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ORIGINAL RESEARCH ARTICLE

Factors Associated with Biosimilar Exclusions and Step Therapy Restrictions Among US Commercial Health Plans

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Abstract

Background Biosimilars have been introduced with the goal of competing with high-priced biologic therapies, yet their adoption has been slower than expected and resulted in limited efficiency gains. We aimed to explore factors associated with biosimilar coverage relative to their reference products by commercial plans in the United States (US).

Methods and Data We identified 1181 coverage decisions for 19 commercially available biosimilars, corresponding to 7 reference products and 28 indications from the Tufts Medical Center Specialty Drug Evidence and Coverage database. We also drew on the Tufts Medical Center Cost-Effectiveness Analysis Registry for cost-effectiveness evidence, and the Merative™ Micromedex® RED BOOK® for list prices. We summarized the coverage restrictiveness as a binary variable based on whether the product is covered by the health plan, and if covered, the difference of payers' line of therapy between the biosimilar and its reference product. We used a multivariate logistic regression to examine the association between coverage restrictiveness and a number of potential drivers of coverage.

Results Compared with reference products, health plans imposed coverage exclusions or step therapy restrictions on biosimilars in 229 (19.4%) decisions. Plans were more likely to restrict biosimilar coverage for the pediatric population (odds ratio [OR] 11.558, 95% confidence interval [CI] 3.906–34.203), in diseases with US prevalence higher than 1,000,000 (OR 2.067, 95% CI 1.060–4.029), and if the plan did not contract with one of the three major pharmacy benefit managers (OR 1.683, 95% CI 1.129–2.507). Compared with the reference product, plans were less likely to impose restrictions on the biosimilar–indication pairs if the biosimilar was indicated for cancer treatments (OR 0.019, 95% CI 0.008–0.041), if the product was the first biosimilar (OR 0.225, 95% CI 0.118–0.429), if the biosimilar had two competitors (reference product included; OR 0.060, 95% CI 0.006–0.586), if the biosimilar could generate annual list price savings of more than $15,000 per patient (OR 0.171, 95% CI 0.057–0.514), if the biosimilar's reference product was restricted by the plan (OR 0.065, 95% CI 0.038–0.109), or if a cost-effectiveness measure was not available (OR 0.066, 95% CI 0.023–0.186).

Conclusion Our study offered novel insights on the factors associated with biosimilar coverage by commercial health plans in the US relative to their reference products. Cancer treatment, pediatric population, and coverage restriction of the reference products are some of the most significant factors that are associated with biosimilar coverage decisions.

1 Introduction

Biologics are medicines derived from living cells or through biological processes [1]. They differ from small molecules based on size and manufacturing process [2]. Biologics are particularly effective in treating a variety of autoimmune diseases, rare diseases, cancers and other diseases with limited treatment options [3], and are a leading driver of increasing United States (US) health care spending. Although only accounting for about 2% of all prescriptions, biologics represent about $120 billion or 37% of net drug spending and 93% of the overall growth in total drug spending since 2014 [4].

Biosimilars are biologic products that are 'highly similar' to the original ('reference') biologics with no clinically

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Key Points

Biosimilars have the potential to reduce spending and increase access to costly biologic therapies, but there are huge variations in how biosimilars were covered, compared with their reference product, by commercial health plans in the United States.

This study explores what characteristics of the biologic–indication pair are associated with the health plan's decision to impose exclusions or step therapy restrictions for the biosimilars compared with their reference product.

Cancer treatment, pediatric population, and coverage restriction of the reference products are some of the most significant factors that are associated with biosimilar coverage decisions.

meaningful differences in safety or effectiveness from US FDA-approved reference products [5]. Biosimilars increase competition and can undercut reference product prices, thereby reducing spending on treatment and increasing access [6]. Mulcahy et al. suggested that the cost savings from biosimilar adoption could range from $24 to $150 billion between 2017 and 2026 [7]; however, biosimilar adoption has faced numerous challenges since the first biosimilar became available to patients in the US in 2015 [8]. Research has shown that the introduction of biosimilar products has affected access to costly biologic therapies in a non-uniform way [9–13]. For example, biosimilar adoption was reported to be more rapid among office- versus hospital-based providers, and among Veterans Affairs versus academic medical centers [10, 12].

One reason for uneven biosimilar adoption is varied coverage decisions across payers [14]: patients' access to new drugs depends largely on their health plans' coverage decisions [15]. A 2019 analysis of coverage decisions among US commercial health plans for biosimilars relative to their reference products indicated that biosimilars were preferred to their reference products in only 14% of coverage decisions, were on par with them in 53% of cases, and were less preferred in 33% of cases [14].

However, studies explaining the mechanism for such variation remain sparse. We investigate the key drivers of biosimilar coverage decisions by commercial payers. We hypothesize a range of factors, including whether drug indication (pediatric and cancer indications), intensity of competition, magnitude of budget impact, availability of the cost-effectiveness evidence, and health plan characteristics, may influence the coverage decisions.

2 Methods

2.1 Data Sources

We used the Specialty Drug Evidence and Coverage (SPEC) database, the Cost-Effectiveness Analysis (CEA) Registry, and the Merative™ Micromedex® RED BOOK® (Red Book) as our data sources. The SPEC database, developed and maintained by the Center for Evaluation of Value and Risk in Health (CEVR) at the Tufts Medical Center, is a database of specialty drug coverage decisions (exclusions and step therapy restrictions) of health plans in the US. It contains specialty drug coverage decisions from 17 of the 20 largest US private insurers, covering 150 million lives, which is approximately 60% of all commercially covered lives in the US [14, 16]. Of the three excluded health plans, two focus exclusively on public payers and one does not make its coverage decisions publicly available [17]. The database provides detailed information on over 290 specialty drugs, over 175 diseases, and the corresponding coverage and step therapy decisions [18]. Each data entry in the SPEC database contains the decision information for a drug–indication pair. If a drug is approved for multiple indications, the database records each drug–indication pair separately. The database is updated three times yearly and our analysis used the data-cut updated in August 2021.

The CEA Registry, also developed and maintained by the CEVR, is a comprehensive database of cost-effectiveness research that provides information on the incremental cost-effectiveness ratio (ICER) for medical procedures, drugs, medical devices, and other interventions published in peer-reviewed medical and public health journals. The CEA Registry is updated annually and includes over 9000 studies reporting over 22,000 cost-effectiveness ratios published between 2000 and 2019 [19].

The Merative™ Micromedex® RED BOOK® is a drug pricing database that includes pricing information for over 300,000 prescription and over-the-counter pharmaceuticals, chemicals, medical devices, and supplies [20]. It provides unit wholesale acquisition costs (WAC) for all the biologics analyzed in this study to calculate annual treatment costs, as shown below. We obtained the latest price information available, and the database was accessed in February 2022 (electronic supplementary material [ESM] 1).

2.2 Measures

Our outcome measure of interest was whether the biosimilar coverage was more restrictive relative to its reference biologic product by indication and commercial payer. We excluded decision entries for biosimilar–indication pairs without definitive decisions (i.e., 'no policy'). The payer's

line of therapy in the SPEC database accounts for step therapy protocols. A step therapy protocol is a requirement that a patient first try and experience treatment failure with an alternative treatment (first-line treatment) before accessing a particular therapy (second-line treatment) [21]. We summarized the coverage restrictiveness as a binary variable determined based on whether the product is covered by the health plan (exclusion), and if covered, the difference of payers' line of therapy between the biosimilar and its reference product (step therapy). It was coded as 'more restrictive than the reference product' if the line of therapy for a biosimilar is higher than its reference product or if the biosimilar is not covered by the health plan, and 'no more restrictive than the reference product' if otherwise.

We included 12 explanatory variables that have either been shown to be associated with restricted drug coverage relative to the FDA label or were believed to impact payer coverage decisions [16, 22]. We included *Cancer treatment*, *Pediatric population*, and *FDA line of therapy* (first- or second-line) to capture how the indication might impact a plan's decision, and *First biosimilar*, *Years since market launch*, and *Number of competitors* to capture how the dynamics of market competition influenced a plan's decision. *Years since market launch* was calculated as the number of years between a biosimilar market launch and the latest update of the latest coverage decision in the SPEC database. The number of competitors was determined based on the number of biologic therapies (reference or biosimilar) that were available to treat the same indication at the time of the decision to reflect the market landscape of the time. Each biosimilar had at least one competitor for each indication, i.e., its reference product.

We included *Disease prevalence* and *Annual savings per patient* to capture the effect of budget impact on a plan's coverage decision. Disease prevalence was characterized as '< 200,000', '200,000–1,000,000', and '> 1,000,000' in the US. We estimated annual treatment costs using list prices from the Red Book, dosing information from the drug's label for each biologic–indication pair, and treatment duration estimate from the literature (ESM 1). We then calculated the annual cost savings as the difference between the annual treatment cost of the reference product and the biosimilar for each indication.

We included *Coverage of the reference product relative to FDA label* because a plan may be less likely to place additional restrictions on biosimilars if it has already restricted access to the reference product. The coverage restrictiveness of the reference product relative to the FDA label was reported in the SPEC database and was discretized similarly to the outcome measure as 'more restrictive' or 'no more restrictive'. While previous research has shown that health plans were more likely to restrict treatments with higher ICER, only one US-based study that directly compared biosimilars with the reference product was found in the CEA Registry [22, 23]. However, the cost-effectiveness profile of their reference products might also have spillover effects on biosimilar coverage decisions. If the cost-effectiveness profile of the reference product was not established, the plans may favor the biosimilars due to the lower cost. As a result, using the CEA Registry, we included *Cost-effectiveness measure availability of the reference product* as an independent variable.

Finally, characteristics of the health plans themselves might also impact coverage decisions. Therefore, we also included *Plan size* (national/regional) and whether the plan was serviced by one of the Big Three *Pharmacy Benefit Managers* (PBMs) [24]. We categorized PBMs as the 'Big Three' (CVS Caremark, Express Scripts, and OptumRx) and the 'others' because the 'Big Three' were much larger compared with other PBMs and processed approximately 80% of all prescription claims [25]. PBMs are contracted by the health plans to manage the benefits and may provide service to multiple plans. By managing substantially larger numbers of lives, the 'Big Three' enjoy a large negotiating power that may enable them to secure more discounts from the manufacturer and pass some of the discounts to the contracted health plans, which alters the cost to the plans and thereby their preferences. While the role of PBMs is smaller in the biologics market than for small molecule drugs, as many biologic products are provider-administered, evidence suggested that PBMs were still influencing the biosimilar adoption [26]. For example, if a drug is dispensed by a retail pharmacy to a patient, who then carries it to the administration site (known as 'brown bagging'), PBMs would be able to influence product choice [27].

2.3 Statistical Analysis

All analyses were conducted using Stata/SE, version 16.0. Descriptive analyses were performed on all variables of interest. Results were stratified by coverage restrictiveness and compared using appropriate statistical tests (*t* tests and Chi-square tests). We then conducted multivariate logistic regression at the decision level to assess factors associated with the likelihood of more restrictive coverage decisions for the biosimilar compared with its reference product, by commercial health plan. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported, and *p* values below 0.05 were considered significant.

We evaluated the model performance by assessing goodness-of-fit and multicollinearity (ESM 2). Using log-likelihood and McFadden's adjusted R^2, we also compared alternative model specifications by excluding

variables not obtained from the SPEC database to address potential uncertainties of the variables (ESM 3).

3 Results

3.1 Sample Characteristics

We identified a total of 1181 biosimilar coverage decisions by 17 health plans from the SPEC database (Table 1). These decisions covered 19 biosimilars, corresponding to 7 reference products and 28 indications (ESM 1). The majority of these decisions were covered through medical benefits, although some products could also be simultaneously covered through pharmacy benefits [28, 29]. Among all biosimilar coverage decisions, 229 (19.4%) were covered more restrictively than their reference products. Among all the biosimilar–indication pairs covered by each health plan, the proportion of the coverage being more restrictive relative to the reference product ranged from 0 to 46.1% (Table 1). Of the 17 health plans, 6 plans (35.3%) imposed exclusions or step therapy restrictions on biosimilars for < 10% of all coverage decisions, while 5 plans (29.4%) imposed restrictions on biosimilars for more than 30% of all coverage decisions.

Without adjustment to any other factors, most of the variables were significantly associated with the likelihood of the biosimilar being more restricted in coverage relative to the reference product, except for *years since market launch*, *cost-effectiveness measure availability*, and *plan size* (Table 2). More than half (55.9%) of the decisions were for *cancer treatments* and 16.3% of the decisions were indicated for *pediatric populations*. Almost half (45.0%) of the decisions pertained to the *first biosimilar entrant* of the market (characterized by the biologic-indication pair) and 68.1% of the decisions concerned biosimilars with more than three competitors in the market. The majority of the decisions concerned *diseases with* prevalence > 1,000,000 in the US, whereas savings were more evenly distributed among the categories. Most of the biosimilar coverage decisions corresponded to a coverage restriction of their reference product relative to the FDA label (71.7%) and had *cost-effectiveness measures available* for their reference product (78.8%). More than half of the decisions were made by *regional health plans* (58.8%).

Table 1 Variation in biosimilar coverage by included health plans

Health plan	Payer size	Serviced by one of the Big Three PBMs[a]	Coverage policies, *N*	Coverage no more restrictive than the reference product, *N* (%)	Coverage more restrictive than the reference product, *N* (%)
Aetna	National	Yes	76	54 (71.1)	22 (29.0)
Anthem	National	No	55	37 (67.3)	18 (32.7)
BCBSFL	Regional	No	73	63 (86.3)	10 (13.7)
BCBSMA	Regional	Yes	75	73 (97.3)	2 (2.7)
BCBSMI	Regional	Yes	60	57 (95.0)	3 (5.0)
BCBSNC	Regional	No	72	64 (88.9)	8 (11.1)
BCBSNJ	Regional	No	76	74 (97.4)	2 (2.6)
BCBSTN	Regional	Yes	66	50 (85.5)	16 (24.2)
CareFirst	Regional	Yes	66	42 (63.6)	24 (36.4)
Centene	National	No	68	68 (100.0)	0 (0.0)
Cigna	National	Yes	76	76 (100.0)	0 (0.0)
Emblem	Regional	Yes	64	39 (60.9)	25 (39.1)
HCSC	National	No	60	43 (71.7)	17 (28.3)
Highmark	Regional	No	76	59 (77.6)	17 (22.4)
Humana	National	No	76	41 (54.0)	35 (46.1)
IndepBC	Regional	No	66	39 (59.1)	27 (40.9)
United	National	Yes	76	73 (96.1)	3 (4.0)
Total	–		1181	952 (80.6)	229 (19.4)

Payer size and PBM servicing data were retrieved from the respective health plans' websites in December 2022. Percentages may not add up to 100% due to rounding

PBM pharmacy benefit manager

[a]The Big Three included CVS Caremark, Express Scripts, and OptumRx

3.2 Determinants of Coverage

After controlling for other variables, health plans were less likely to impose coverage exclusions or step therapy restrictions compared with the reference product on biosimilar–indication pairs that were indicated for *cancer treatment* (OR 0.019, 95% CI 0.008–0.041), but were more likely to do so if the indication was for the *pediatric population* (OR 11.558, 95% CI 3.906–34.203) (Table 3).

Biosimilars that were the *first entrant to market* (OR 0.225, 95% CI 0.118–0.429) and that had two *competitors* (reference product + another biosimilar; OR 0.060, 95% CI 0.006–0.586) were less likely to have coverage restricted relative to their reference products. Plans were more likely to impose restrictions if the biosimilars were indicated for a disease with *prevalence > 1,000,000* in the US (OR 2.067, 95% CI 1.060–4.029), but were less likely to place restrictions if the biosimilars could generate *savings of more than $15,000* (OR 0.171, 95% CI 0.057–0.514). If the health plan had already restricted the coverage of the reference product for an indication compared with the FDA label, then the coverage of the biosimilar was less likely to be more

Table 2 Coverage decision characteristics

Characteristics	Total, no. (%)	Biosimilar has no more restrictions than biologic, no. (%)	Biosimilar has more restrictions, no. (%)	*p* values
N	1,181	952	229	–
Cancer treatment	660 (55.9)	625 (65.7)	35 (15.3)	< 0.001
Pediatric population	192 (16.3)	129 (13.6)	63 (27.1)	< 0.001
FDA line of therapy				< 0.001
1	968 (82.0)	838 (88.0)	130 (56.8)	
2	213 (18.0)	114 (12.0)	99 (43.2)	
First biosimilar	531 (45.0)	480 (50.4)	51 (22.3)	< 0.001
Years since market launch, mean (SD)	2.5 (1.5)	2.5 (1.5)	2.6 (1.6)	0.362
No. of competitors				< 0.001
1	13 (1.1)	10 (1.1)	3 (1.3)	
2	364 (30.8)	361 (37.9)	3 (1.3)	
3+	804 (68.1)	581 (61.0)	223 (97.4)	
Disease prevalence				0.009
< 200,000	242 (20.5)	212 (22.3)	30 (13.1)	
200,000–1,000,000	243 (20.6)	191 (20.1)	52 (22.7)	
> 1,000,000	696 (58.9)	549 (57.7)	147 (64.2)	
Annual savings per patient				< 0.001
< $5,000	293 (24.8)	258 (27.1)	35 (15.3)	
$5,000–$9,999	350 (29.6)	294 (30.9)	56 (24.5)	
$10,000–$14,999	302 (25.6)	220 (23.1)	82 (35.8)	
> $15,000	236 (20.0)	180 (18.9)	56 (24.5)	
Coverage of the reference products related to FDA label				< 0.001
Not more restrictive	334 (28.3)	208 (21.9)	126 (55.0)	
More restrictive	847 (71.7)	744 (78.2)	103 (45.0)	
Cost-effectiveness measure availability of the reference product				0.549
Available	930 (78.8)	753 (79.1)	177 (77.3)	
Not available	251 (21.3)	199 (20.9)	52 (22.7)	
Plan size				0.932
National	487 (41.2)	392 (41.2)	95 (41.5)	
Regional	694 (58.8)	560 (58.8)	134 (58.5)	
Pharmacy benefit manager				0.048
Big Three[a]	559 (47.3)	464 (48.7)	95 (41.5)	
Others	622 (52.7)	488 (51.3)	134 (58.5)	

Percentages may not add up to 100% due to rounding. *T* tests and chi-square tests assessed the difference in characteristics by coverage decisions

[a]Big Three included CVS Caremark, Express Scripts, and OptumRx

restricted than the reference product for the same indication (OR 0.065, 95% CI 0.038–0.109). If there were *no relevant cost-effectiveness data* for the health plans to review, then they were less likely to impose greater restrictions on the biosimilars (OR 0.066, 95% CI 0.023–0.186). Finally, health plans whose pharmacy benefit was not managed by the 'Big Three' were more likely to impose greater restrictions on the biosimilars (OR 1.683, 95% CI 1.129–2.507).

In alternative specifications (ESM 3), we excluded variables that were not innate in the SPEC databases to assess model fit and robustness of the results. Exclusion of each of those variables resulted in a lower adjusted R^2, suggesting a better fit by the model that included all proposed variables. There are some variations among the specifications. For example, when *Cost-effectiveness measure availability of the reference product* was excluded, the result for *Pediatric population* was no longer significant, which could result from a relatively high correlation between the two variables ($\rho = 0.50$), but overall, we observed a good level of robustness among different specifications. For example, biosimilars with a cancer indication and biosimilars that were first to the market were less likely to be restricted relative to the reference product in all specifications.

Table 3 Characteristics associated with more restrictive coverage

	Odds ratio (95% CI)
Total, *N*	1181
Cancer treatment	0.019** (0.008–0.041)
Pediatric population	11.558** (3.906–34.203)
FDA line of therapy	
1	Reference
2	0.521 (0.270–1.007)
First biosimilar	0.225** (0.118–0.429)
Years since market launch	0.823 (0.659–1.028)
No. of competitors	
1	Reference
2	0.060* (0.006–0.586)
3+	3.194 (0.462–22.082)
Disease prevalence	
< 200,000	Reference
200,000–1,000,000	2.000 (0.854–4.685)
> 1,000,000	2.067* (1.060–4.029)
Annual savings per patient	
< $5,000	Reference
$5,000–$9,999	0.534 (0.273–1.046)
$10,000–$15,000	0.474 (0.213–1.055)
> $15,000	0.171** (0.057–0.514)
Coverage of reference product relative to FDA label	
Not more restrictive	Reference
More restrictive	0.065** (0.038–0.109)
Cost-effectiveness measure availability of the reference product	
Available	Reference
Not available	0.066** (0.023–0.186)
Plan size	
National	Reference
Regional	1.511 (0.981–2.329)
Pharmacy benefit manager	
Big Three[a]	Reference
Other	1.683* (1.129-2.507)

CI confidence interval

*$p < 0.05$, **$p < 0.01$

[a]Big Three included CVS Caremark, Express Scripts, and OptumRx

4 Discussion

To our knowledge, this is the first paper that examines the factors associated with US commercial health plan biosimilar coverage. We found substantial variations in biosimilar–indication coverage. According to the FDA, biosimilars are as well tolerated and effective as the original biologic [30]. Given that their list prices tend to be lower than those of their reference products, biosimilars would generally be expected to receive comparable, if not more favorable, coverage compared with their reference products. When coverage of biosimilars is more restricted relative to their reference products, their potential to increase access by reducing the cost of treatment is reduced. Furthermore, the coverage variation may also negatively impact patient access to care (e.g., patients having to switch treatments when changing plans) and increase the workload for physicians and hospitals when administering and stocking the biosimilars [31, 32]. A number of factors may contribute to a more restrictive biosimilar coverage decision. Discounts to reference products following biosimilar entry have been documented in the past [33]. Alternatively, the manufacturer of the reference product may bundle biologics facing biosimilar competition with another blockbuster drug, and negotiate coverage of both treatments jointly [34, 35]. Some health plans may also favor the reference products due to a lack of experience with biosimilars and comparably limited real-world evidence supporting their use, since even small alterations to the manufacturing and formulation processes can result in adverse effects [36, 37].

We identified multiple drivers of commercial plans' coverage decisions of biosimilars relative to that of their reference products. Health plans were less likely to impose restrictions on biosimilars for cancer treatment. This is consistent with previous research showing cancer treatments are usually received favorably and are covered equally or more generously than the FDA label [16, 38, 39]. On the other hand, we found that plans were more likely to impose restrictions on biosimilars for pediatric use, while past literature suggests the opposite for all specialty drugs [16]. One potential explanation is that health plans are more cautious in

the pediatric patient population or have developed favorable coverage terms for reference biologics in such indications. Further investigation is warranted to explain this finding.

Health plans' coverage decisions are also influenced by market competition. The first biosimilars to enter market are less likely to have more restrictive coverage. A potential explanation for this is that the first biosimilar entrant has more time to establish its real-world safety and effectiveness profile and hence gain more trust from the plans. In addition, first-to-market products may be favored due to provider prescribing habits as well as negotiated discounts (e.g. through preferred placement on formularies or favorable rates negotiated by PBMs) [40, 41]. These factors may increase the plans' willingness to offer non-restrictive coverage.

Overall budget impact may be considered by health plans, but only biosimilars whose list price savings were higher (relative to reference products) than $15,000 or more per patient per year were significantly less likely to be restricted in coverage. This suggests that the likelihood of coverage is highest where cost savings are relatively the highest (before discounts and rebates) [42]. However, conditional on list price savings, plans were actually more likely to impose restrictions on biosimilars indicated for diseases with higher prevalence. This is consistent with previous research, which reported a higher likelihood of being restricted for non-orphan drugs relative to orphan drugs [43]. This may seem counterintuitive since high disease prevalence would mean a larger savings potential. However, since diseases with higher prevalence may be larger drivers of spending for health plans, plans may have negotiated relatively more favorable prices for existing reference products and thus be more cautious when providing access to a biosimilar product [44].

If a plan imposes restrictions on the reference product relative to the FDA label, this may imply the plan's preference for the biosimilar. Indeed, we observed that biosimilars whose reference products were covered more restrictively were less likely to be restricted themselves. Previous research has shown that cost effectiveness was also considered by the health plans when determining coverage restrictiveness [22, 45]. However, the specific ICER is less relevant in this scenario because the biosimilar and the reference product would differ primarily by the cost (net price) but have very similar effectiveness [46, 47]. Nonetheless, in our model, the availability of cost-effectiveness evidence is significantly associated with less restrictive coverage. This may reflect a concern about the lack of evidence on value or a concern about low value due to the potential publication bias (since most published analyses report favorable ICERs, those without any ICER estimates are less likely to be cost effective [48]). In either case, when the value of the reference biologic has not been formally established, health plans favor biosimilars.

Large PBMs such as the 'Big Three' possess significant power in drug price negotiation. By leveraging access to the number of lives managed by themselves, larger PBMs are able to secure larger rebates that can be passed to the health plans, thereby reducing the cost of coverage for health plans [49]. This power is attenuated for biologics because many biologics are administered by providers and are outside of the PBM-retail pharmacy payment channel [26]. However, there may be exceptions. For example, trastuzumab can be administered via intravenous infusion in hospital or via subcutaneous injection at home [28]. The subcutaneous formulation of trastuzumab is likely to be covered through the pharmacy benefit, preventing further differentiation between the medical benefit and the pharmacy benefit. Additionally, biologic products dispensed via 'brown bagging' are adjudicated by the PBMs and therefore may be another channel PBMs can impact biosimilar adoption. Our findings that health plans whose pharmacy benefits were managed by the 'Big Three' PBMs were less likely to impose restrictions on biosimilar coverage relative to the reference product suggests that smaller PBMs, who are less likely to secure large rebates, may favor reference products. This may seem counterintuitive since PBMs with larger negotiating power should favor the pricier reference products to obtain more rebates. However, it has been posited that the bargaining power of larger PBMs may be so significant that biosimilar manufacturers may sometimes raise list prices, and hence rebates, to obtain a place on the formularies of large PBMs. This would leave smaller PBMs with higher list prices but smaller rebates due to their relatively smaller bargaining power, in which case the biosimilars bring less value to them [50]. This may explain how PBMs' profit motive driven by rebates may slow down biosimilar adoption and hinder price competition.

4.1 Limitations

Our study has several limitations. First, we only considered biosimilars that were approved through the 351(k) abbreviated pathway in our analysis. However, other biologics exist that are similar to biosimilars but were approved in a standalone 351(a) biologics license application (BLA). They may be *de facto* a part of the biologic–indication market without the biosimilar status. For example, tbo-filgrastim provides similar effectiveness to filgrastim and competes with filgrastim for treating neutropenia [51]; however, it was not considered a biosimilar and was excluded from our analysis because its application was filed before the biosimilar approval pathway was established. Second, we calculated annual savings using the list prices, which might not reflect the true savings to the health plans since plans generally obtain biologics at

prices lower than their list prices [52]. While estimates of net prices are available in other data sources, they typically provide information for fewer biologic products than those included in our analysis. Therefore, we used list prices instead to avoid selection bias. In addition, while we used the latest list price information from the Red Book, the price may have changed by the time of the coverage decision. Third, we estimated annual per-patient savings for each biosimilar–indication pair using the dosing information on the FDA label, but this may not reflect the actual utilization pattern for some populations. Fourth, our outcome variable accounts for exclusions and step therapies but health plans may use other utilization management strategies to restrict biosimilar access, e.g., prior authorization and tiering, that are not distinctly captured in the SPEC database. However, since all drugs in the SPEC database are subject to coverage policies, i.e., documents that outline the criteria patients must meet in order to be eligible for the therapy, it is safe to assume that some form of prior authorization is required for all drugs in this analysis. Fifth, our study only evaluated a sample of the largest commercial plans but not Medicare, Medicaid, or VA plans. Therefore, our findings may not be generalizable to public health plans or to all commercial health plans in the US. Sixth, our study only included seven reference products, which may have impacted the results. The biosimilar coverage landscape may change as more biosimilars become available in the future. Seventh, PBMs' involvement in the medical benefit (e.g., 'brown bagging') and some products' dual administration mechanism (e.g., trastuzumab) made it difficult to distinguish between pharmacy and medical benefits. Eighth, other drivers of coverage, including the quality of clinical and real-world evidence and resource utilization, may contribute to plans' decision making, which we have not accounted for [53].

5 Conclusion

We found substantial variation in how biosimilars are covered by US commercial health plans included in the Tufts Medical Center's SPEC database. Our study identified a number of factors associated with health plan decision making related to biosimilar coverage, including cancer treatment, pediatric population, and coverage restriction of the reference products. Future research is needed to identify the effects of such restrictions and other market forces (such as price negotiations by commercial plans and PBMs) on the efficiency of the market and resulting patient access to costly biologic therapies.

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Declarations

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Conflict of interest Tianzhou Yu and Shihan Jin report receiving fellowship stipend support from AbbVie that was unrelated to this work. Chang Li, James D. Chambers, and Jakub P. Hlávka have no conflicts of interest to report.

Ethics approval This was an observational study, therefore no Ethics Committee review was required.

Consent to participate Not applicable.

Consent to publish Not applicable.

Data availability The data that support the findings of this study are available from the Center for the Evaluation of Value and Risk in Health (CEVR) at Tufts Medical Center in Boston and from Merative™ Micromedex® RED BOOK®.

Code availability The code used for data analysis is available from the corresponding author on reasonable request.

Author contributions JPH conceptualized the study and acquired the data. JPH, TY, SJ, and CL contributed to the planning of the manuscript. TY and SJ conducted the data analysis. TY led the manuscript and wrote the first draft. JPH, SJ, CL, and JDC provided revisions to the manuscript. All authors reviewed and approved the final version of the manuscript.

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