evidence to support their use, they can have important consequences on a patient's eligibility for a treatment. For instance, plans may require patients with spinal muscular atrophy to have a certain number of copies of the SMN2 gene, which is linked to disease severity, to gain access to treatments, making some patients ineligible for care. In these circumstances, a patient would remain ineligible for treatment unless the patient successfully appealed their coverage denial or until the plan reviewed and adjusted their coverage criteria (eg, following the emergence of new clinical data).[13] Additionally, plans may impose age-based restrictions that are different from either a drug's FDA label indication or the inclusion criteria of the drug's pivotal clinical trial and that are not necessarily reflective of the severity of the patient's condition, resulting in delays or ineligibility. In contrast, patients may eventually overcome step therapy requirements by working their way through required regimens, and they may overcome plan-imposed prescriber criteria by seeking care from the specified clinician. Although such coverage requirements may reduce inappropriate use, the time it takes to meet these requirements for appropriate use may result in irreversible changes for patients with progressively debilitating diseases.

About 1 in 5 coverage policies for orphan and FDA-expedited drugs impose patient subgroup restrictions. For orphan drugs, this analysis is consistent with the findings from previous research.[14] Orphan and FDA-expedited drugs are approximately twice as likely to have patient subgroup restrictions as nonorphan and non–FDA-expedited drugs.

Crucially, because plans differ in terms of how they apply these restrictions, patient access to these drugs can depend on which health plan happens to provide their coverage. For example, some coverage policies require patients with hereditary angioedema to have severe symptoms to gain access to lanadelumab-flyo, whereas other plans require that patients have moderate-to-severe symptoms. Such differences may complicate care access for patients switching health plans and can mean a loss of eligibility or a lack of eligibility altogether.

It is unclear what criteria individual plans use when imposing patient subgroup restrictions. It is possible that differences arise from budgetary considerations. Studies have shown that a drug's budget impact seems to influence coverage restrictiveness.[2,14] Alternatively, plan differences may reflect each organization's independent assessment of the evidence beyond the FDA label and subsequent determination regarding the population of patients for whom a drug represents a "medical necessity." This difference may reflect the fact that the FDA is willing to extrapolate beyond the pivotal trial's eligibility criteria in the label,[15] whereas health plans may be less likely to do so.

FIGURE 2 Consistency of Plan-Imposed Coverage Restrictions With Pivotal Clinical Trial Eligibility Criteria



Note: FDA-expedited programs, including accelerated approval, breakthrough therapies, fast track designation, and priority review, are all considered FDA-expedited approval pathways.

[a]*Consistent: the clinical criterion was included in the trial eligibility criteria.*

[b]*Same measure, less stringent: the clinical criterion used the same measure as included in the trial's eligibility criteria but used a less stringent threshold.*

[c]*Same measure, more stringent: the clinical criterion used the same measure as included in the trial eligibility criteria but used a more stringent threshold.*

[d]*Not consistent: the clinical criterion did not feature in the clinical trial's eligibility criteria.*

FDA=US Food and Drug Administration.

It is also important to consider the consistency of subgroup restrictions and eligibility requirements of the pivotal trials. Plans may apply the same measure, even if the specific criteria are more or less stringent than the criteria in the pivotal trial. The fact that plans often build the same measures into their policies suggests plan officials closely scrutinize pivotal trial data when adjudicating drug coverage. Nevertheless, this study's finding that patient subgroup restrictions were inconsistent with the pivotal trial eligibility criteria one-fifth of the time raises questions about how plans selected certain clinical criteria.

Notably, plan patient subgroup restrictions were more likely to be consistent with pivotal trial eligibility criteria for recently approved drugs than for drugs approved less recently. This finding may reflect the fact that the pivotal trial may represent the only source of clinical data available for recently approved therapies. In contrast, drugs approved less recently have likely accumulated additional supporting evidence, making health plan officials less dependent on the original pivotal trial results and increasing the possibility that the coverage criteria will diverge from the eligibility criteria in the pivotal trial.

Because the FDA and health plans rely on different decision-making criteria, differences between a drug's FDA approval and a health plan's coverage policy are unsurprising. Unlike the FDA, which focuses on pivotal clinical trial(s) data when judging a drug's safety and efficacy,[16] health plans must account for a range of clinical and economic factors when formulating drug coverage policies. Plans can use patient subgroup restrictions to restrict coverage to that portion of the FDA-approved indication for which supporting evidence is most compelling. However, it is important to ensure that any patient subgroup restrictions imposed with the intent of controlling costs do not compromise sound clinical decision-making and patient health outcomes.

FUTURE RESEARCH

Future research should further examine health plan evidentiary requirements. It should also explore the association between coverage stringency and patients' access to care and health outcomes. Research evaluating the evolution of coverage policies and the evidence plans rely on to establish policy would also be valuable.

LIMITATIONS

This study has limitations. First, the findings may not generalize to other commercial health plans or to public payers (eg, those with Medicare and Medicaid). The included coverage policies represent the plans' standard book of business and do not account for custom or different pharmacy coverage policies that plans may have in operation for specific employer groups. Second, coverage consistency was assessed with regards to pivotal clinical trials but not with other published clinical trials, real-world evidence studies, or recommendations from clinical guidelines. Third, this study did not account for differences in the drugs' pivotal clinical trial(s), such as differences in sample sizes. Nor did this study account for the strength of FDA advisory committees' recommendations about the approval of the drugs in the sample. Fourth, this study did not assess how frequently patient subgroup restrictions prevented patients from gaining access to a drug despite a health care provider's published policy. Fifth, this study did not account for plan appeals processes that patients may use when denied coverage. Finally, this study did not account for the fact that specific subgroup restrictions can differ in terms of their impact on patient access (ie, the percentage of patients who would be restricted).

Conclusions

Plans were more likely to impose patient subgroup restrictions on orphan drugs and drugs included in an FDA-expedited program. Moreover, these patient subgroup restrictions for orphan drugs and FDA-expedited drugs varied substantially across health plans. They tend to be consistent with eligibility criteria specified in pivotal clinical trials. However, patient subgroup restrictions were inconsistent with the pivotal trial's eligibility criteria roughly one-fifth of the time, raising questions about how health plans developed those criteria and the potential impact on patients' ability to access a given therapy.

DISCLOSURES

This study was funded by Sarepta Therapeutics, Inc. Alexa C Klimchak and Lauren E Sedita are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company.

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