

# Provider Differences in Biosimilar Uptake in the Filgrastim Market

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Accounting for 38% of all prescription drug spending in 2015 and 70% of drug spending growth from 2010 to 2015, biologic drugs are fueling interest in policies to develop and use biosimilars.<sup>1</sup> Biosimilars are clinically equivalent therapeutic alternatives to biologics, and some policy makers have conjectured that biosimilars can reduce drug spending, as generics have done for small molecules.<sup>2-4</sup> Although biosimilars are widely prescribed in Europe, they are less common in the United States, in part because of regulatory and developmental differences. As of May 2019, the FDA had approved 19 biosimilars, whereas the European Medicines Agency had approved 61.<sup>5</sup> Of the 19 US-approved biosimilars, only 7 had been launched by May 2019.

The penetration of approved biosimilars has also disappointed some observers. Many approved biosimilars in the United States experience delayed launches because of patent litigation. For example, 3 approved biosimilars to trastuzumab (Herceptin), a therapy for early-stage breast cancer, faced patent infringement litigation before coming to market. Early surveys suggest that uptake has been hampered by factors such as insufficient provider awareness and lackluster price competition.<sup>6,7</sup> Although biosimilars appear to generate some reductions in net prices, prices may not decline as quickly or significantly as some expect.<sup>8</sup> Recently, some investigators have even suggested that biosimilars should be abandoned altogether in favor of government-imposed price controls on originator biologics once their patent protection has lapsed.<sup>9,10</sup>

Assessing the viability of the US biosimilar market requires a better understanding of factors that have affected biosimilar adoption. Once a biosimilar has regulatory approval, providers play a key role in the decision to prescribe it or its reference biologic.<sup>11</sup> In many cases, biologics and their biosimilars are physician administered, and physicians have discretion over which drug to prescribe. Even when a biologic is filled at a retail pharmacy, pharmacists cannot automatically substitute an approved biosimilar for a biologic prescription, as they can do for generic versions of small molecule drugs, because the FDA has not yet established that any biosimilars and biologics on the market are interchangeable; pharmacists must dispense only the drug prescribed by the provider.<sup>12</sup> In July 2018, then–FDA

## ABSTRACT

**OBJECTIVES:** To identify differences in biosimilar uptake across providers and to examine the association between provider biosimilar uptake and observable practice-level characteristics.

**STUDY DESIGN:** A retrospective analysis of 100% of a commercial medical claims database from June 2015 to June 2018.

**METHODS:** We focused on providers of biologic (Neupogen) and biosimilar (Zarxio) filgrastim. We compared trends in biosimilar uptake across 2 dimensions: provider's place of service and provider's prescribing exclusivity. We then used multivariate regression analysis to estimate the association between any biosimilar uptake and practice-level characteristics, controlling for geography and time fixed effects.

**RESULTS:** Relative to hospital-based providers, office-based providers were earlier and quicker adopters of the biosimilar filgrastim. Across all places of service, providers predominantly prescribed either the biosimilar or biologic, exclusively, for all their patients. Any biosimilar uptake was more common among providers in office-based settings, providers with larger practice sizes, and providers with a higher share of health maintenance organization patients, nonwhite patients, and younger patients.

**CONCLUSIONS:** This study uncovers important associations between provider practice characteristics and biosimilar uptake. Our findings suggest that provider awareness and incentives can be important levers to strengthen US biosimilar market penetration and competition.

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Commissioner Scott Gottlieb, MD, concluded that “the ability for [biosimilars] to penetrate clinical practice, and gain acceptance, is still not firm,” and the FDA’s Biosimilar Action Plan consequently prioritized resources to improve provider understanding of biosimilar drugs.<sup>13,14</sup>

In this study, we explore the dynamics of biosimilar uptake. Our study represents the first provider-specific analysis of the US market uptake of a biosimilar drug relative to its biologic.

Although our analysis cannot uncover causal relationships between provider characteristics and biosimilar uptake, it identifies factors that are associated with biosimilar use. Uncovering any such relationship is a necessary first step in highlighting whether provider incentives can be used to increase biosimilar adoption.

## METHODS

### Study Sample

We focus on the uptake of the first US-approved biosimilar drug, Zarxio (filgrastim-sndz), the only biosimilar in the United States with more than 2 years of data by 2018. Zarxio is a biosimilar to Neupogen (filgrastim), a man-made granulocyte colony-stimulating factor (G-CSF) used to treat conditions such as febrile neutropenia. G-CSF drugs are predominantly administered by physicians in an outpatient setting to patients with cancer who are also receiving chemotherapy or undergoing bone marrow transplants or to patients with severe chronic neutropenia.<sup>15</sup>

First approved in the United States in 1991, Neupogen’s US patent expired in December 2013. Granix (tbo-filgrastim), which is not considered a biosimilar to Neupogen in the United States, entered the US market in November 2013. Although Granix’s structure, formulation, and mechanism do not differ significantly from Neupogen’s, Granix was reviewed prior to the adoption of the Biologics Price Competition and Innovation Act of 2009.<sup>16</sup> As such, it was approved through the biologics license pathway, and it was approved for only 1 of the 5 filgrastim indications.<sup>17</sup> Therefore, Granix covers a different on-label market than Neupogen. In contrast, Zarxio—approved in March 2015 and launched in September 2015—was the first drug approved through the biosimilar pathway, and it was approved for all 5 of the filgrastim indications. Because our focus is on the US biosimilar market, our analysis focuses on Neupogen (the biologic) and Zarxio (its biosimilar). However, in the **eAppendix** (available at [ajmc.com](http://ajmc.com)), we show that including Granix in our sample does not materially change the results of our analysis.

### Data

Our primary data came from the 100% sample of a commercial medical claims database from July 1, 2015, to June 30, 2018, covering approximately 9 million commercial and Medicare Advantage members. We used only claims for injection or infusion of filgrastim products (Neupogen and Zarxio). We also examined data on the

## TAKEAWAY POINTS

- ▶ After 3 years, the share of filgrastim claims that are biosimilar rose to 60% among office-based providers and 49% among providers at outpatient hospitals.
- ▶ Very few providers simultaneously offered both biologic and biosimilar filgrastim; providers generally prescribed only 1 version.
- ▶ Office-based settings and health maintenance organization contracting are associated with increased biosimilar uptake and should be further examined.

average sales price (ASP) of filgrastim products from CMS ASP Drug Pricing Files.

### Approach

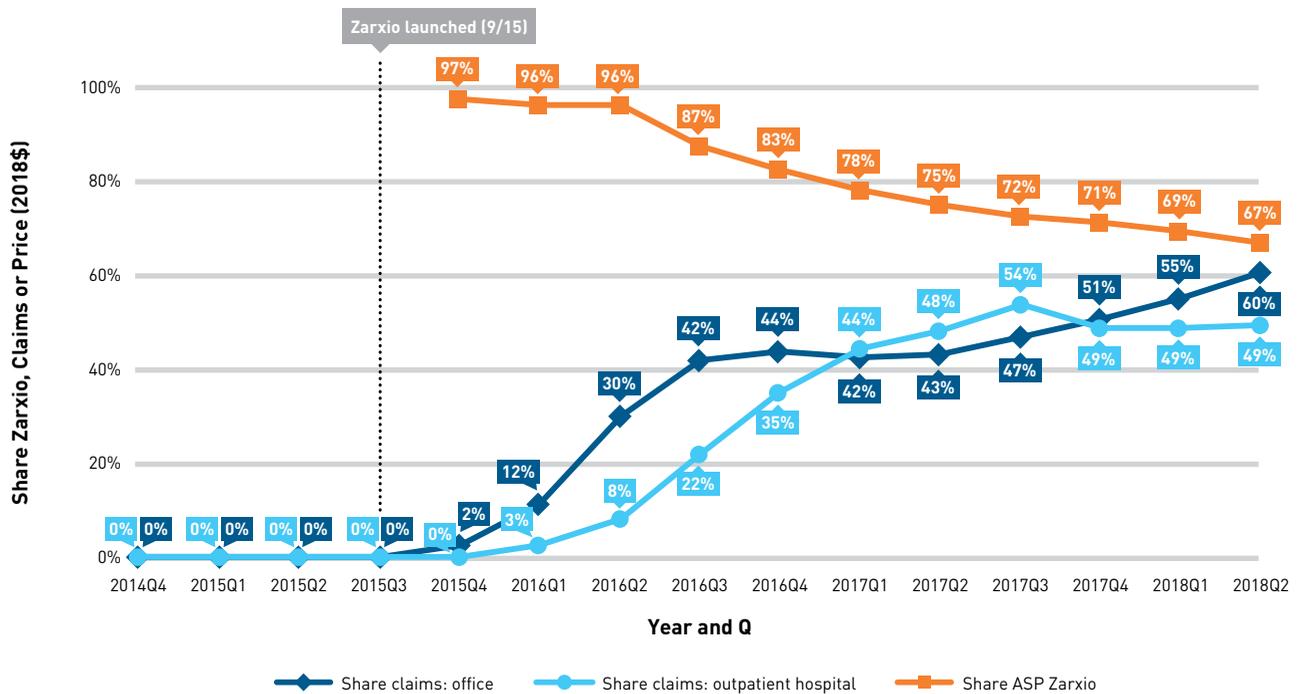
We assessed trends in biosimilar filgrastim uptake in relation to trends in the relative biosimilar ASP. We considered 2 dimensions of provider biosimilar uptake. In each quarter, we first categorized filgrastim providers as being based in a physician office or outpatient hospital. We omitted subgroup analyses for other facilities, which constituted only 2% to 4% of the sample. Second, we examined separate trends for providers who, in a given quarter, administered (1) only the biologic Neupogen, (2) only the biosimilar Zarxio, or (3) both Neupogen and Zarxio.

Next, with the data at the provider-year level, we used univariate linear regressions to test for mean differences in provider practice characteristics between providers who administered the biosimilar Zarxio (either partly or exclusively) and those who exclusively provided the biologic. We weighted each provider by the number of filgrastim claims administered to adjust for those with larger market shares. Provider practice characteristics included an indicator equal to 1 if the provider was office based, the total number of filgrastim claims administered, the share of each practice’s filgrastim claims reimbursed under a health maintenance organization (HMO) contract, and the average sociodemographic characteristics of each provider’s patients receiving filgrastim, including patient age, share male, and share black, Hispanic, or Asian.

We estimated ordinary least squares regressions in which the dependent variables described provider biosimilar uptake. Our key independent variables were the aforementioned provider practice characteristics, plus Census division and year fixed effects to account for variation across geographies and over time. By controlling for geographic variation, we can identify whether differences across regions—due to heterogeneity in negotiated rebates and discounts, physician preferences, disease prevalence, or other factors—can explain some of the variation in biosimilar uptake.<sup>18-20</sup>

## RESULTS

Using data through mid-2018, we found that the uptake of Zarxio has increased steadily since its launch in September 2015 (**Figure 1**). After 3 years, the share of filgrastim claims that are biosimilar (ie, Zarxio as a share of Zarxio and Neupogen claims) rose to 60%

**FIGURE 1.** Share of Biosimilar Filgrastim Claims and Relative Price, by Provider Place of Service\*

ASP indicates average sales price; Q, quarter.

\*Data from a commercial medical claims database and the CMS ASP Drug Pricing Files. Zarxio pricing is first available in Q4 of 2015, and the share ASP equals the ASP for 1 mcg of Zarxio divided by that for Neupogen. Share claims equals number of Zarxio claims divided by number of all filgrastim (Zarxio and Neupogen) claims, by place of service.

among office-based providers and 49% among providers at outpatient hospitals. When additionally considering Granix in the filgrastim market, we still find that the share of biosimilar filgrastim was higher among office-based than outpatient hospital-based providers, at 54% and 35%, respectively (eAppendix Figure 1). This biosimilar adoption rate is within the range of Europe's experience: After 3 years, biosimilar filgrastim garnered between 45% and 87% of European market share, depending on the country.<sup>21</sup> The observed increase in Zarxio adoption reflects increases in both relative and absolute levels; the total count of filgrastim claims (ignoring the cyclicity of claims across quarters) has been increasing across both places of service since mid-2016 (eAppendix Figure 2).

Notably, although the biosimilar's ASP had fallen to 67% of the biologic's ASP by mid-2018, office-based providers began adopting biosimilar filgrastim prior to any significant reduction in ASP. Office-based providers were also earlier and more rapid adopters than hospital-based providers, whose adoption of the biosimilar more closely mirrored reductions in ASP. As office-based adoption rates have continued to rise, adoption rates in the hospital setting have plateaued at around 50%. These differential adoption patterns suggest a nuanced and dynamic market in which factors besides price play an important role in encouraging or discouraging biosimilar uptake.

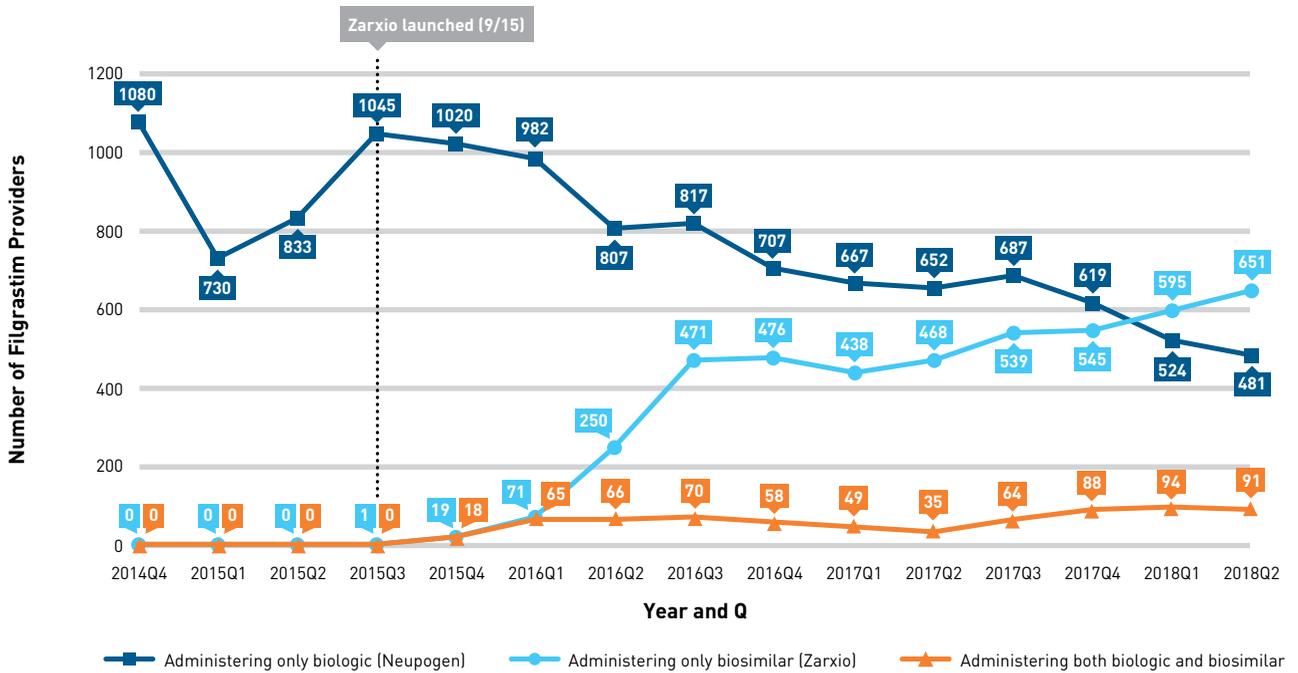
Next, we consider differences in biosimilar uptake by the provider's prescribing practices. Figure 2 shows that the uptake of biosimilar

filgrastim occurred predominantly through providers who treated all their patients receiving filgrastim with the biosimilar version. Very few providers simultaneously offered both biologic and biosimilar filgrastim. By quarter 2 of 2018, approximately 61% (742 of 1223) of providers were offering some Zarxio; of this group, 88% (651 of 742) were offering exclusively Zarxio. This pattern is evident across both office- and hospital-based providers (eAppendix Figure 3).

Table 1 reports summary statistics and univariate differences in practice characteristics across providers who did not adopt Zarxio and those who provided some Zarxio. Providers averaged 67 filgrastim claims per year, with those using some Zarxio prescribing more filgrastim (82 claims) than those prescribing no Zarxio (53 claims) (Table 1). On average, 18% of any provider's filgrastim claims were associated with an HMO contract, with that share rising to 22% among those providing some Zarxio compared with 14% among those providing only Neupogen. The average patient receiving filgrastim was 70 years old; 22% were nonwhite, and 42% were male. Relative to providers of only Neupogen, those who administered some biosimilar tended to have patient populations who were younger (by 2 years), more nonwhite (4.9 percentage points), and slightly more male (1.8 percentage points).

The magnitude and significance of these differences persist when controlling for variation across geographic regions and years (Table 2). Relative to hospital-based providers, office-based

**FIGURE 2.** Provider Provision Patterns of Biologic or Biosimilar Filgrastim<sup>a</sup>



Q indicates quarter.

<sup>a</sup>Data from a commercial medical claims database. We show the number of providers who administer only the biologic filgrastim (dark blue), number of providers who administer only the biosimilar filgrastim (light blue), and those providing both biologic and biosimilar versions (orange).

**TABLE 1.** Summary Statistics, by Provider Type<sup>a</sup>

	(1) All	(2) Providers of Only Neupogen	(3) Providers With Some Zarxio	(4) Difference
	Mean (SD)	Mean (SD)	Mean (SD)	Coefficient (SE)
Number of filgrastim claims per year	67.33 (93.41)	53.42 (58.02)	82.45 (118.81)	29.03*** (0.645)
Provider practice characteristics				
Share of providers who are office based	0.740 (0.439)	0.709 (0.454)	0.773 (0.419)	0.064*** (0.003)
Share HMO	0.179 (0.325)	0.142 (0.288)	0.220 (0.356)	0.078*** (0.002)
Average patient age in years	69.94 (9.24)	70.89 (9.07)	68.90 (9.31)	-1.99*** (0.063)
Share black, Hispanic, or Asian	0.219 (0.295)	0.196 (0.294)	0.245 (0.295)	0.049*** (0.002)
Share male	0.415 (0.313)	0.407 (0.332)	0.425 (0.290)	0.018*** (0.002)
Number of observations	86,420	45,021	41,399	

HMO indicates health maintenance organization.

\*\*\*P < .01.

<sup>a</sup>Data from a commercial medical claims database, quarter 3 of 2015 to quarter 2 of 2018, at the provider-year level, weighted by the number of filgrastim claims per provider. Column 4 shows the result from univariate regressions of the provider characteristic with the dependent variable equal to 1 if the provider provides some Zarxio. In that column, standard errors are shown in parentheses. Stata 14 [StataCorp; College Station, Texas] was used for estimations.

providers were 10.5 percentage points, or 22% (calculated from 0.105/0.479), more likely to have adopted the biosimilar version. This effect size decreases slightly to 21% (0.0993/0.479) after we control for other observables. Larger providers were more likely to adopt Zarxio: An increase of 10 filgrastim claims in the year was associated with a 1.5% ( $[10 \times 0.0007]/0.479$ ) increase in biosimilar adoption. A 10% increase in the share of HMO claims was associated

with a 0.9 percentage point, or 1.9% ( $[10\% \times 0.0899]/0.479$ ), increase in biosimilar adoption.

A practice's average patient characteristics were also associated with biosimilar adoption. A 10-year increase in average patient age and a 10% increase in the share of nonwhite patients were associated with a 6.4% ( $[10 \times 0.0031]/0.479$ ) decrease and a 2.5% ( $[10\% \times 0.122]/0.479$ ) increase in the likelihood of biosimilar adoption, respectively. A

**TABLE 2.** Provider of Zarxio Linear Probability Models\*

Provider and Patient Characteristics	Dependent Variable: Provider Prescribes Some Zarxio (1/0)		
	(1)	(2)	(3)
Place of service is individual office	0.105*** (0.0039)	0.106*** (0.0039)	0.0993*** (0.0039)
Number of filgrastim claims	0.0008*** (0.00002)	0.0008*** (0.00002)	0.0007*** (0.00002)
Share HMO		0.0808*** (0.0052)	0.0899*** (0.0052)
Average patient age			-0.00306*** (0.0002)
Share black, Hispanic, or Asian			0.122*** (0.0055)
Share male			0.0272*** (0.0049)
Year fixed effects	Y	Y	Y
Census division fixed effects	Y	Y	Y
Mean of dependent variable	0.479	0.479	0.479
Number of observations	86,420	86,420	86,420
Mean variance inflation factor	1.22	1.24	1.23

HMO indicates health maintenance organization; Y, yes.

\*\*\* $P < .01$ .

\*Data from a commercial medical claims database, quarter 3 of 2015 to quarter 2 of 2018, at the provider-year level, weighted by filgrastim claims per provider. Models compare filgrastim providers who provide both Zarxio and Neupogen or only Zarxio (= 1) with those who provide no Zarxio (= 0). All regressions control for 3 year dummies and 9 Census division dummies (not reported). Robust standard errors in parentheses. See eAppendix Table 1 for full regression results. Stata 14 (StataCorp; College Station, Texas) was used for estimations.

10% increase in the share of male patients was associated with a negligibly small, although statistically significant, 0.6% ( $[10\% \times 0.0272]/0.479$ ) increase in the likelihood of biosimilar adoption. The full regression results are shown in eAppendix Table 1. A variance inflation factor analysis displayed in eAppendix Table 2 confirms that the predictors examined are not multicollinear.

## DISCUSSION

After 3 years on the market, biosimilar filgrastim was being used in more than 50% of the filgrastim claims in our sample. This adoption rate is markedly higher than what has been documented using less recent Medicare or sales data: Kozlowski et al<sup>22</sup> and Sarshad<sup>23</sup> found 32% and 15% biosimilar penetration, respectively, by quarter 4 of 2016.

We found that at any point in time, most providers were using either the biosimilar or the biologic for all their patients receiving filgrastim. This pattern suggests that, at least within a provider group, patients were unlikely to have been presented with the option to choose between the biologic and the biosimilar, which highlights the importance of the provider's role in biosimilar adoption. It also suggests that, relative to practice-level decisions, patient-specific factors play a considerably smaller role in biosimilar filgrastim adoption decisions.<sup>24</sup> In addition, although lack of information

and widespread physician awareness may be a barrier to biosimilar adoption, our results suggest that, once providers are comfortable with biosimilar use, they tend to adopt biosimilars exclusively, discontinuing any use of the biologic.

Several factors are correlated with provider uptake. In particular, providers with more HMO-based reimbursements were more likely to use the biosimilar, perhaps because capitation strengthens incentives to reduce the costs of care. Providers with patients who might be more burdened by the costs of care, such as younger patients who do not meet the age-eligibility requirement for Medicare coverage or nonwhite patients of likely lower socioeconomic status, were more likely to use the biosimilar.<sup>25</sup> Uptake of Zarxio also increased with practice size. Because the associations between these factors and provider uptake remained after including region and year fixed effects, it suggests that these factors are not explained by variation over geography or time.

Of note, the largest factor associated with uptake was the provider's office setting. Weaker uptake among hospital-based providers compared with their office-based counterparts suggests that healthcare costs for filgrastim treatments will be higher in hospital-based outpatient settings, a result that is consistent with existing literature documenting higher cancer-related costs in such settings due to differences in product prices.<sup>26,27</sup>

Several factors may explain the differential adoption pattern between office- and hospital-based providers. First, reimbursement formulas differ between the 2 groups. Compared with office-based providers, hospital-based providers are more likely to be reimbursed as a percentage of hospital charges, where the charges are set by the hospitals themselves and include significant profit margins on physician-administered drugs.<sup>28,29</sup> If hospitals charge more for biologic drugs than for biosimilars, their reimbursement will also be higher for biologics, leading to higher profits from using biologics rather than biosimilars in the treatment of commercially insured patients.

The federal 340B program, which provides discounts on outpatient drugs for hospitals that qualify for 340B status, may also play a role in these differential uptake patterns. Depending on the prevalence of 340B program participation among the hospitals versus physician offices in our sample and the changing 340B reimbursement rules over this period, 340B discounts may have weakened hospitals' incentives to adopt biosimilars relative to physician offices, particularly in the early part of our sample. This dynamic would be similar to the observation that providers with fewer HMO contracts have weaker incentives to use a less expensive substitute.

It is also possible that hospital-based providers have slower adoption rates because of institutional barriers such as strict protocols set by hospital pharmacy and therapy committees that may delay more immediate responses to biosimilar availability.<sup>30</sup>

## Limitations

Our study has several limitations. First, we are limited to the observable factors in the data and cannot account for unobserved

determinants, such as provider reimbursements and drug rebates. As such, we cannot pinpoint which of the aforementioned factors are most responsible for the observed difference between office- and hospital-based provider uptake patterns. Second, our analysis focused on Zarxio adoption within hospitals and offices, and our results may not generalize to Zarxio adoption in other places of service or to the adoption of other biosimilar drugs, particularly those administered in predominantly inpatient settings or those for chronic conditions. Third, our results are based on a subset of commercial claims data. Although our data capture a geographically diverse population, they come from a single large insurer, which may not be representative of the commercially or publicly insured populations in the United States.

## CONCLUSIONS

Our study is the first to highlight the provider's role in the uptake of biosimilars. We find that providers who adopt the biosimilar tend to convert all their patients receiving filgrastim to the biosimilar, and we demonstrate that place of service, and its attendant incentives and insurer contracts, are important determinants of biosimilar uptake. These results suggest that provider awareness and incentives can be important levers to increase biosimilar market penetration.

Although frustrations over the slow pace of biosimilar introduction and adoption in the United States have led some to abandon hope that a competitive biosimilar market will produce lower prices, our study findings underscore the need for additional research on the mechanisms of uptake as promising policy targets to strengthen competition in US biosimilar markets.<sup>3,10</sup> ■

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**eAppendix Table 1. Full Regression Results: Provider of Zarxio Linear Probability Models**

	<b>Dependent Variable: Provider Prescribes Some Zarxio (1/0)</b>		
	(1)	(2)	(3)
<b>Year Fixed Effects</b>			
Year 2	0.243***	0.246***	0.245***
	(0.0037)	(0.0037)	(0.0037)
Year 3	0.416***	0.420***	0.415***
	(0.0037)	(0.0037)	(0.0037)
<b>Census Division Fixed Effects</b>			
East North Central	-0.0806***	-0.0770***	-0.0541***
	(0.0051)	(0.0051)	(0.0052)
East South Central	0.0228***	0.0226***	0.0180**
	(0.0082)	(0.0082)	(0.0081)
Middle Atlantic	-0.00255	0.00392	0.0104*
	(0.0061)	(0.0061)	(0.0062)
Mountain	0.226***	0.198***	0.203***
	(0.0056)	(0.0059)	(0.0059)
New England	0.165***	0.174***	0.192***
	(0.0107)	(0.0107)	(0.0109)
Pacific	0.0493***	0.0425***	0.0459***
	(0.0075)	(0.0075)	(0.0073)
West North Central	0.219***	0.197***	0.204***
	(0.0051)	(0.0054)	(0.0054)
West South Central	0.208***	0.202***	0.168***
	(0.0053)	(0.0053)	(0.0055)
<b>Provider Characteristics</b>			
Place of Service is Individual Office	0.105***	0.106***	0.0993***
	(0.0039)	(0.0039)	(0.0039)
Number of filgrastim claims	0.000752***	0.000722***	0.000712***
	(1.52e-05)	(1.57e-05)	(1.57e-05)
Share HMO		0.0808***	0.0899***
		(0.0052)	(0.0052)
Average Patient Age			-0.00306***
			(0.00012)
Share Black, Hispanic, or Asian			0.122***
			(0.0055)
Share Male			0.0272***
			(0.0049)
Constant	0.0448***	0.0345***	0.215***
	(0.0044)	(0.0044)	(0.0140)
R-Squared	0.194	0.196	0.204
Number of Observations	86,420	86,420	86,420

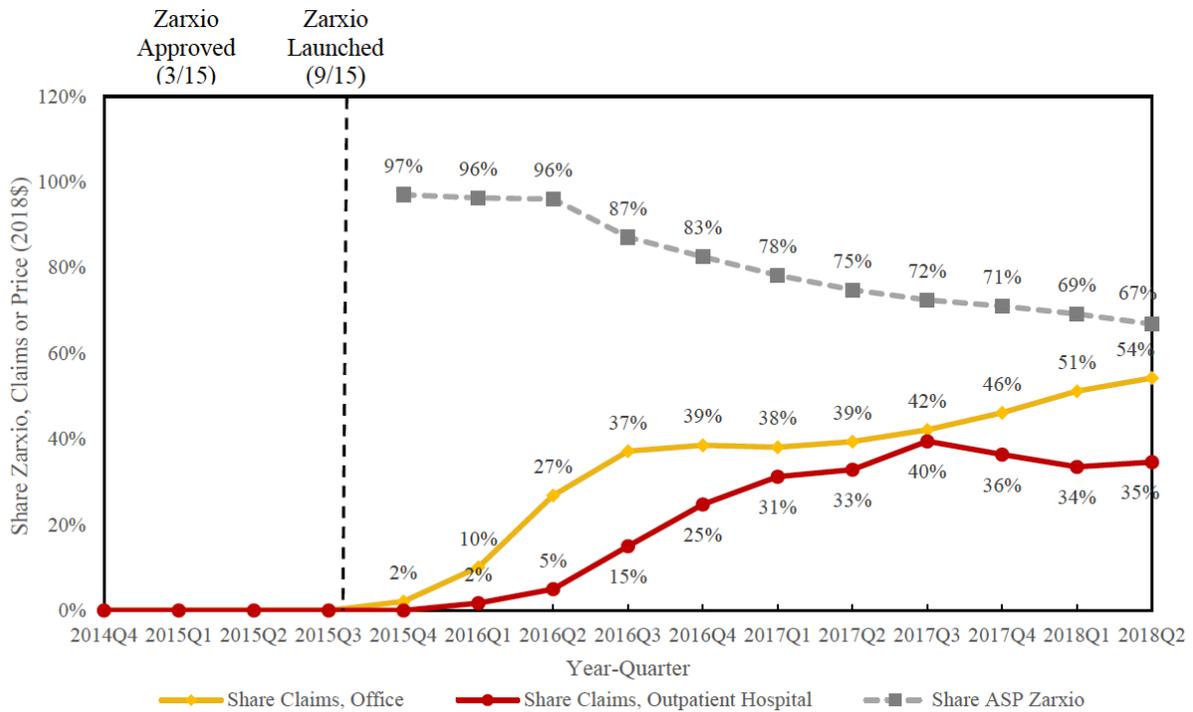
Notes: See notes to Table 2. Reference Census division is South Atlantic.

**eAppendix Table 2.** Variance Factor Analysis Assessing Multicollinearity

<b>Variable</b>	<b>VIF</b>	<b>1/VIF</b>
Place of Service is Individual Office	1.26	0.794
Share HMO	1.26	0.791
Number of Filgrastim Fills	1.21	0.823
Average Patient Age	1.17	0.856
Share Black, Hispanic, or Asian	1.11	0.904
Share Male	1.02	0.984
Year FE		
Year 2016	Reference	Reference
Year 2017	1.46	0.684
Year 2018	1.48	0.674
Division		
East North Central	1.30	0.768
East South Central	1.09	0.921
Middle Atlantic	1.20	0.836
Mountain	1.38	0.725
New England	1.07	0.934
Pacific	1.11	0.901
West North Central	1.38	0.725
West South Central	1.25	0.801
Mean Variance Inflation Factor	1.23	

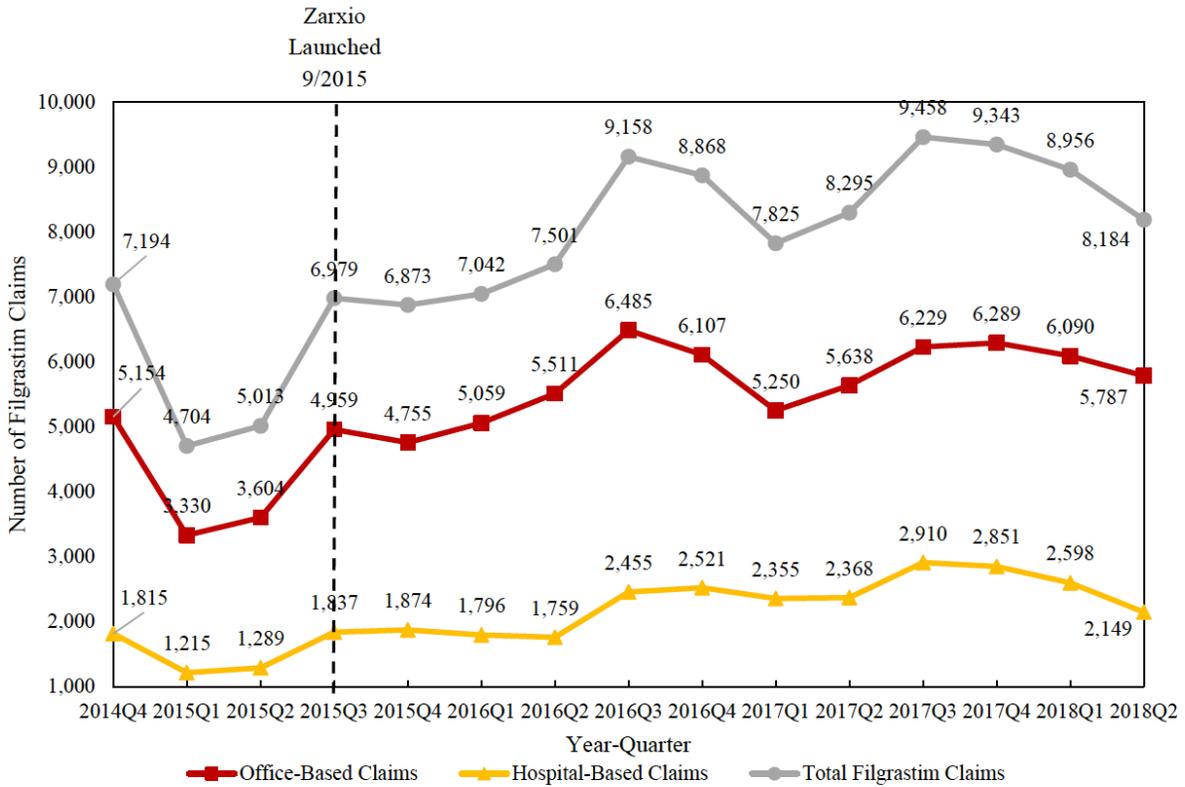
Notes: See notes to Table 2. This table shows the variance factor analysis that corresponds to the regression shown in Table 2, Column 3.

**eAppendix Figure 1.** Share of Zarxio Among Filgrastim and tbo-Filgrastim Claims and Relative Price, by Provider Place of Service



Data from a commercial medical claims database and the Centers for Medicare and Medicaid Services Average Sales Price (ASP) Drug Pricing Files. Zarxio pricing is first available in 2015Q4, and the share ASP equals the ASP for one microgram of Zarxio divided by that for Neupogen. This plot differs from Figure 1 by considering Granix: the share claims equals number of Zarxio claims divided by number of all filgrastim or tbo-filgrastim claims (Zarxio, Neupogen and Granix), by place of service.

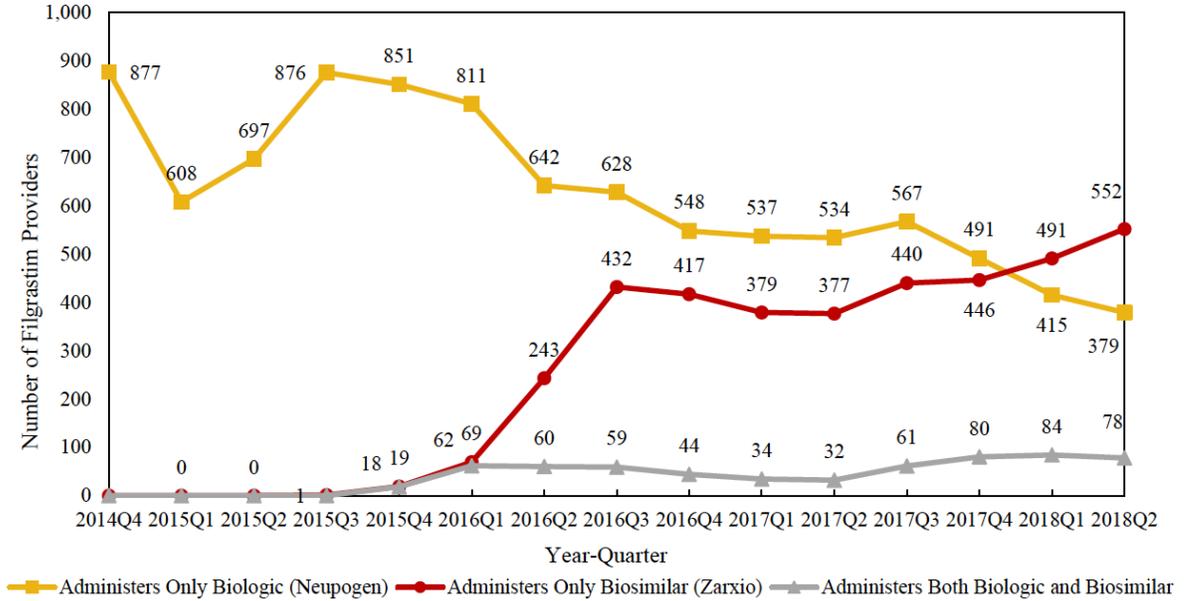
**eAppendix Figure 2. Total Filgrastim Claims, by Place of Service**



Data from a commercial medical claims database. This figure documents the total filgrastim claims in the hospital-outpatient setting (yellow), office setting (red), and all settings (grey) over time. The dotted line at 2015Q3 denotes the time in which the biosimilar filgrastim (Zarxio) was approved.

**eAppendix Figure 3. Provider Provision Patterns of Biologic or Biosimilar Filgrastim, By Place of Service**

**(a) Provider Offices**



**(b) Outpatient Hospital**

