Exploring the uptake of value-based formulary strategies and their application to specialty drugs

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Abstract

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Background: Value-based formularies (VBF) are a way to implement the overarching idea of value-based insurance design (VBID) by tying pharmacy cost-sharing to value based on cost-effectiveness evidence. Empirical evidence over the last decade has shown that this strategy can reduce patient costs, increase drug adherence, and be cost neutral for payers when applied to many traditional drugs, such as antihypertensive and antihyperlipidemic therapies. It is unclear whether these same outcomes could be achieved if VBF strategies were applied to other drugs, such as specialty drugs. Specialty drugs are broadly defined as expensive, complex, and requiring special handling. Their high costs make them an attractive candidate for cost-containment policies such as VBF, however the potential lack of therapy alternatives to some specialty drugs along with the ubiquitous practice of manufacturer patient assistance programs may undermine the influence of payers' cost-sharing strategies.

Objective: This dissertation seeks to evaluate the potential of value-based formulary strategies to effectively improve access and affordability of specialty medications.

Aims: The first aim seeks to estimate the implicit adoption of cost-effectiveness driven value-based formularies in private health insurance (2010-2013) by using a random effects model of the effect of value tier on out-of-pocket costs over time. The second aim seeks to estimate the price elasticity of demand for multiple sclerosis (MS) specialty medications in the Kaiser Permanente Washington system accounting for copay assistance using a two-part model with patient assistance programs as a source of price variation.

Study Implications: This dissertation will provide evidence to stakeholders (particularly payers) regarding 1) the potential utility of value-based formularies in the face of diminishing marginal gains from increased generic drug use, and 2) the impact of patient assistance programs on patient demand for specialty drug therapies and the subsequent implications for applying VBID strategies to specialty medications.

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Chapter 1. INTRODUCTION

Health insurance, introduced in the first half of the 20th century in the United States, started as a way for people to buy protection from the cost of catastrophic health events, and over time grew to include coverage for chronic health conditions, including medication. Most health insurance plans impose some form of patient cost-sharing per health service used or product purchased, in order to prevent moral hazard. The RAND health insurance experiment of the late 1970's provided robust evidence that cost-sharing generally amount affected quantity of health services demanded, a finding that has been mostly corroborated in natural experiments ever since.(1) In the late-1980's, payers started distinguishing cost-sharing amounts among different pharmaceutical products depending on their generic status and the prices negotiated for branded drugs.(2) While this formulary system incentivized generic drug use overall, formulary placement was largely been based on drugs' overall cost. As drug costs increased over the past decade, plans increased copayments to slow the growth of prescription expenditures, which some worried would lead to underutilization of high-value drugs.(3, 4) This disconnect between cost-sharing and clinical value prompted the idea for value-based formularies.

The value-based formulary (VBF) is an insurance design that ties cost-sharing for pharmaceutical products to cost-effectiveness evidence in order to incentivize patients to both use and stay adherent to high-value drugs. This insurance design was first generally posited as "benefit-based copay" by Mark Fendrick and colleagues in 2001.(5) Over time, the framework grew to be called value-based insurance design (VBID), of which VBF would be a specific application. VBID posits that patient OOP costs should be lowered or waived for medications where higher adherence is associated with large reductions in illness or death. Without a cost barrier, patients would be more

adherent to high-value drugs, which could lead to better health outcomes. This could be implemented in a variety of ways, such as providing entire classes of preventive medications, like statins or blood pressure medication, without cost-sharing. VBID could also be implemented by incentivizing patients to choose specific therapies over others within a single medication class based on cost-effectiveness value. In increasing patient adherence to high-value drugs or incentivizing patients to choose more cost-effective alternatives, there would be potential for better health outcomes downstream. While payers might face increased costs upfront from lower cost-sharing, there would be potential for reduced health plan costs later. Elements of this theory have supporting evidence in the literature, via economic theory and empirical evidence.(6-9)

Empirical evidence for the effectiveness of VBFs is largely from programs that target specific patient populations or specific classes of drugs. A 2013 systematic literature review identifying 9 VBID programs applied to diabetes and hypertension medications found these programs increased adherence by an average of 3% within one year and lowered OOP spending, but did not significantly change overall medical spending for patients or payers.(8) A 2018 systematic literature review of VBF programs found 21 studies reporting the impact of value-based insurance design on medication adherence, and found VBID improved medication adherence (0.1%-14.3%) without an effect on total health care spending.(9) Programs highlighted in these reviews focused drug classes with certain characteristics: the drugs were generally inexpensive, had relatively little debate about their high value, and had a positive correlation between medication adherence and positive health outcomes. Several federal government programs have also implemented types of VBID principles, such as demonstration programs in Medicare Advantage and TRICARE.(10, 11)

The 2010 Affordable Care Act also required private payers to cover specified preventive services without copay or contribution toward a deductible.(12)

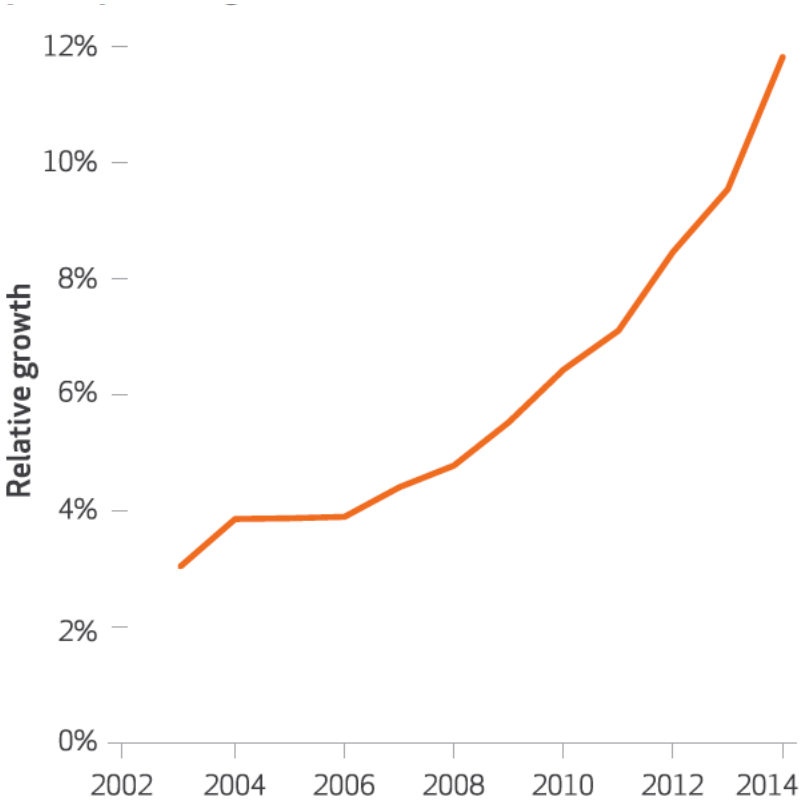
There have been discussions in the literature about expanding value-based insurance design beyond these relatively straight-forward implementations. A 2019 survey found significant shifts toward VBID in large employers while health care experts were calling VBID a major health care trend in the US for the past 10 years.(1, 13) Mark Fendrick, the co-creator of the VBID, posited with colleagues that "further research on the application of VBID to such services would allow policy makers to use it as a complement to existing health reform programs such as bundled payment and initiatives for cost containment."(9) Discussions of expanded application have noted, however, that the success of VBID of VBF depends on two key dynamics: consumers' elasticity of demand to out of pocket costs for a pharmaceutical, and the subsequent relationship between adherence to that pharmaceutical and health outcomes.(9)

Only one program, to my knowledge, has implemented an entire formulary based on cost-effectiveness.(14) Premera Blue Cross, a large non-profit health plan in the Pacific Northwest, implemented a value-based formulary in 2010 that explicitly used cost-effectiveness ranges to determine formulary cost-sharing. Their goal was, in part, to address design limitations of current VBID plans by simultaneously increasing cost-sharing for low-value drugs while decreasing cost-sharing for high-value drugs. They also distinguished value of drugs within classes rather than simply between classes. Analyzing the effects of this intervention, Yeung et al (2017) found that member medication expenditures increased and health plan medication expenditures decreased, resulting in a net decrease in medication expenditures of 10%.(14)

One area of interest for expanding value-based costing principles is specialty drugs, a class of drugs generally defined as expensive, complex, and requiring special handling.(15) Specialty drug use and costs have increased rapidly in the past decades, with the proportion of specialty products in commercial plans quadrupling from 2002 to 2012 (3% to 12%, Figure 1).(16) From 2008 to 2017, the per capita spending on medicine doubled for specialty drugs, and they accounted for one third of all spending on drugs in United States (Figure 2).(17, 18) Of 42 new medicines launched in 2017, 32 were in specialty therapy areas.(18) The increasing cost burden of these drugs have driven many payers to shift drug costs to patients, some by adding a specialty drug tier to their formularies in order to increase coinsurance rates.(3, 19) In discussing the adaptive strategies that payers have taken in light of increasing specialty drug costs, Chambers and colleagues concluded that: "Payers have not yet found the formula for managing specialty drugs. Insurers should continue to experiment with a combination of existing formulary management tools and novel strategies to maximize patient access to specialty drugs while minimizing their cost."(19) According to recent literature reviews, those formulary management tools have not included value-based insurance design, although there is acknowledgement that increased adherence would lead to better clinical outcomes among many specialty drugs indications.(9)

This dissertation, therefore, explores two key questions regarding the potential for expanding the use of value-based insurance design principles in general, and specifically to specialty drugs. The research question in chapter one explores whether there is room and/or interest among private payers in the US to apply VBF principles across drugs in their formulary. Should the first aim provide evidence that there is room for more granularity in tying drug cost-sharing to value among

high-cost drugs such as specialty drugs, the next question is whether it would be feasible to apply VBF to specialty drugs. Given that the success of VBF depends in part on consumers' responsiveness to changes in out-of-pocket spending, the research question in chapter two explores whether patients are responsive to changes in OOP costs for a class of specialty drugs given the widespread use of manufacturer-supplied copayment assistance. The final chapter will summarize the likely opportunities and barriers to applying value evidence to specialty drug cost-sharing and insurance design.



SOURCE Author's analysis of data from the 2003–14 outpatient prescription drug files of the Truven Health Analytics MarketScan Commercial Claims and Encounters Database. **NOTES** A drug was categorized as a specialty drug in a given year if the median reimbursement for a thirty-day fill was at least $600. All dollars were inflation-adjusted to 2014 levels before categorization.

Figure 1.1. Unique specialty drugs as a percentage of total prescription drugs (16)

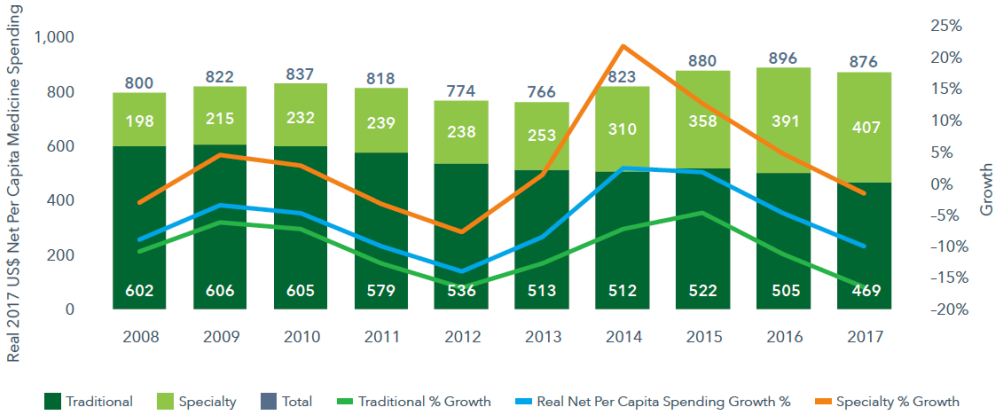


Figure 1.2. Real net per capita medicine spending and growth by product type US$ (18)

Chapter 2. ADOPTION OF COST-EFFECTIVENESS-DRIVEN VALUE-BASED FORMULARIES IN PRIVATE HEALTH INSURANCE 2010-2013

2.1 INTRODUCTION

While prescription drug expenditure rates fluctuate depending on new products and patent expirations, experts project per capita drug spending in the United States to grow between 4%-6% annually through 2024(4). Stakeholders have advanced multiple models to obtain greater value on drug spending, including indication-based pricing and outcomes-based arrangements, while new technologies are subject to budget impact analysis before their uptake(20-22). Because approximately half of Americans have private insurance, private insurance companies have significant potential to influence drug demand and costs(23). Value-based insurance design (VBID), where insurance schemes align patient cost-sharing with the value of services, is one payer-based strategy to improve medication adherence without increasing total health costs(9).

There appears to be some enthusiasm for VBID among private and public payers, with various plans being suggested or implemented (7, 24-28). One particular payer, Premera Blue Cross of Washington, implemented a design known as the Value-Based Formulary (VBF) that used cost-effectiveness analysis (CEA) to determine cost-sharing(29). Copayments for drugs with low (high) ICER, high (low) value drugs were lowered (increased) accordingly. Several studies analyzed Premera Blue Cross' transition from cost-based to value-based insurance formulary in 2010, the only private insurance company to explicitly transition their formulary.(14, 29, 30) They found that their value-based tiering decreased spending on medication per member per month compared to non-VBF tiering, and that medication utilization, health services utilization,

and non-medication expenditures did not change(30). Evidence from programs applying VBID to specific drugs (but not full formularies) is optimistic but not conclusive about the exact benefits of shifting to value-based decision-making in private plans(9).

Beyond those explicitly aligning formulary placement with value evidence, it is unknown to what degree commercial plans at large are using value evidence in decision-making. One study found that two case study formularies were only partially aligned with cost-effectiveness evidence (31). More recently, a study found that drugs exclusion lists in large PBMs were not significantly associated with value evidence(32). Further, there is little published evidence of programs using VBID to discourage use of low-value services and drugs by increasing cost-sharing, although existing studies show this strategy could be cost saving(14, 33). And most studies of VBID focus on a narrow portion of medications used to treat chronic conditions, such as cardiovascular disease, diabetes, or asthma, for which generic alternatives are available(9, 34). There is a gap in the literature regarding formulary-wide alignment with value evidence, and whether cost-sharing is being used to drive behavior around both high-value and low-value drugs.

Insurance plans that implement a type of VBID must be clear about which elements of value they are using. Cost-effectiveness analysis (CEA) is the most widely accepted metric for determining the value of drugs globally, often combined with other aspects of value such as availability of alternative treatments, novelty, and disease severity. CEA is generally a good measure for assessing changes in value trends in benefit design because it can be used across health conditions and has a broad base of data available for many common drugs (35, 36). In a recent

interview regarding value assessment frameworks, private insurance representatives claimed most insurers do not have formal policies regarding the use of CEA research. And while private insurers are under pressure to cover a majority of drugs regardless of value evidence, CEA may inform formulary placement if alternatives exist(37).

To understand the extent to which private insurance companies are aligning (implicitly or otherwise) formulary cost-sharing with evidence of drug value, and factors influencing that shift, we analyzed the out-of-pocket (OOP) costs for medication fills from 2010-2013 using a large commercial claims database and drug-specific cost-effectiveness value designations. If private insurance companies were using cost-effectiveness evidence in formulary placement decisions, we would expect an increasing gap in the nominal amount of cost-sharing between high and low levels of drug value as measured by cost-effectiveness. To our knowledge, this is the first empirical study in a large sample of commercial health plans to evaluate whether OOP costs in the US are aligned with cost-effectiveness estimates. Secondarily, we use our dataset to evaluate the overall cost-effectiveness of drug usage over this period, that is whether the utilization weighted average cost-effectiveness of drugs have changed over the study timeframe.

2.2 METHODS

2.2.1 *Data*

We used data from three sources. First, we obtained pharmacy claims data from IBM® MarketScan® Commercial Database. This dataset contains claims level data from over 115 million unique patients with employer-based private health insurance, including information on

co-payments, deductible amounts, drug code, therapeutic class, prescription drug payment, plan type, and location. Second, we obtained a dataset that contained drug-specific value designations from the 2010 value-based formulary of a large insurer in the Pacific Northwest described below. This drug specific dataset was applied to claims data collapsed to the drug-year level, with unique drugs defined by unique combinations of dosage form, active ingredient, and generic status. Finally, we added data from the American Medical Association on private insurance market concentration at the metropolitan statistical area level(38).

2.2.2 *Tier Definitions*

Each drug in Premera Blue Cross' 2010 value-based formulary is categorized into one of five ordinal tiers based on their cost-effectiveness, with each tier representing a cost-effectiveness range (Table 1). The tiers range from 0-4, with 0 being the highest value and 4 being the lowest. There are two sets of tier definitions with corresponding cost-effectiveness ranges to separate typical drugs and special case drugs; the special case drug category was created to allow for additional considerations for drugs with established clinically meaningful benefits, such as ethical issues, rarity, or unmet clinical needs. Premera Blue Cross collected cost-effectiveness values for each drug from published literature, the Tufts CEA registry, Cochrane reviews, manufacturer models, and HTA assessment organization reports, using the societal perspective when available(29). "Tier," as defined by Premera, is used in this study as a proxy for value level and the terms are used interchangeably throughout.

Table 2.1. Value-Based Formulary Tier Definitions and Cost-Effectiveness Ranges

Tier	ICER Ranges for Typical Drugs	Average group cost-effectiveness ratio estimate			ICER Ranges for Special Case Drugs
		low	midpoint	high	
0	Cost-saving and/or preventive	$0	$0	$0	Cost-saving and/or preventive
1	Cost-saving or < $10,000/QALY	$0	$5,000	$10,000	Cost-saving or <$50,000/QALY
2	$10,000-50,000 /QALY	$10,000	$30,000	$50,000	$50,000-150,000 /QALY
3	$50,000-150,000 /QALY	$50,000	$100,000	$150,000	>$150,000 /QALY
4	>$150,000 /QALY, or insufficient evidence to determine ICER	$150,000	$575,000	$1,000,000	Insufficient evidence to determine ICER

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year
*Value tier ICER ranges and tiers defined by Premera Blue Cross drug benefit formulary in 2010(29); Special case: drugs that had additional value not reflected by their ICER. These values include ethical issues, rarity, unmet clinical needs, regulatory requirements, and other societal considerations.

2.2.3 *Collapsed claim data at drug-year level*

We constructed a drug-year level dataset that had four observations for each unique drug representing the four first quarters of years 2010-2013. Since we sought to understand how plans set cost-sharing for each unique drug over time, we dropped claims outside of the first quarter of each year since these were likely to be affected if individuals exceeded their out-of-pocket maximum payments (which is more likely to occur at the end of the year).

To calculate mean OOP cost for each drug-year, we added all OOP costs (copayments, coinsurance, and deductible charges) for each prescription drug claim and standardized them to a 30-day supply, dropping all observations less than zero. Generic status was defined as a categorical variable with four options: brand name (with or without an available generic), multisource generic, single-source generic, and other (which included over the counter drugs and

no longer available). Mean average wholesale price (AWP) was the average of a drug's AWP over all claims during the first quarter of each year standardized to a 30-day supply. Plan payment was the average amount the insurance company paid for a drug excluding patient out-of-pocket costs, in each quarter 1, standardized to a 30-day supply. We then collapsed the dataset, taking the average variable value for each unique drug and year combination.

2.2.4 *Regression analysis*

We ran a random effects model with robust standard errors clustered on drug id (*i*) at the year (*j*) level:

$$Y_{ij} = \mu + \beta_1 Tier_i + \beta_2 Year_{ij} + \beta_3 Year_{ij} * Tier_i + \beta X + \varepsilon \quad (1)$$

The outcome variable (Y_{ij}) was the natural log of mean OOP cost, interpreted as percent change over time. The explanatory variables of interest were year, value designation (i.e. tier) as a categorical variable with tier 0 as the reference group, and the interaction of year and value designation. Additional vector of covariates (βX) included the 2010 generic status of each drug, logged average wholesale price, and logged average plan payment. These control variables were added as generic status and drug price could potentially affect cost-sharing amounts and obscure the relationship of interest.

We repeated the same analysis using four additional models to check the robustness of our results: an OLS clustered on drug ID; a population average model with an unstructured correlation matrix; a population average model with an autoregressive order correlation matrix with a lag of 1; a fixed effects model; and a random effects model (available in appendix).

2.2.5 *Association of Organizational and Regional Market Characteristics on Value Trends*

We next ran equation (1) on two additional datasets, data collapsed by plan type and data collapsed by metropolitan statistical area (MSA), to understand factors associated with the relationship of cost-sharing and value over time. For insurance plan type, each line of data was a unique combination of drug, year, and plan type. Plan type categories included health maintenance organizations (HMOs), preferred provider organizations (PPOs), point of service plans (POS, both with and without capitation), high deductible health plans (HDHPs), and Other (Basic/Major Medical, Comprehensive, Exclusive Provider Organization). Because the level of insurance market competition may also have bearing on a payer's ability to set formulary prices, we considered market competition as an associated factor. We collapsed the data so each observation was a unique combination of drug, year, and MSA, and linked the claims data to MSA-level market concentration. Market concentration was measured via 2013 Herfindahl-Hirschman Index (HHI), which measures market competition amongst firms in a similar sector, for 388 metropolitan statistical areas (MSAs) as defined by the US Office of Management and Budget. We used the HHI numbers for 2013 for all four years in question because other studies have found that the HHI for insurance markets by MSA did not change significantly over that time period(39). We categorized each MSA into three categories based on the United States Department of Justice antitrust thresholds: unconcentrated markets had an HHI of 1,500 or less, moderately concentrated markets had an HHI between 1,500 and 2,500, and markets with an HHI above 2,500 were considered highly concentrated(40).

2.2.6 *Estimated average drug value*

We conducted additional analyses to estimate the alignment of actual prescription drug utilization volume with CEA-based value estimates to evaluate the overall "value" of prescription drugs used by this population. Premera assigns drugs to copayment tiers based on ICER ranges. We estimated low, midpoint, and high ICER values for each drug based on the range of its assigned tier to calculate an average cost-effective estimate for all drugs in the sample weighted by their relative use (Table 1). Cost-saving drugs were assumed to have an ICER of $0 per QALY to avoid problems of interpreting negative cost-effectiveness ratios and to err on conservative valuation. Because we cannot parse out which drugs in tier 0 are cost-saving and which are preventive, drugs in the tier 0 were assumed to have a range of ICERs between $0 and $10,000 per QALY, the same as tier 1. While preventive medications may have a range of cost-effectiveness ratios depending on factors such as the population targeted, the placement of a drug in a tier with zero cost-sharing indicates it has high value for the plan and therefore a low ICER. The upper bound of $10,000 is a conservative estimate based on the next highest tier. We assumed the maximum CEA ratio for the drugs in tier 4, whose definition includes all drugs with an ICER above $150,000 per QALY, would be $1,000,000 per QALY as most drugs do not exceed this amount(41).

To get yearly average ICER estimates, we multiplied the drug-specific ICER estimate (low, midpoint, or high value of the cost-effectiveness range) by the drug-specific total days' supply of medication for all quarters over the entire observation period divided by total days' supply for all drugs over the same period and summed across all drugs. To test significance, we ran three linear

regressions with low, middle, and high ICER estimates as the outcome variable; quarter and generic status were the predictors of interest, weighted by the number of claims in each quarter.

2.2.7 *Software and Data Permissions*

MarketScan data manipulation was done with SAS 9.3 software. Value designation data by drug provided from Premera Blue Cross of Washington. Regression analyses were done with Stata v14.

2.3 RESULTS

2.3.1 *Descriptive Statistics*

We mapped 1,720-1,896 unique drugs (depending on year) as defined by dosage form, active ingredient, and generic status from the Premera value-based formulary to a major commercial claims database. Of these drugs, about 50% were multi-source generic and 40% were brand-name. 57% of the drugs identified were in tiers 0 and 1 (preventative, cost-saving, or had a CE ratio under $10,000 per QALY). Tier value overwhelmingly aligned with generic status. 98% of generic drugs were in tier 0 or 1 while 90% of brand name drugs were in tiers 2-4, and the percent of drug claims for generics increased over time (72% to 82% in 2010 to 2013 respectively). By number of claims, most prescriptions were for high value (tier 0 and 1) and generic drugs.

The average OOP costs by drug ranged from $6.87 to $62.22, while the average plan payments by drug ranged from $18.19 to $286.17 (each standardized to a 30-day prescription). The mean

percent cost-sharing, weighted by number of claims, ranged from 27% to 56% among the value tiers.

There was a general trend in increasing out of pocket costs and total plan payment comparing tier 0 with tier 1 and tiers 2-4 (Table 2). Tiers 2-4 had similar plan payment amounts and OOP costs. Percent cost-sharing, weighted by number of claims, clustered in two groups with an average 55% cost-sharing for tiers 0-1 and 28% for tiers 2-4.

Most of our claims data were from PPO (67%) and HMO (14%) insurance plans. HMO insurance plans had universally lower OOP costs, but similar or higher total mean plan payment costs. Most claims also came from highly concentrated insurance markets (>70%). Unconcentrated markets had slightly lower plan payment costs but similar OOP costs per pharmacy claim compared to moderately and highly concentrated insurance markets.

Table 2.2. Descriptive Drug Statistics By Value Tier

	Drug Value Tier (Typical Case Definitions)					
	Preventative and Cost-Saving (0)	Cost-Saving or <$10K/QALY (1)	$10K-$50K/ QALY (2)	$50K-$150K/ QALY (3)	>$150K/ QALY (4)	Total
Total Number of Unique Drugs (2010)	195	792	323	291	119	1,720
MS Generic	178	661	5	2	3	849
SS Generic	7	42	2	1	1	53
Brand Name	6	63	274	252	113	708
Other	4	26	42	36	2	110
Mean OOP Cost Per Pharmacy Claim ($)						
Total (Weighted)	$6.87	$22.62	$62.22	$57.36	$59.85	$27.14
Total (Unweighted)	$10.07	$29.55	$81.47	$82.43	$84.67	$49.73
HMO Insurance Plans	$10.03	$24.69	$61.52	$73.72	$64.86	$40.82
Non-HMO Insurance Plans	$12.83	$41.35	$111.43	$108.71	$127.63	$68.20
Unconcentrated Markets	$8.63	$26.38	$86.65	$80.32	$101.51	$43.66
Moderately Concentrated Markets	$9.34	$27.21	$74.28	$79.49	$78.92	$44.51
Highly Concentrated Markets	$9.11	$27.38	$75.24	$80.12	$80.48	$44.64
Mean Total Plan Costs Per Pharmacy Claim ($)						
Total (Weighted)	$18.19	$55.83	$286.17	$226.49	$269.82	$91.61
Total (Unweighted)	$43.08	$144.28	$511.30	$382.86	$596.59	$271.89
HMO Insurance Plans	$45.94	$155.00	$517.39	$410.94	$642.77	$285.11
Non-HMO Insurance Plans	$44.45	$146.14	$485.67	$388.44	$619.87	$269.74
Unconcentrated Markets	$33.34	$97.18	$381.64	$307.47	$649.27	$184.66
Moderately Concentrated Markets	$36.33	$124.86	$433.68	$363.09	$530.67	$229.29
Highly Concentrated Markets	$34.09	$119.01	$419.42	$351.09	$502.99	$218.30
Mean % Cost Sharing Per Pharmacy Claim						
Total (Weighted)	55%	56%	29%	28%	27%	50%
Total (Unweighted)	44%	41%	31%	31%	25%	37%
HMO Insurance Plans	46%	37%	27%	28%	21%	34%
Non-HMO Insurance Plans	48%	49%	39%	38%	32%	44%
Unconcentrated Markets	46%	46%	32%	32%	29%	41%
Moderately Concentrated Markets	46%	43%	31%	30%	26%	38%
Highly Concentrated Markets	48%	45%	31%	31%	29%	40%

*All currency is reported in 2013 US Dollars; Weighted data is weighted by number of claims for each unique drug each year; All costs are weighted unless otherwise specified; OOP costs calculated using first quarter data only to avoid the effect of exhausting deductibles or reaching max out of pocket payments; Total plan payment is defined as the sum of out of pocket (OOP), cost of business (COB), and insurance payment; Percent cost sharing is calculated as OOP divided by the sum of OOP and total plan payment at the drug-year level; Insurance markets are defined as Metropolitan Statistical Areas (MSAs); Unconcentrated Markets (HHI<1,500); Moderately Concentrated (1,500<HHI<2,500); Highly Concentrated (HHI>2,500).

°Abbreviations: QALY, quality-adjusted life-year; OOP, out of pocket; MS, multi-source; SS, single-source; HMO, health maintenance organization;

2.3.2 *Regression Results*

We found similar results across all models, which suggests robustness of results. We report the random effects model results as it accounted for repeated observations in our panel dataset and allowed greater estimation efficiency, with an overall r^2=0.736 and rho=0.847. (Full regression output in appendix).

In the base year of 2010, OOP costs for tiers 1-4 were 52%, 76%, 91% and 78% higher than the reference group (tier 0), respectively (Table 3). OOP costs for drugs in tiers 0 and 1 decreased over the study timeframe at about 5% per year ($p<0.001$) and were not statistically different from one another. OOP costs for tiers 3 and 4 decreased at about 2.4% and 2.2% per year ($p =0.007$ and 0.011 respectively) and were not statistically different from one another. OOP costs did not change significantly for tier 2 ($p=0.312$).

These trends were slightly more pronounced with PPO insurance plans, which comprise 67% of the data, and slightly less pronounced in HMO plans, which comprised 16% of the data. In PPOs, OOP costs decreased at about 6% per year for tiers 0 and 1 ($p<0.001$) and at about 2% per year for tiers 2-4 ($p=0.006$, 0.00, and 0.06 respectively). The tiers within these two groups were not significantly distinct from each other, but the groups were ($p<0.001$). OOP costs were not clearly delineated between tiers 2-4 in any insurance plan type. High deductible health plans (HDHPs) generally had the most variability and growth in OOP costs, while HMOs were the only plan type to have no significant change in patient costs over the timeframe in three of the five drug value categories.

At all levels of market concentration, OOP costs for higher value drugs decreased at a faster rate than lower value drugs, although the trend was more pronounced in unconcentrated markets. In unconcentrated markets, OOP costs decreased at 8.5% per year for tier 0 drugs ($p=0.016$), while the same drugs in moderately and highly concentrated markets decreased at around 5% annually ($p<0.001$). OOP costs for tier 1 drugs decreased at around 4% annually ($p<0.001$) in highly concentrated markets, while changes in OOP costs for tiers 2-4 (lower value drugs) were small.

Table 2.3. Estimated Change in Out of Pocket Costs by Value Tier and Year Using a Random Effects Model

Group	Tier	% difference in average OOP in 2010 (Compared to tier 0)	Annual % Change in OOP	Std Err	P-value	98% CI	Pair-Wise Chi-Squared Test p-values			
							0	1	2	3
All	0	-	-4.91%	0.009	0.000	(-6.61%, -3.20%)	-	-	-	-
	1	52.59%	-4.46%	0.005	0.000	(-5.50%, -3.41%)	0.84	-	-	-
	2	76.25%	-0.75%	0.007	0.312	(-2.20%, 0.70%)	0.04	0.01	-	-
	3	91.42%	-2.41%	0.007	0.001	(-3.79%, -1.04%)	0.93	0.91	0.02	-
	4	78.33%	-2.16%	0.011	0.046	(-4.28%, -0.04%)	0.76	0.62	0.21	0.69
PPOs Only	0	-	-6.00%	0.007	0.000	(-7.45%, -4.56%)	-	-	-	-
	1	55.72%	-6.14%	0.005	0.000	(-7.14%, -5.15%)	0.85	-	-	-
	2	81.68%	-2.02%	0.007	0.006	(-3.44%, -0.59%)	0.00	0.00	-	-
	3	94.86%	-2.37%	0.006	0.000	(-3.63%, -1.10%)	0.00	0.00	0.69	-
	4	82.25%	-1.99%	0.011	0.060	(-4.07%, 0.08%)	0.00	0.00	0.99	0.75
HMOs Only	0	-	-1.84%	0.011	0.086	(-3.95%, 0.26%)	-	-	-	-
	1	53.05%	-3.97%	0.005	0.000	(-4.92%, -3.02%)	0.04	-	-	-
	2	91.37%	-1.33%	0.009	0.123	(-3.01%, 0.36%)	0.69	0.00	-	-
	3	115.30%	-3.55%	0.009	0.000	(-5.37%, -1.73%)	0.19	0.66	0.06	-
	4	96.08%	-3.21%	0.016	0.044	(-6.34%, -0.08%)	0.46	0.64	0.28	0.85
HDHPs Only	0	75.43%	-14.87%	0.013	0.000	(-17.44%, -12.31%)	-	-	-	-
	1	106.50%	-6.52%	0.011	0.000	(-8.62%, -4.43%)	0.00	-	-	-
	2	113.38%	-6.66%	0.010	0.000	(-8.67%, -4.65%)	0.00	0.91	-	-
	3	118.66%	-5.29%	0.010	0.000	(-7.24%, -3.34%)	0.00	0.29	0.26	-
	4	0.00%	-9.37%	0.014	0.000	(-12.08%, -6.66%)	0.00	0.05	0.07	0.01
Unconcentrated Markets Only	0	-	-8.53%	0.016	0.000	(-11.59%, -5.48%)	-	-	-	-
	1	50.99%	-4.17%	0.011	0.000	(-6.28%, -2.05%)	0.02	-	-	-
	2	107.98%	-2.83%	0.020	0.164	(-6.83%, 1.16%)	0.02	0.55	-	-
	3	105.86%	-0.12%	0.022	0.957	(-4.53%, 4.28%)	0.00	0.10	0.36	-
	4	96.59%	-0.43%	0.042	0.918	(-8.59%, 7.73%)	0.07	0.38	0.60	0.95
Moderately Concentrated Markets Only	0	-	-5.17%	0.002	0.000	(-5.48%, -4.86%)	-	-	-	-
	1	59.72%	-3.92%	0.001	0.000	(-4.12%, -3.73%)	0.00	-	-	-
	2	95.82%	-0.16%	0.002	0.370	(-0.50%, 0.19%)	0.00	0.00	-	-
	3	108.92%	0.86%	0.002	0.000	(0.53%, 1.19%)	0.00	0.00	0.00	-
	4	97.04%	-1.70%	0.003	0.000	(-2.37%, -1.04%)	0.00	0.00	0.00	0.00
Highly Concentrated Markets Only	0	-	-5.86%	0.001	0.000	(-6.08%, -5.64%)	-	-	-	-
	1	59.71%	-4.11%	0.001	0.000	(-4.25%, -3.97%)	0.00	-	-	-
	2	92.34%	-0.16%	0.001	0.207	(-0.41%, 0.09%)	0.00	0.00	-	-
	3	105.41%	0.75%	0.001	0.000	(0.51%, 0.99%)	0.00	0.00	0.00	-
	4	92.67%	-1.56%	0.002	0.000	(-2.05%, -1.08%)	0.00	0.00	0.00	0.00

2.3.3 *Estimated average drug value model results*

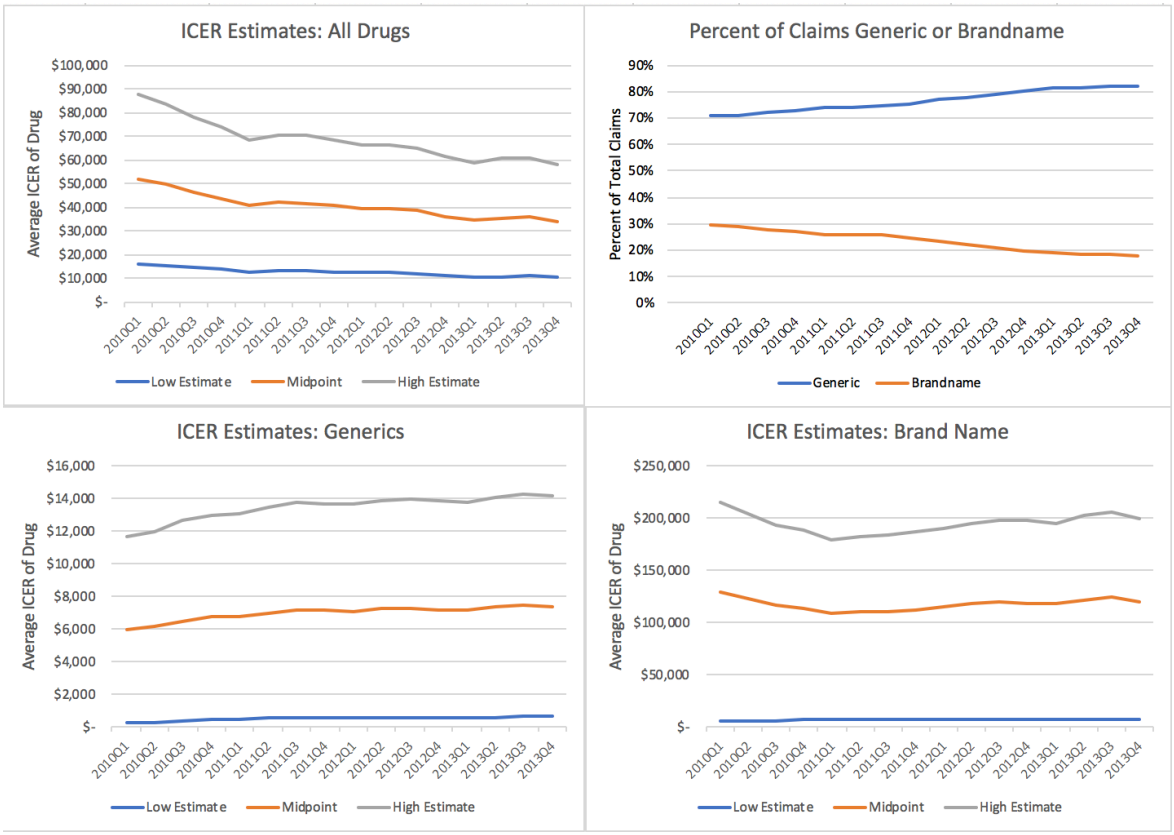
Generic status acts as a confounder in estimating the average weighted ICER of drug claims between 2010-2013. Before splitting the data by generic status, it appears that the weighted average ICER for drug claims were decreasing over time, regardless of low, middle, or high estimates. When stratified by generic status, the weighted average ICER for drug claims increases over time in both generic and name brand drugs at between $210 - $550 per year (p-value<0.001) (Table 4). The average estimated ICER for name brand drugs was on average between $40,000-$180,000 higher than for generics (p<0.001). Examining the percent of claims each year by tier and generic status shows an increase in claims for drugs in tiers 0 and 1 (22% to 25%, and 52% to 59% respectively) and an increase in generic drug use over the time period (72% to 82%).

Table 2.4. Estimated Average Cost-Effectiveness Value by Generic Status and Year

Percent of claims each year by tier and by generic status						
Tier	Range	2010	2011	2012	2013	TOTAL
0	Preventive or Cost-Saving	22%	23%	24%	25%	24%
1	Cost-saving or <10,000	52%	54%	57%	59%	55%
2	>10,000 and <50,000	12%	11%	8%	6%	9%
3	>50,000 and <150,000	10%	9%	9%	8%	9%
4	>150,000	4%	3%	3%	2%	3%
-	Generic	72%	75%	79%	82%	77%
-	Brand Name	28%	25%	21%	18%	23%
Average drug $/QALY estimates by year and generic status						
Status	CER	2010	2011	2012	2013	TOTAL
All	Low-estimate	$11,660	$10,080	$9,123	$8,071	$9,734
All	Midpoint	$37,245	$31,912	$29,314	$26,487	$31,225
All	High-estimate	$62,830	$53,745	$49,505	$44,903	$52,715
Generic	Low-estimate	$250	$371	$406	$437	$370
Generic	Midpoint	$4,353	$4,835	$4,986	$5,100	$4,836
Generic	High-estimate	$8,457	$9,299	$9,566	$9,763	$9,301
Brand Name	Low-estimate	$40,179	$37,935	$40,300	$41,314	$39,752
Brand Name	Midpoint	$119,826	$110,038	$117,000	$120,353	$116,348
Brand Name	High-estimate	$199,473	$182,142	$193,699	$199,391	$192,944

*Abbreviations: QALY, quality-adjusted life-year; CER, cost-effectiveness ratio;
All values in 2013 US dollars.

Figure 2.1. Average ICER of Drugs by Generic Status Over Time



*Abbreviations: ICER, incremental cost-effectiveness ratio; Q1-Q4, annual quarters 1-4;
*Time on the x-axis is years 2010-2013 by quarter; all currency is in 2013 US dollars

2.4 Discussion

2.4.1 *Value versus generic status*

In this study, we explored the extent to which commercial insurance plans aligned with, and shifted to, value-based cost-sharing for prescription drugs. We applied drug-specific ICER estimates from one payer to observed drug-specific OOP costs from a large commercial claims dataset to infer benefit design over this period. The results provide evidence that most plans in 2010 already aligned value-based cost-sharing to some extent, with lower average OOP drug costs for higher value drugs. Results also suggest that OOP costs were decreasing over the time frame in two trajectories: OOP drug costs for higher value drugs (in tiers 0 and 1, costing up to

$10,000/QALY) decreased faster than OOP costs for lower value drugs (tiers 2-4, costing over $10,000/QALY). This trend was particularly clear for PPO insurance plans, which comprised about 70% of the claims data.

One explanation for this trend may be that commercial formulary decisions consider generic status more than explicit value. Generic drugs were overwhelmingly in tiers 0-1 and brand name drugs in tiers 2-4 in our sample. Despite a wide range of cost-effectiveness values (from $10,000 to over $150,000 per QALY), tiers 2-4 were not statistically significantly different in cost-sharing compared to each other either at baseline or over time. This is supported by the large literature base that has shown the longstanding endeavor of US payers to increase use of generic medications(42). Indeed, a recent paper puts the generic utilization rate (i.e. the proportion of prescription drug volume ascribed to generics) to be the highest among 10 high income developed countries(43).

Our average ICER estimates weighted by drug-specific utilization also underscore the importance of generic versus name-brand status. Table 4 and Fig 1 show that there is an overall trend of decreasing average ICERs over time. However, when stratifying brand-generic status, this trend seems to largely disappear except for the high estimate trend for branded drugs in 2010. Over this period, we observe increasing proportion of generic utilization in our sample (Fig 1). This data suggests that commercial plans and their insured population have been moving towards value over time as evaluated by OOP costs and by total utilization, respectively. However, such movement appears to be driven by brand-generic status rather than by cost-effectiveness evidence.

This is an important distinction because there is likely a limit to substantial future gains from continuing to pursue increased generic utilization. In fact, more recent data shows that although there is continued increases in unbranded generic drug utilization in the US, the proportion of total drug spending attributed to branded drugs has been increasing simultaneously, especially with the rising spending on branded specialty drugs(42). These results also provide evidence that insurance plans may be decreasing cost-sharing for high value drugs, but are not increasing cost-share of low-value drugs as an offset (an issue that not many studies have addressed)(9). Our results also reflect the fact that over half (56%) of all private insurance formularies have three or less tiers, allowing for less nuance in cost-sharing between drugs relative to Premera's five-tier formulary(44).

Another potential reason for the similarity in cost-sharing for drugs valued over $10,000 per QALY may be because Premera's value designations do not necessarily reflect negotiated drug prices for the commercial insurance payers in our sample. We include a plan payment variable in the model, but this does not account for confidential rebates paid by manufacturers to health plans; their absence potentially means that plan costs are not accurately captured. Hence, to the degree that Premera's negotiated plan costs for drugs differ from the observed plan costs in our dataset, there will be misclassification of plan-drug-specific value.

2.4.2 *Influence of plan type and market competition*

Analysis results stratified by plan type revealed significant differences between HMOs and the four other plan types. HMO plans showed no significant change in patient costs over the time

frame for any value designation compared to significant changes in all other plan types, as well as the lowest markups for brand name and SS generics, and the biggest discounts on MS generics. The constant term for HMOs is not higher than the other plans, indicating the trends were not due to differences in initial cost-sharing levels. HMOs may have other levers to influence health care use other than cost-sharing. For example, staff model HMOs may have stronger influence on physician prescribing behavior to affect utilization, reducing the need for demand price levers. Further, because of stronger utilization management, they also may be able to negotiate better prices, reducing the need for high cost-sharing.

The association between market competition and drug cost-sharing is complex. The model indicates that there was lower cost-sharing in competitive markets in 2010, but that patient costs increased faster in competitive markets, catching up to cost-sharing levels of monopolies and monopsonies. Further research may illuminate differences in shifts toward VBID by geographic region rather than by insurance market concentration.

2.4.3 *Limitations*

Our analysis should be interpreted with the acknowledgement of several limitations. Firstly, our data is based on a large, non-random cross-section of employer-based private health insurance enrollees, and therefore cannot be generalized to the entire US population or publicly sponsored health insurance programs. Secondly, the data is constrained to years 2010-2013 to avoid confounding effects from the Affordable Care Act (ACA), however there still may have been some anticipatory pricing changes such as early adoption of high deductible health plans in our timeframe as the deadline to implement ACA policies approached. The ACA specifically

influenced cost-sharing for high-value drugs, as insurance companies were required to provide many preventive services without cost-sharing(25). Other policies enacted during that time may also have influenced our results; future work should consider payer adoption of value as influenced by the implementation of the ACA and other policies.

There were also limitations to our value designations. Premera Blue Cross's 2010 value-based formulary was based on public literature but may have taken into account their firms' specific negotiated rates. Because the value designations are Premera-specific, these figures will not correspond exactly to the range of privately negotiate drug prices that most commercial health insurers and pharmacy benefit managers use. Negotiated prices or rebates are not evenly distributed across the database either, as rebates for branded drugs are likely to be more substantial. Although we do our best to control for the total amount paid for each drug claim, there is no way to perfectly align overarching value designation with each firm-specific value. An additional limitation is that the value data is from 2010, and it is possible that there were changes over the 4-year period in drug price or effectiveness evidence. This limitation is less of a concern given the short time frame of the study.

Lastly, our estimation of average weighted value for drugs over time did not factor in the additional formulary categories for special case drugs, which were give more generous ICER ranges. Using these higher ranges would have resulted in even higher estimated ICERs, however their influence is likely to be minimal given the small proportion of drug volume for which these specialty drugs account.

2.5 CONCLUSION

Private payers have considerable potential to influence use of prescription drugs. Our analysis suggests that payers appear to be designing cost-sharing to align with value. However, this movement appears to be through the mechanism of brand-generic status rather than finer cost-effectiveness estimates. There may be potential gains from applying cost-effectiveness approach to informing cost-sharing for branded medications.

Chapter 3. CHARACTERIZING PATIENT ASSISTANCE PROGRAM USE AND PATIENT RESPONSIVENESS TO SPECIALTY DRUG PRICE FOR MULTIPLE SCLEROSIS IN ONE MID-SIZE INTEGRATED HEALTH SYSTEM

3.1.1 *Introduction*

There is an ongoing public conversation about patient drug costs in the United States, and how those costs can affect patient access and adherence to necessary medication.(45) The specific concern is that out-of-pocket (OOP) costs are too high, disincentivizing optimal medication use through lowered adherence, skipped prescriptions, or discontinued use.(1, 45)

A significant omission in this conversation, however, is manufacturer-provided patient OOP assistance, also referred to as copay coupons, or, as we will refer to them in this study, patient assistance programs (PAPs). A practice that emerged in the mid-2000's, PAPs are defined as drug manufacturer paying for some or all of a patient's OOP charges at the point of sale.(46, 47) The use of PAPs can be suggested by a physician if a patient has concerns about covering a drug cost or advertised in the general media, and redemption materials can be printed out online, sent in the mail, or requested at the pharmacy.

The use of PAPs can be difficult to track, however, and their use is generally omitted from claims analysis. Whether PAP use is captured depends on the data sharing between the provider, payer, and dispensing pharmacy, as well as the method by which a manufacturer directly or indirectly pays for a drug claim.(48) One source with access to PAP data found that the practice is growing

in prevalence, used in an estimated 18% of all branded prescriptions and 42% of all specialty prescriptions in 2018.(18) Another study estimated that 46% of claims for specialty drugs treating multiple sclerosis (MS) used patient assistance programs, producing an average 61% reduction in OOP charges.(49)

Despite the growth in PAPs, there is not broad consensus regarding the practice's overall impact on pharmaceutical access and costs. Some argue the practice is necessary for patients to be able to afford their clinically necessary medication, particularly if there is no generic or less costly alternative.(50) PAPs may also serve to undercut insurance levers meant to steer patients toward payers' preferred therapeutic alternatives, however, ultimately increasing payer costs and potentially increasing patient costs through other channels such as raised premiums.(51, 52)

One integrated managed care organization in the US, Kaiser Permanente Washington (KPWA), has embraced the practice, however, through a unique specialty pharmacy disease management program that, among other things, actively helps patients to obtain PAP reimbursement in order to encourage drug adherence.(53) Given the growing use and prices of specialty drugs, and the relatively opaque practice of patient assistance programs, our research goal was to characterize the use of PAPs in this specialty drug program, and to estimate patients' price elasticity of demand for those medications using copay assistance as a source of price variation. We focus on specialty drugs indicated for Multiple Sclerosis (MS).

3.2 METHODS

We describe trends of 13 months of observational, cross-sectional, pharmacy claims data for seven unique molecules used to treat MS (ten branded drugs), focusing on the presence and magnitude of patient assistance programs. We also use a two-part model to estimate the demand for MS drugs, and calculate the PED associated with patient assistance-based price variation. All analyses were performed using Stata version 15.1, with IRB approval from the University of Washington and Kaiser Permanente Washington.

3.2.1 *Data*

Claims data came from Kaiser Permanente Washington system, a large health maintenance organization serving over 700,000 patients in Washington state. All claims for multiple sclerosis drugs, as defined by their national drug code (NDC), that fell between 12/01/2017 – 12/31/2018 were included in the initial dataset, excluding patients under age 18, patients using Medicaid as their primary payer, and patients without six months continuous enrollment prior to their first claim. This resulted in approximately 7,000 person-months of data. We studied MS drugs during 13 months (December 2017 – December 2018) when secondary payer information was available. We focused on MS, and omit other types of specialty drugs, like anti-inflammatory medications, because the form of copay assistance (prepaid debit cards) was not observable in our data.(48)

Spending data included the total cost of a drug claim to the plan, the amount charged to the patient (OOP charged), whether there was a secondary payer, and if so, the amount the secondary payer covered, and the amount the patient ultimately paid OOP after patient assistance (actual OOP paid). All cost data is reported in 2018 US$. In addition to cost data and drug code, the claims data

included the following variables: patient id, sex, zip code, age grouped in five-year increments, brand and generic drug name, generic status, mode of administration (subcutaneous injection, intramuscular injection, and oral), dispense date, days of the drug supplied, binary indicator of Charlson comorbidity index score >/=1 based on prior 12 months of medical claims data, whether it was the patient's first claim for that drug, primary insurance provider, and mail order status. To supplement this data, we linked zip code with demographic indicators (median income and percent of population that was non-white) produced by Washington State Office of Financial Management.(54) We also estimated medication possession ratio (MPR) by patient using dispense date and days covered for each relevant patient-drug combination. Descriptive statistics were derived from data at both the claim- and the patient-level.

3.2.2 *Defining patient assistance program (PAP) use*

We defined a claim as using PAP if it had a secondary payor (an entity other than the patient's primary insurer) paying a non-zero amount toward the patient's cost-share. Claims with secondary payors in the form of additional insurance, however, such as Kaiser Permanente financial assistance or Medicare Part D, were not defined as using a PAP and the charged OOP amount for those claims was defined as the OOP amount after accounting for all insurance contributions.

3.2.3 *Drugs considered*

We analyzed 10 unique branded drugs (7 unique molecules) indicated for MS treatment. Because insurers negotiate and set their formularies for specific brands of drugs, we performed analyses and displayed results at the single-source brand name level.

3.2.4 *Missing data imputation*

Data were collapsed at the patient*month*drug level, taking the sum of costs and days supplied for any patient claims for a single drug during a month. This resulted in 7,063 patient-months of data. After an individual's first observed fill in the data, any subsequent months without an observed fill were assumed to have 0 days supplied. In these months with 0 days supplied, we imputed the patient and drug characteristics from the non-missing months for the same individual and drug, and thus expanded the dataset to include 3,532 additional observations. The imputation is described below. In months with greater than 31 days supplied, the subsequent month was assumed to carry over the extra days from the previous month; in those cases, the imputed month (182 observations) were dropped. Missing months were assumed to not be a first fill or a mail order drug.

We performed multiple imputation by chained equations to estimate the OOP charge and whether a PAP was used for the missing months, using 10 iterations of predictive mean matching from 500 nearest neighbors for each imputed variable. Predictive mean matching was the most appropriate way to impute plausible values for the missing observations given the continuous but non-normal cost variable with a large number of zeros.(55) Matches were based on month, drug, age, sex, zip code characteristics, and Charlson comorbidity index.

3.2.5 *Two-part model*

1st Part

$$P(Q > 0) = B_1 * OOP\ Charge_{pre-PA} + B_2 * PA\ Indicator + B_X * X + \varepsilon \quad (1)$$

2nd Part

$$E(Q|Q > 0) = B_1 * OOP\ Charge_{pre-PA} + B_2 * PA\ Indicator + B_X * X + \varepsilon \quad (2)$$

We used a probit model in the first part of the two-part model to estimate the probability of any claim in the patient*drug*month, controlling for age, sex, Charlson comorbidity index, binary indicators for drug and month, insurance source (health care exchange, employer-based, Medicare, etc), drug administration method, and county-level demographics (Equation 1). Standard errors were clustered at the patient level. The independent variables of interest in the first part of the main model were OOP charge and a binary indicator of patient assistance. While we initially intended to include a variable for PAP amount, we found that PAP amount largely equaled OOP charge leading to collinearity, leading us to include patient assistance as an indicator variable.

We then ran a zero truncated negative binomial model with standard errors clustered at the patient level to estimate the days supplied of the drug given there was a claim in that month (Equation 2). This model had the same independent variables of interest and controls as the probit model, with the added variables of whether the claim was via mail order, and whether the claim was a patient's first fill. Total quantity demanded was a product of the estimated outcomes from both parts of the model. The two-part model was run on the empirical data to estimate factual demand, and then the same model coefficients were used to estimate counterfactual predictions given patient assistance was set to zero.

3.2.6 *PED Estimation*

$$Price\ Elasticity\ of\ Demand = \frac{\%\ \Delta\ Quantity}{\%\ \Delta\ Price} = \frac{\left(Q_1 - Q_2 / \bar{Q}\right)}{\left(P_1 - P_2 / \bar{P}\right)} \quad (3)$$

We used the recycled predictions method in the two-part model to estimate the change in quantity demanded due to copay assistance (Equation 3). After estimating the quantity demanded in the data (Q1), we set the PAP indicator variable to zero and estimated the quantity demanded within the model if no one had copay assistance (Q2). This informed our change in quantity demanded and the mid-point quantity demanded (Q-bar). The change in price (P1-P2) was the copay assistance amount, where the average price (P-bar) was the mid-point between the pre- and post-copay assistance amounts. These elements, estimated for each line of data, informed our average price elasticity of demand equation. This exercise was completed for the entire dataset, as well as on subsets of data for each individual drug, with the results interpreted as the association of PAP amount and drug demand. We bootstrapped with 1000 iterations to estimate confidence intervals and p-values for price elasticity estimates by drug and overall.

3.2.7 *Sensitivity Analysis*

Our measure of demand is days supplied as measured first by existence of any claim and then by days supplied given a claim existed. Other analyses have used prescription abandonment, initiation, discontinuation, number of claims, and drug spending as measures of demand.(56) Due to data limitations, we did not have the scope to consider drug initiation or prescription abandonment as measures of demand. In the event that there was not enough variation in days supplied or that days supplied did not adequately capture patient demand for medication, we report

the marginal effect of patient assistance on the probability of getting any claim from the first part of the two-part model as an additional source of information about patient behavior. To investigate the effect of model specification on our results, we ran a sensitivity analysis including the PAP indicator, OOP charge, and their interaction to capture differences in patient response to price change given the presence of PA. While we did not include the interaction term in our main analysis due to the potential for bias from collinearity, we believe it is a useful sensitivity analysis to test the validity of our results. Additionally, we noted that certain types of PAPs are legally prohibited within federal health insurance plans such as Medicare due to the federal anti-kickback statute.(57) To assess whether the inclusion of Medicare patients in the analysis impacted our results, we ran a sensitivity analysis excluding all Medicare claims (1,185 person-months) included in the appendix as Table A1.

3.3 RESULTS

3.3.1 *Sample description*

Our sample of claims for MS drugs during the timeframe of 12/01/2017 to 12/31/2018 included 789 unique patients and 7,465 claims (Table 1). Of the 789 patients in the sample, 550 unique patients (69.6%) used some sort of secondary payer to cover their out of pocket responsibility. The majority of claims with secondary assistance were manufacturer provided, aka PAPs (92%), however patients also received OOP assistance from Kaiser's financial assistance program (8%) and secondary insurance such as Medicare Part D and Medicaid (1%).

Table 3.1. Characteristics by use of patient assistance programs

At Person Level	No Patient Assistance	>/=1 Claim with Patient Assistance	Overall Sample	Significance~
Number of unique patients	258	531	789	
Number of claims per patient	8.78	9.79	9.46	p=0.002
% Male	27.1%	24.5%	25.3%	p=0.422
% Charlson comorbidity score >1	36.4%	26.4%	29.7%	p=0.004
Medication Possession Ratio	0.927	0.935	0.932	p=0.446
% Non-White (County-Level)	30.3%	29.7%	29.9%	p=0.373
Median Income (County-Level)	$75,028	$74,421	$74,622	p=0.575
% using Intramuscular Route	23.9%	13.1%	16.6%	p<0.001
% using Oral Route	27.5%	46.9%	40.6%	p<0.001
% using Subcutaneous Route	48.6%	39.9%	42.8%	p=0.020
Age Ranges				p=0.102
18-39	11.6%	16.8%	15.1%	
40-59	53.9%	56.7%	55.8%	
60+	21.7%	12.2%	29.1%	
Insurance groups				p<0.001
Employer-Sponsored Insurance	80.2%	71.2%	74.1%	
Health Insurance Exchange	4.3%	19.0%	14.2%	
Other (including Medicare Part D)	15.5%	9.6%	11.5%	
At Person-Drug-Month Level	**No Patient Assistance**	**Used Patient Assistance**	**Overall Sample**	**Significance**
Average total claim amount*	$5,503.66	$6,168.68	$5,951.22	p<0.001
Average OOP charged to patient*	$42.35	$294.48	$212.04	p<0.001
Average OOP paid by patient*	$42.35	$7.22	$18.71	p<0.001
Annual drug costs to plan	$66,200.05	$71,482.58	$69,755.21	p=0.001
Annual OOP savings per patient***	$0.00	$3,493.56	$2,351.18	p<0.001

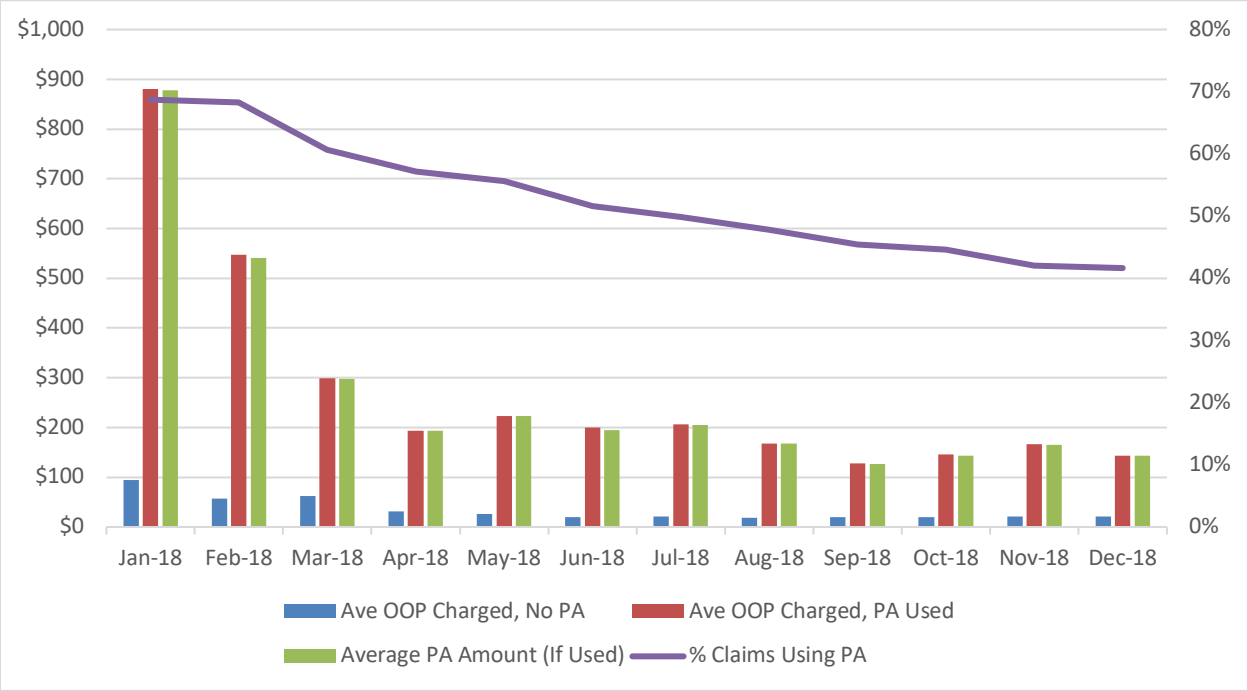
*Standardized to a 30-day claim using days supplied
**Annual costs calculated at the claim-level by dividing the cost by days supplied and multiplying the result by 365.25 days.
~Significance determined via t-test or chi-squared test
All monetary units reported in 2018 USD.
Patient-level data was tracked using de-identified patient id numbers from KPWA medical claims data.
Medication possession ratio was calculated as the quotient of days of medication supplied and days between first claim and end of coverage of the last claim at the patient level for the entirety of the year analyzed.
Median Income and % Non-White data from Washington State Office of Financial Management 2018. (54)

3.3.2 *Characterization of patient assistance*

Out of the entire sample, 531 patients (67.2%) used manufacturer-provided PAPs in at least one claim during the time period of 13 months. Those who used a PAP at least once during the year varied in their consistency of patient assistance use. The slight majority of patients using PAPs (51.7%) used them for every pharmacy claim. Less than a quarter of the patients (22.3%) used PAPs for less than half of their pharmacy claims, while 26% used PAPs for more than half, but not all of their claims.

People who used patient assistance programs had, on average, less comorbidities as measured by the Charlson comorbidity index, and were more likely to use a drug via subcutaneous injection than one via oral or intramuscular injection administration. (Table 1) They were also more likely to have insurance through the health care exchange. There was no significant difference between those using PAPs and those not in age, gender, drug adherence as measured by medication possession ratio, or in the median income or racial make-up of the counties where patients lived. PAP use was highest in January and tapered off throughout the year, mirroring trends in the magnitude of OOP charges over the year (Figure 1).

Figure 3.1. Out of pocket (OOP) charges and patient assistance amounts by month



OOP=Out of Pocket; PAP=Patient assistance program
All data from KP-WA from 01/2018 – 12/2018, cost data in 2018 USD
Percent claims using PAPS calculated at the month-level using the date the claim was picked up.
Patient assistance use defined as secondary payer assistance from a non-insurance or charity source.
Average OOP charged defined as the patient's financial responsibility for a claim, as charged by KPWA before applying any manufacturer financial assistance.

Patients who used any PAP had more expensive average total claims ($6,169 vs $5,504) and higher OOP (the amount charged to the patient before any secondary payer assistance is applied; $294 vs $42), but lower final OOP costs (the amount the patient ultimately paid for a claim; $42 vs $7) than their counterparts who did not use PA. (Table 1) Copay assistance covered 100% of OOP costs for 98% of claims using them. When considered for a year's supply of medication, patients who used PAPs cost their plan an additional $5,2833 per patient ($71,483 vs $66,200), not adjusting for other characteristics. Patient assistance also reduced patient actual OOP costs by $3,494 annually compared to non-users.

3.3.3 *Patient assistance programs among specific drugs*

According to KPWA's MS treatment guidelines, interferon B-1a, interferon B-1b "E", and glatiramer acetate "C" are the insurer's preferred brand drugs, with glatiramer acetate "G" being the only generic drug in the sample.(Table 2) Additionally, KPWA identifies fingolimod as being a "highly effective" MS drug, indicating that it should be considered when first line drugs fail. Approximately one fifth of the patients in the sample used each of the following drugs: interferon B-1a "A", fingolimod, glatiramer acetate "C", and dimethyl fumarate, with the remaining fifth of the sample spread between the other six drugs.(Table 2)

Table 3.2. Drug costs and patient assistance by brand name drug

Brand Name (Generic Name "Identifier")	Number of Claims (% of total)	Difference in average OOP charge (PAP users-nonusers)^	% PAP Users	Average PAP Amount (if used)^
Total (All Drugs)	7,465 (100.0%)	$276.76	52%	$305.19
AUBAGIO (teriflunomide)	196 (2.6%)	$197.56	64%	$194.18
AVONEX** (interferon beta-1a "A")	1,383 (18.5%)	$255.75	43%	$294.31
BETASERON (interferon beta-1b "B")	51 (0.7%)	$154.71	71%	$166.50
COPAXONE (glatiramer acetate "C")	262 (3.5%)	$404.39	49%	$415.58
EXTAVIA** (interferon beta-1b "E")	417 (5.6%)	$315.77	56%	$327.57
GILENYA~ (fingolimod)	1,433 (19.2%)	$171.56	65%	$206.18
GLATOPA**† (glatiramer acetate "G")	1,586 (21.3%)	$390.34	35%	$412.17
PLEGRIDY (peginterferon beta-1a)	19 (0.3%)	$48.35	32%	$60.71
REBIF** (interferon beta-1a "R")	546 (7.3%)	$231.12	73%	$254.94
TECFIDERA (dimethyl fumerate)	1,572 (21.1%)	$341.80	56%	$373.73

OOP= Out of pocket; PAP= Patient assistance program
All cost data in 2018 USD
Rows divide data by branded drug name with name of generic active ingredient and the first initial of the branded name as an identifier in parentheses to reflect KPWA's formulary designations.
Total number of claims excludes imputed data (months with no claim).
~ KP Considers "highly effective" in formulary designations
** KP preferred brand in formulary designations
† Generic
^Standardized to a 30-day supply

For each drug, the OOP charge for PAP users was higher than the OOP charge for non-PAP users, indicating PAP use was associated with higher OOP charges. Some drugs were associated with higher PAP use, however, including teriflunomide, interferon beta-1b "B", interferon beta-1b "E", fingolimod, interferon beta-1a "R" and dimethyl fumarate. The remaining drugs (interferon beta-1a "A", glatiramer acetate, and peginterferon beta-1a) had more claims without PAP use than with PAP use. Higher PAP usage did not appear to be associated with a brand's preferred status on the Kaiser formulary or average PAP amount. (Table 2)

3.3.4 *Price elasticity of demand*

The first part of the two-part model estimated PAP users were associated with a 1.9% higher probability of filling a claim than non-PAP users, although this was not significant (95% CI: -1.4% to 5.2%, p=0.26). This result did not change in significance when including an interaction term between PAP use and OOP charge (1.65%, 95%CI: -1.6% to 4.9% p=0.32). This effect was further attenuated in the second part of the model. The absence of patient assistance for a prescription fill in our sample was associated with an average $168 increase in patient cost and a 0.08% increase in demand, which translated to a price elasticity of 0.005 (95% CI: -0.05 to 0.06, p=0.852). While point estimates for PED varied by drug, none of the estimates were statistically different from zero.(Table 3) The average changes in patient cost by drug ($24 to $216) in the absence of patient assistance were statistically significant, however the average change in quantity demanded, as measured by days' supply given a claim is present, was not different from zero for any drug or overall. Excluding Medicare patients from the sample did not change these results.(Table A4)

Table 3.3. Price elasticity of demand (PED) by brand

Brand Name (Generic)	Number of person-months (n)	Change in Demand (Days supplied given a claim)	Change in Price (2018 USD)	Price elasticity of demand given PAP use	SD	95% CI	p-value
Total	3,683	-0.05	-$168.21	0.005	0.028	(-0.05 to 0.06)	0.852
AUBAGIO (teriflunomide)	118	-0.05	-$134.79	0.004	0.024	(-0.04 to 0.05)	0.862
AVONEX** (interferon beta-1a "A")	554	-0.04	-$139.07	0.004	0.027	(-0.05 to 0.06)	0.862
BETASERON (interferon beta-1b "B")	35	-0.06	-$122.01	0.006	0.039	(-0.07 to 0.08)	0.859
COPAXONE (glatiramer acetate "C")	124	-0.05	-$211.21	0.019	0.098	(-0.17 to 0.21)	0.830
EXTAVIA** (interferon beta-1b "E")	224	-0.05	-$193.20	0.004	0.028	(-0.05 to 0.06)	0.863
GILENYA~ (fingolimod)	872	-0.06	-$143.26	0.004	0.025	(-0.05 to 0.05)	0.856
GLATOPA**† (glatiramer acetate "G")	535	-0.04	-$150.52	0.004	0.029	(-0.05 to 0.06)	0.865
PLEGRIDY (peginterferon beta-1a)	6	-0.03	-$24.04	0.006	0.048	(-0.09 to 0.1)	0.878
REBIF** (interferon beta-1a "R")	370	-0.07	-$199.43	0.005	0.028	(-0.05 to 0.06)	0.851
TECFIDERA (dimethyl fumerate)	845	-0.05	-$216.71	0.004	0.022	(-0.04 to 0.05)	0.856

PAP= Patient assistance program; PED= Price elasticity of demand; SD= Standard deviation; CI= Confidence interval;
All cost data in 2018 USD
Rows divide data by branded drug name with name of generic active ingredient and the first initial of the branded name as an identifier in parentheses to reflect KPWA's formulary designations.
Total number of claims excludes imputed data (months with no claim) and claims without patient assistance (no price variation).
~ KP Considers "highly effective" in formulary designations
** KP preferred brand in formulary designations
† Generic
^Standardized to a 30-day supply

Table 3.4. Probability of filling a claim based on use of patient assistance

Probit Model: Specification of independent variables of interest	Difference in predicted probability of a claim	SE	p-value	95% CI
PAP Indicator, OOP Charged as individual variables	1.90%	0.0168	p=0.258	-1.39% to 5.18%
PAP Indicator, OOP Charged, PAP Indicator*OOP Charged, included individually and with interaction term	1.65%	0.0167	p=0.321	-1.61% to 4.92%

PAP= Patient assistance program; OOP= out of pocket; SE=standard error by delta method; CI=confidence interval.
*Positive value indicates higher probability of a claim given patient assistance
Outcomes are the results of running a probit model on the probability of a patient getting a claim given their OOP charge, patient assistance, and control variables, with standard errors clustered at the patient level.

Differences in predicted probability of a claim calculated using the margins command in Stata v15 over the variable for whether a PAP was used.
P-value based on chi-squared test for the PAP indicator variable with one degree of freedom.
All probit model specifications contained the same control variables described in the text.

3.4 DISCUSSION

Although PAPs are prevalent for high-priced pharmaceuticals, their use and impact are not well understood, particularly among specialty drugs. With data from all KPWA patients using drugs for multiple sclerosis during the period from December 2017 through the end of December 2018, we assessed patterns in PAP use and whether they were associated with drug demand. We found that KPWA's specialty pharmacy program, which works with patients to find financial support when needed and supports the use of manufacturer-sponsored patient assistance, succeeds in keeping out-of-pocket payments very low for its patients (average actual OOP cost for all patients <$20). Our evidence suggests that this PAP use was not associated with a change in demand for drugs, although significant selection bias may have produced results biased toward the null.

One key finding from this study is that a mid-sized integrated managed care organization in Washington state who embraced PAPs for specialty drugs significantly decreased their patients' actual OOP costs, and for many, eliminated patient OOP costs altogether. This runs counter to evidence from other patient populations regarding the high cost of specialty drugs to patients and concerns about high coinsurance rates in specialty drug tiers, and may be encouraging news for those concerned with drug adherence, as patients with less than $250 copay are less likely to abandon therapy.(2, 49) The uptake of this strategy by other payers may be complicated by a national trend of payers using copay accumulator programs. These programs, used in a growing minority of health insurance plans, prohibit patients from using pharmaceutical claims to reach

their deductibles in instances they have used PA, which may in turn negate any cost savings from PAP use.(58)

This study may also provide evidence that PAP use is associated with higher payer costs. A prior study of KPWA disease management programs for MS patients found that enrollment in their disease management program increased annual health plan spending on MS medication per patient by $15,000 ($p<0.001$), which was attributed to increased drug prices, increased adherence, and patients switching to more costly medications.(53) This analysis omitted discussion of PAPs, increased access to which may have facilitated patients to increasing their adherence or switching to more costly medications. It is also possible that a generous specialty pharmacy program would increase costs due to adverse selection in their patient population, with more costly enrollees attracted by the sanctioned use of PAPs.

Our analysis found that patient demand for MS specialty medication did not change significantly given the availability of PA. There are several likely reasons for this to be the case. Foremost, in the data we saw that there was strong selection bias for those with high OOP charges to seek secondary payer assistance, which came predominantly from PAP use. Therefore, annual patient medication costs seen in this dataset did not approach previously identified inflection points for prescription abandonment.(59) Additionally, this patient population had a high baseline adherence level due to their disease management program.(53) Due to the severity of their condition, patients have strong incentives to be adherent if prices stay within a reasonably affordable range.(60) Patients in this dataset therefore have strong support in addressing barriers to their medication,

which indicates results should not be extrapolated to other populations without OOP and adherence support.

Prior research on PAPs used for specialty drugs help put our research into context. A study using similar techniques to link pharmacy sales data to claims in order to identify PAP use among MS patients during a single year (2013) found comparable OOP charges and plan costs per claim.(49) Our findings from five years later indicate that, at KP-WA, the number of patients using PAPs for MS has increased from 46% to 60%, and that PAPs are now covering the entirety of patient costs as opposed to an average 61%. PAP use in other therapeutic areas may be less extensive; a study from 2013-2015 found PAP for oral cancer medications were only used in 12% of prescriptions, for which they covered less than 25% of the price charged.(61)

This study fits into a larger conversation about the role of cost-sharing for specialty medication, and whether value-based insurance design theories could be successfully applied to specialty drugs. Cost-sharing in health service utilization is meant to make patients at least minimally sensitive to the price the health goods and services they consume to prevent overconsumption and moral hazard. For pharmaceuticals, cost-sharing is also used as a lever to direct patient consumption between substitutable drugs, with lower cost-sharing amounts for generic or preferred brand-name drugs compared to non-preferred drugs. Beyond basic insurance design, cost-sharing is also at the center of other insurance reform proposals, such as VBID, where cost-sharing may be tied to clinical value.(60)

In light of this, insurers may need to reconsider formulary policies for specialty drugs. Patients in this cohort, when seeking aid, were able to get 100% of their cost-sharing responsibility paid for by drug manufacturers, effectively negating cost-sharing as a behavior modifier and instead making it effectively another form of reimbursement from manufacturers. Without cost-sharing to influence patients' decisions, insurers would need to rely more heavily on other management techniques such as prior authorization, step therapy, preferred status in clinical guidelines, and formulary exclusion in order to direct patient behavior, many of which KPWA already does with its specialty drugs.

This case study also provides evidence that patients with insurance akin to Kaiser Permanente may be almost completely insulated from their medication costs and accompanying annual price increases. Prior work at KPWA found that although disease management programs in MS increased payer costs through increased adherence and patient use of more expensive drugs, a significant portion of increased costs came was attributable to drug price inflation for patients who did not switch medications.(53) Other studies have found that a majority of PAPs are for therapies where a generic equivalent exists, and that PAPs increase branded drug use over generic drug use.(47, 62) Current state laws in Massachusetts and California have tried to address this issue by banning PAPS only for drugs with generic equivalents. Potentially just as problematic, however, is the fact that PAPS mask annual price increases, which can be substantial for specialty drugs that have no generic alternatives and are taken chronically.(50, 63) Future research should investigate the effect of PAPs on price inflation for drugs with no generic substitutes.

3.4.1 *Limitations*

Our study should be interpreted bearing its limitations in mind. It cannot be assumed that our results are generalizable to other patient populations; rather, our results provide insight into the potential outcomes of specialty drug programs like KPWA. Additionally, KPWA specifically stands out amongst its peers in its embrace of PAPs for specialty drug users in order to decrease financial barriers for patients, but this policy led to selection bias within our data. We used coupon use as a source of price variation to calculate our price elasticity estimates, however that variation was not randomly distributed among patients. Most patients with higher OOP charges used PA, and we therefore did not have adequate data to predict patient behavior in the face of high OOP charges without PA. This likely biased our PED estimates toward the null. Our price elasticity estimates, therefore, cannot be interpreted as causal. It is also difficult to generalize claims analysis for specialty drugs as many of these medications are administered intravenously and can therefore be covered by medical benefit, which would not be captured in pharmaceutical claims. Future analyses should take care in capturing specialty drug use in both medical and pharmacy benefit contexts.

In terms of interpreting our statistical analysis, the price variation in our study only goes one way (patients face the charged OOP cost, or a lower cost with the use of PA), so we can only comment on patient demand in relation to PAPS and not in relation to any change in OOP price. While we do our best to measure demand by both probability of a claim and total days supplied, we were unable to identify patients who fail to start their medication because of prices i.e. non-initiation. In terms of PAP identification, we cannot identify the use of pre-paid debit cards or direct to patient OOP reimbursement, and we may therefore be underestimating the magnitude of copay assistance.

We did not estimate impact on health outcomes or nondrug medical service use and expenditures, however this has been analyzed to some extent in other studies.(53)

3.5 CONCLUSION

As specialty drugs continue to consume a larger portion of our national drug spending, payers and patients alike must contend with high drug costs. Payers should consider the prevalence and impact of manufacturer-provided PAPS when considering cost-sharing rates in their formularies, and before implementing any sort of value-based insurance design aimed at specialty medications.

Chapter 4. ARGUMENT FOR EXPANDING VALUE-BASED INSURANCE DESIGN APPLICATIONS TO SPECIALTY DRUGS AND ISSUES PRESENTING BARRIERS AND OPPORTUNITIES FOR THAT EXPANSION

4.1 Introduction

This dissertation sought to discuss the potential for both cost containment and health gains by further applying value-based insurance design in the private US payer market (aim 1), but that the current ubiquity of full-coverage copay coupons for specialty drugs likely dampens patient responsiveness to changes in out-of-pocket costs, particularly for high-cost specialty drugs (aim 2). In this chapter, we discuss:

1) a brief overview of current value-based insurance design programs in the United States,

2) the argument for expanding VBID applications to specialty drugs, and

3) the issues presenting barriers to and opportunities for expansion of those principles to specialty drugs

4.2 Overview of VBID in the United States

Value-based insurance design (VBID) is the overarching concept that health insurance should vary cost-sharing for products and services with their clinical and economic value (cost-

effectiveness). The logic behind this idea is that patients will maintain access to a wide range of medical products and services but will be incentivized to use a higher amount of services with a robust evidence base for producing the most health. The hypothesized benefits of this idea were first published in 2001, and numerous studies have since been published to underscore its theoretical and empirical validity.(5, 6, 9)

One of the most straight-forward and common ways of implementing VBID has been through its application to pharmaceutical products, an area in which cost-effectiveness evidence has become increasingly widespread. In theory, cost-sharing for high value drugs is greatly reduced or eliminated altogether while cost-sharing for low-value drugs increases. Both private and public payers in the United States have implemented versions of VBID, including demonstration programs in Medicare Advantage, TRICARE, and several state employee plans.(11, 24, 25, 27, 28) A 2018 systematic review of programs implementing VBID to increase medication adherence found 21 published studies which compared the effects of VBID to traditional prescription drug plans. The aggregated evidence suggested that VBID improved medication adherence (0.1%-14.3%), decreased out-of-pocket spending, and had variable effects on overall health spending.(9) Other literature reviews of VBID's application to medication found similar results of increased medication adherence and variable effect on costs. (64-66)

One specific type of VBID implementation is a value-based formulary (VBF), where medications offered by a payer are sorted into cost-sharing tiers based on cost-effectiveness evidence. Only one private payer to date has explicitly implemented an entire formulary based on cost-effectiveness thresholds, finding a net decrease in health care expenditures of $8 per

member per month.(14) Aim 1 of this dissertation found minimal uptake of value-based formulary design in private insurance plans during the years before the Affordable Care Act was implemented (2010-2013), suggesting decreasing OOP costs for generic drugs and no significant differentiation of drugs valued $10,000/QALY and over.(67)

4.3 ARGUMENT FOR EXPLORING THE APPLICATION OF VBID TO SPECIALTY DRUGS

In a 2010 *Health Affairs* article, a Dr. Robinson claimed that, "for value-based design principles to have a stronger clinical and economic impact, they should be extended to expensive services and to those for which the evidence is limited or controversial."(68) His argument rested on the logic that cost containment in health care can only have a big impact when applied to areas with the biggest costs. In pharmaceutical spending, the fastest growing area is specialty drugs. While there is no universal definition for specialty drugs, Medicare defines them as drugs for which the negotiated monthly price is $670 or higher; in addition to being expensive, they are complex molecules requiring specialty distribution, handling and/or administration.(56)

Pharmaceutical spending has shifted dramatically to specialty medicines in the past decade. Of net spending on pharmaceuticals, the share of specialty drugs rose from 25% in 2008 to 47% in 2017, becoming almost half of all US spending on pharmaceuticals despite making up only 1-2% of claims.(18, 69) Beyond the high cost of specialty drugs, part of the reason for this increase in spending was the increased number of specialty drugs on the market.(70) The largest proportion of new medicines launched from 2013-2018 were specialty drugs.(18) From 2003-2014, the number of unique specialty drugs as a percent of all prescription drugs quadrupled, from 3% to

12% of total drugs. During this same time period, fills for specialty drugs increased by 200%, spending increased by almost 300% (as percentages of total drug fills and spending).(16)

In light of this transition, specialty drugs are increasingly expensive for both patients and payers. Patients with illnesses for which specialty drugs are indicated have been experiencing higher amounts of cost-sharing, particularly relative to other drugs. From 2003-2014, median OOP spending increased by 46% for specialty drugs and decreased by 57% for non-specialty drugs.(16) In 2018, the total annual OOP costs in Medicare Part D for specialty drug indications were $5,000, $6,700, and $9,200 for rheumatoid arthritis, multiple sclerosis, and chronic myeloid leukemia respectively.(71) A 2019 paper estimated annual OOP costs for MS patients in the US ranged from $6,500-$7,500 (72).

Payers have been dealing with the increased specialty drug costs in a number of ways, including passing along more costs to patients through coinsurance and specialty drug tiers. A 2018 report of health insurance benefits found 52% of workers at large firms were subject to at least one specialty drug tier, 60% of which had coinsurance.(3) Payers have struggled with balancing the costs of specialty drugs with maintaining patient access to their potential benefits. In 2017, the *Health Affairs* blog called payer management of specialty drugs a "more difficult and unsettled situation… making the top tier work as a restraint on high specialty prices is still an ongoing project." (2) Specialty drug coverage expert, James Chambers, claimed in 2014 that "[p]ayers have not yet found the formula for managing specialty drugs. Insurers should continue to experiment with a combination of existing formulary management tools and novel strategies to maximize patient access to specialty drugs while minimizing their cost."(19)

Having established that specialty drugs are a large, and growing, portion of pharmaceutical spending in the United States, we need to next explore whether VBID principles could be successfully applied to the drug class. The two key drivers of VBID success, as described in a paper co-authored by VBID creator A. Mark Fendrick, are patient responsiveness to OOP cost changes and increased adherence leading to better clinical outcomes.(9) Patients must be able to change their behavior to a certain extent in response to OOP costs, opting for higher value products when available, and then be more optimally adherent to those products given more affordable prices. That adherence should then equate to better clinical outcomes for patients in order to prevent downstream healthcare costs.

There is a good amount of published evidence of patients being responsive to OOP costs for pharmaceutical products. Price elasticity of demand (PED) for traditional drugs is estimated to be between -0.33 to -0.12, meaning for every 100% increase in OOP cost for a traditional drug, demand will decrease between 12-33%.(1, 73) There is reason to believe PED for specialty drugs may be different. Patients may have a stronger demand for specialty drugs if there are no desirable or therapeutically equivalent alternatives, and yet the significantly higher OOP costs may exceed patients' willingness or ability to pay. Recent reviews of cost-sharing responsiveness with specialty drugs found that higher cost sharing is associated with reductions in utilization of specialty drugs for RA, MS, and cancer, but were not as strong for specialty drugs as found with traditional pharmaceuticals (elasticities ranging from -0.07 to -0.21).(56, 74) Comparing studies using different measurement of demand and adherence, they found outcomes were stronger for non-initiation or abandonment of a prescription at a pharmacy, and were smaller for refill

behavior and drug spending once a patient had initiated therapy.(56) One paper found that, for multiple sclerosis drugs, drug use and adherence only started to diminish for patients at annual OOP payments of over $442 and $890 respectively.(59) In the second aim of this dissertation, we discuss that these elasticity estimates may not capture the full situation, however, given the prevalence of copayment coupons for specialty drugs. Our findings suggest that patients are responsive to OOP costs only when faced with the full OOP amount absent a coupon.

The second key to a successful VBID application is for increased adherence to lead to better clinical outcomes, and although it varies by condition, there is evidence that increased adherence to specialty drugs can do this.(75, 76) A review of Kaiser Permanente Washington's integrated multiple sclerosis disease management program, for example, found that patients with MS are less likely to have relapses, emergency department visits and hospitalizations if they are adherent to disease-modifying treatments such as specialty medication.(53) The high clinical benefit of being adherent to many specialty drugs is indeed what is often driving the conversation for applying VBID to specialty drugs.(9, 71) One article put it this way: "Evidence from value-based health plan design has focused primarily on chronic disease medications with generic competitors, but this approach could also be used to offer specialty drugs with very high clinical benefit to patients with less out-of-pocket obligation. Conceptually, it would be reasonable to steer patients to the most effective option within a specialty class (for example, the best tumor necrosis factor inhibitor for rheumatoid arthritis)."(69) Beyond clinical outcomes, VBID applied to specialty drugs may also address other important factors, such as ability to work: "From a policy perspective, consideration should be given to whether value-based insurance design approaches may offer more optimal strategies for facilitating drug access to high-value specialty

medications. Such an approach may be particularly sensible for employers who are also invested in broader outcomes, such as reducing the absenteeism and lost productivity that are associated with poor medication adherence."(56)

There is relative consensus about the overarching cost burden of specialty drugs and payers' need to think creatively about how to handle that burden. The first aim of this dissertation provided evidence that there is further room in modern formularies to distinguish high-cost drugs by value.(67) Additionally, there is an inverse relationship between OOP costs and demand specialty drugs, to whom being more adherent would lead to clinical and productivity-related benefits. Meeting the conditions to successful application of VBID is therefore necessary but not sufficient for the policy to be enacted. In the next section, we outline current barriers to more public and private payers applying VBID to specialty medications and potential opportunities for overcoming those barriers.

4.4 Barriers and opportunities in US payers applying VBID to specialty medications

4.4.1 *Traditional Formulary Structures*

One of the primary ways in which payers determine pharmaceutical cost-sharing levels is through formulary tiers. Traditionally, the first tier in formularies are for generic medications and have the lowest cost-share, the next two tiers are for preferred and non-preferred brand name drugs with increasing cost-shares, respectively. Many payers have recently started including at least one specialty drug tier as well. In 2018, 98% of private insurance plans covered specialty

drugs, with 52% of those plans having at least one specialty drug tier.(3) Specialty drug tiers shared drug costs primarily through co-insurance (59% of specialty tiers with an average rate of 26%) or copay (34% of specialty tiers with an average copay of $99).(3) Most use coinsurance in order to pass along greater portions of drug costs, which is inherently a cost-based insurance design, although restrictions and exclusions vary broadly based on drug characteristics within these plans.(77) It would be difficult to apply VBID to specialty drugs in smaller formularies because there is little room for value-based nuance when all specialty drugs are in a single tier.

One option for payers that would allow them to keep a traditional formulary structure would be to move higher value specialty drugs to non-specialty tiers, potentially applying a set cost-share amount in place of coinsurance. Fendrick et al (2014) advocate for high-value drugs to have cost-sharing levels no greater than cost-sharing for non-specialty, non-preferred branded medications, an approach has been mandated in places like New York and Vermont.(60) Another option would be to increase the number of tiers to create preferred and non-preferred specialty tiers.(3) This was put forward as an option in 2010 by Robinson et al as an alternative to moving high-value specialty drugs to an existing tier (such as the preferred brand tier) in order for a distinction to be made between specialty drugs by value.(68)

Alternatively, payers could apply VBID principles to other utilization management tools beyond cost-sharing to influence prescription behavior, including variations of step therapy, prior authorization, deductibles, and formulary exclusion. Step therapy and prior authorization would require patients to try high value drugs before moving to those considered lower value, unless they have a particular circumstance granting prior authorization. Plans seem to be doing this

already for specialty drugs, incorporating step edits into their decisions for drugs like multiple sclerosis and rheumatoid arthritis, although these would need to be based on a measure of value like cost-effectiveness to be value-based. Fendrick et al additionally suggest step therapy with copayment relief, or not punishing the good soldier, suggesting that payers "…selectively reducing cost-sharing for specialty medications if the patient does not respond as desired to another medication." This structure would "offer relief from higher cost-sharing for biologics after failure of the more preferred regimen."(60) This VBID implementation idea acknowledges that there should be incentives to use preferred medications, but also acknowledges that each patient is going to have different needs and responses to medication. In cases where patients fail the preferred medication, the 2nd and 3rd line drugs have higher value and cost-sharing can reflect that.(60)

A more blunt instrument would be formulary exclusion, where drugs over a certain cost-effectiveness threshold would not be covered at all. Most health plans have exclusions, although their reasons for excluding specific therapies may vary. One study found that health plans will more often restrict coverage of drugs if their indicated conditions have multiple therapeutic alternatives.(77) For example, rheumatoid arthritis drugs, of which there are many therapy options, were restricted in seventy-five percent of formularies considered.(77) Another study found that Medicare Part D plans varied in their specialty drug exclusions depending on rebates and discounts leveraged by excluding competitor's products from the formulary. Only one payer, to my knowledge, has publicly proposed a plan with value-based drug exclusion. CVS Caremark, a large pharmacy benefit manager in the United States, proposed offering plans excluding drugs that cost over $100,000/QALY, however they did not ultimately implement the plan due to

pushback.(24) Total exclusion based on drug value may be too broad to gain widespread support, as payers will still want patients to have access to drugs under appropriate circumstances.(19) A more nuanced interpretation could be to restrict coverage by indication or subgroup. For drugs without practical alternatives, coverage may be restricted to certain subgroups, such as patients meeting certain criteria under which the drug is cost-effective or for those with a specific presentation of a condition.(77)

4.4.2 *Value and Generic Status*

There are several issues with applying the concepts of generic status and value to specialty drugs. Generic status and value are two distinct concepts for pharmaceutical products, but they have a strong association due to brand name monopoly pricing power. High prices of brand drugs are used as the numerator in cost-effectiveness equations, generally linking branded drugs to higher cost-effectiveness ratios (lower value) and generic drugs to lower cost-effectiveness ratios (higher value). As seen in Brouwer et al (2019), payers have historically tended to use generic status to set their formularies rather than more nuanced cost-effectiveness information.(67) Prior iterations of VBID have also used generic status as a proxy for value by removing cost barriers to high-value generics or incentivized patients to switch to higher value generic alternatives, and payers seem to be more comfortable placing restrictions on drugs with generic alternatives.(9, 77)

One major barrier to applying VBID to specialty medications is that many specialty medications do not have generic versions, and if they do, the generic versions do not have the same price reduction as traditional pharmaceuticals. Research on the effect of generic entry on specialty

drugs is limited but there is early evidence of that prices do not significantly reduce for these drugs following generic availability.(78) There are several potential reasons for this: small potential market size and availability of second generation drugs may discourage generic entrants, and fewer generic entrants mean less price competition.(78) Additionally, it is much more costly to produce biosimilar drugs than to produce traditional generic drugs, leading to a price reduction of 10-50% rather than the typical 80-85% for traditional generics.(71) Barriers to generic entry for specialty medications, and smaller reductions in price upon for generics that enter the market, will lead to less obvious differences in value based on cost-effectiveness ratios.

Basing decisions on cost-effectiveness evidence can be problematic for specialty drugs for other reasons as well. Specialty drugs often have higher ICER values than traditional drugs, with one study estimating that 26% of specialty drugs having an ICER of over $150,000 compared with only 9% of traditional drugs.(19) The same study also found that, despite higher costs, specialty drugs generally offer higher QALY gains as compared to non-specialty drugs, so their cost-effectiveness ratios can be difficult to compare.(19) Beyond the simple interpretation of cost-effectiveness ratios, specialty drugs often have multiple indications and patient subgroups that are associated with varying cost-effectiveness levels, which can make it hard to apply value judgements to an aggregated population.(68) One way to address the issue of specialty drug value would be to apply different ICER thresholds to specialty drugs than to traditional drugs, particularly if they treated subgroups for which society made exceptions. For example, one study found that US health insurance plans put less restrictions on drugs for cancer, orphan diseases, and pediatric populations, indicating different willingness to pay thresholds that a VBID structure should reflect.(77)

Another way to address concerns regarding specialty drug value would be for payers to avoid a complete classification of products, but rather to target and protect specific specialty drugs for which value is demonstratively clear.(68) These drugs could then be targeted for formulary structures outlined above. At baseline, specialty drugs that could be considered for value-based insurance design would need to have multiple therapeutic alternatives among which a patient could reasonably choose. Plans know this to a certain extent.; a 2018 study found plans had more restrictions for specialty drugs in therapeutic areas with more alternatives, like rheumatoid arthritis.(77) Those drugs would also need to have a clear connection from adherence to health outcomes that have the potential to save costs downstream, and some meaningful variation in cost-effectiveness estimates between therapies.

4.4.3 *Copay Coupons and the Effectiveness of Cost-Sharing*

Another potential hurdle for applying value-based formulary principles to specialty drugs is that drug manufacturers have developed programs to subsidize patient out-of-pocket costs and undermine the influence of cost-sharing. These copay assistance programs have become increasingly prevalent and are disproportionately applied to specialty drugs.(49) One study estimated that as many as 46% of claims for multiple sclerosis drugs used copayment assistance programs and 42% of specialty drug claims overall, producing an average 61% reduction in out of pocket costs. (18, 49) More recent data from the second aim of this dissertation suggests that, in one mid-sized regional integrated health system that actively assists patients in obtaining coupons, coupons are even more widely available for conditions like multiple sclerosis and will cover 100% of the OOP charge. Their impact on demand and drug choice is difficult to measure,

however, because the occurrence and magnitude of copay assistance is rarely captured in claims data or is masked through various schemes, such as drug manufacturers issuing untraceable debit cards to patients. Aim 2 of this dissertation explored the impact of these copay coupon programs on patient demand and found that, while patients are relatively inelastic to cost-sharing for pharmaceuticals in general, copay coupons in the absence of copay accumulators likely negate any mediating impact of cost-sharing on patients.

Payers could potentially integrate the practice of copay coupons with value-based insurance design. Kaiser Permanente Washington, the integrated care community providing data for the second aim of this dissertation, embraced the practice of copay coupons and connected specialty drug users with copay assistance without restrictions.(53) While this policy increased patient adherence to multiple sclerosis drugs, it did not correspondingly decrease any health care service use and therefore significantly increased overall plan costs in the year after implementation.(53) To harness the benefits of VBID in the face of copay coupons, payers could accept the use of support for consumer cost-sharing, but only in specific circumstances. For example, payers could allow copay assistance for high-value medications when clinically appropriate and forgo utilization management in these situations to encourage medication use.(79) This strategy could be implemented in place of or in combination with the growing use of copay accumulators, which prohibits industry-funded copay assistance from counting toward a patient's deductible.(71) It is difficult to predict the effect of copay accumulators on this relationship, however, as increasing numbers of payers using them will compete with state legislation banning their use in certain situations.(58)

4.4.4 *Risks and Uncertainties*

Decreasing cost-sharing for high value specialty medications (and subsequently increasing cost-sharing of low value alternatives) has both potential benefits and drawbacks for payers. The uncertainty around the magnitude of those risks and benefits may be a large barrier to VBID's explicit application to specialty drugs. Increased patient adherence to specialty drugs may increase payer costs in the short term without assurance that there will be decreased health care service utilization downstream to offset those costs.(1) Another potential risk is that increasing patient costs for low-value specialty drug could lower adherence or stop patients from using medication at all, which could in turn increase health care service utilization downstream and increase costs.(80) While economic theory and empirical data from traditional drugs offer us insight into possible outcomes, there is very little evidence of how VBID would ultimately affect payer costs as applied to specialty drugs or how changes in OOP costs affect nondrug medical service use and expenditures.(56) There will need to be more research on specific applications of VBID to specialty drug classes and estimates of the impact on costs for the payers and patients before there is likely to be broad uptake of VBID in the specialty drug arena.

4.5 CONCLUSION

VBID shows promise in increasing patient adherence to medication while not increasing plan costs across many medication classes. Payers are looking for ways to contain the costs of specialty drugs, the largest growing area in pharmaceutical spending, without unreasonably restricting patient access. Many have suggested VBID principles be applied to specialty medication, however no empirical evidence exists of payers explicitly applying value principles to specialty drugs in their formularies. This is likely to due to several key barriers, including

existing formulary structure, disagreement on the valuation of specialty drugs, the effectiveness of various utilization management tools, and uncertainty around effects on payer costs.

More research is needed to understand the specific circumstances and applications in which value-based decision making could be effectively used to contain costs for both payers and patients for specialty medications. Future studies should follow trends in copayment coupon distribution to identify patient populations that have more or less exposure to them to help payers identify when cost-sharing tools would be most effective. Payers will also need to understand the real-world effectiveness of implementing value-based formulary adjustments, such as preferred and non-preferred specialty drug tiers and comparing the use of copay versus coinsurance within those tiers. Within those tiers, researchers should also think about the specific conditions for which tying cost-sharing to cost-effectiveness would be most effective, for example comparing treatments for chronic disease (such as multiple sclerosis, rheumatoid arthritis, HIV) to curable conditions (hepatitis C).

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APPENDIX A

Table A1. Regression output for effect of value designation on average out of pocket drug cost

Variable	Log-OLS	PA (unstr)	PA (AR1)	Random	Fixed
year	-0.058	-0.053	-0.045	-0.049	-0.045
(se)	0.01	0.01	0.01	0.01	0.01
Tier					
1	0.514	0.524	0.534	0.526	(omitted)
(se)	0.03	0.03	0.03	0.03	
2	0.665	0.744	0.759	0.762	(omitted)
(se)	0.07	0.08	0.08	0.08	
3	0.796	0.895	0.899	0.914	(omitted)
(se)	0.07	0.08	0.08	0.08	
4	0.659	0.763	0.767	0.783	(omitted)
(se)	0.08	0.08	0.08	0.08	
Tier*Year					
1	-0.004	0.002	-0.004	0.005	0.008
(se)	0.01	0.01	0.01	0.01	0.01
2	0.041	0.04	0.037	0.042	0.05
(se)	0.01	0.01	0.01	0.01	0.01
3	0.026	0.023	0.024	0.025	0.033
(se)	0.01	0.01	0.01	0.01	0.01
4	0.029	0.026	0.023	0.028	0.034
(se)	0.01	0.01	0.01	0.01	0.01
Brand Name Indicator	0.291	0.31	0.291	0.305	(omitted)
(se)	0.07	0.07	0.07	0.07	
Over the counter Indicator	-0.036	0.02	0.001	0.013	(omitted)
(se)	0.09	0.09	0.09	0.09	
Single Source Generic Indicator	0.037	0.043	0.046	0.047	(omitted)
(se)	0.07	0.07	0.08	0.06	
Ln(Average Wholesale Price)	0.207	0.148	0.145	0.142	0.099
(se)	0.02	0.02	0.02	0.02	0.02
Ln(Payer Cost)	0.232	0.23	0.233	0.229	0.203
(se)	0.02	0.02	0.02	0.02	0.02
Constant	0.725	0.963	0.959	0.989	2.038
(se)	0.07	0.06	0.06	0.06	0.11

*Abbreviations: Log-OLS, logged ordinary least squares model; PA(unstr), population average with an unstructured correlation matrix; PA(AR1), population average with an auto-correlated ; random, random effects model; fixed, fixed effects model; se, standard error

Table A2. Model Output by Insurance Plan Type

Variable	PPO	HMO	POS	HDHP	Other
year	-0.06	-0.018	-0.068	-0.149	-0.063
(se)	0.01	0.01	0.01	0.01	0.01
Tier					
1	0.557	0.53	0.635	0.754	0.596
(se)	0.03	0.04	0.04	0.06	0.03
2	0.817	0.914	0.917	1.065	0.946
(se)	0.08	0.09	0.09	0.12	0.09
3	0.949	1.153	1.084	1.134	1.046
(se)	0.08	0.09	0.1	0.12	0.09
4	0.822	0.961	0.938	1.187	0.92
(se)	0.08	0.1	0.1	0.12	0.09
Tier*Year					
1	-0.001	-0.021	-0.02	0.084	0.018
(se)	0.01	0.01	0.01	0.01	0.01
2	0.04	0.005	0.052	0.082	0.029
(se)	0.01	0.01	0.01	0.01	0.01
3	0.036	-0.017	0.033	0.096	0.04
(se)	0.01	0.01	0.01	0.01	0.01
4	0.04	-0.014	0.034	0.055	0.018
(se)	0.01	0.02	0.01	0.02	0.02
Brand Name Indicator	0.28	0.388	0.376	0.371	0.362
(se)	0.07	0.08	0.08	0.08	0.08
Over the counter Indicator	-0.031	0.085	-0.018	-0.402	0.034
(se)	0.1	0.1	0.11	0.12	0.1
Single Source Generic Indicator	0.046	0.068	-0.024	0.569	0.063
(se)	0.06	0.07	0.08	0.06	0.07
Ln(Average Wholesale Price)	0.124	0.122	0.186	0.538	0.166
(se)	0.02	0.02	0.03	0.05	0.02
Ln(Payer Cost)	0.24	0.077	0.084	0.027	0.123
(se)	0.01	0.01	0.02	0.02	0.02
Constant	1.031	1.451	1.215	0.403	1.028
(se)	0.06	0.07	0.09	0.19	0.07

Abbreviations: HMO, health maintenance organization; PPO, preferred provider organization; POS, point of service plan; HDHP, high-deductible health plan; se, standard error

legend: * $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table A3. Random effects regression output of effect of value designation on OOP drug costs, stratified by insurance market concentration

	Not Concentrated	Moderately Concentrated	Highly Concentrated
Variable	HHI<1,500	1,500<HHI<2,500	HHI>2,500
year	-0.085	-0.052	-0.059
(se)	0.02	0	0
Tier			
1	0.51	0.597	0.597
(se)	0.05	0.01	0
2	1.08	0.958	0.923
(se)	0.11	0.01	0.01
3	1.059	1.089	1.054
(se)	0.11	0.01	0.01
4	0.966	0.97	0.927
(se)	0.13	0.01	0.01
Tier*Year			
1	0.044	0.012	0.018
(se)	0.02	0	0
2	0.057	0.05	0.057
(se)	0.03	0	0
3	0.084	0.06	0.066
(se)	0.03	0	0
4	0.081	0.035	0.043
(se)	0.04	0	0
Brand Name Indicator	0.266	0.36	0.383
(se)	0.1	0.01	0.01
Over the counter Indicator	0.157	-0.036	0.028
(se)	0.11	0.01	0.01
Single Source Generic Indicator	0.089	0.124	0.106
(se)	0.1	0.01	0.01
Ln(Average Wholesale Price)	0.468	0.284	0.319
(se)	0.03	0	0
Ln(Payer Cost)	-0.048	0.026	0.007
(se)	0.02	0	0
Constant	0.194	0.808	0.691
(se)	0.1	0.01	0.01

HHI=Herfindahl-Hirschman index; OOP=out of pocket costs; se, standard error

Table A4. Price elasticity of demand (PED) by brand excluding Medicare patients

Brand Name (Generic)	Number of person-months (n)	Change in Demand (Days supplied given a claim)	Change in Price (2018 USD)	Price elasticity of demand given PAP use	SD	95% CI	p-value
Total	3,288	-0.05	-204.34	0.004	0.023	(-0.05 to 0.06)	0.852
AUBAGIO (teriflunomide)	105	-0.06	-130.92	0.004	0.027	(-0.05 to 0.06)	0.856
AVONEX** (interferon beta-1a "A")	474	-0.04	-108.24	0.004	0.027	(-0.05 to 0.06)	0.869
BETASERON (interferon beta-1b "B")	35	-0.06	-122.99	0.005	0.042	(-0.08 to 0.09)	0.888
COPAXONE (glatiramer acetate "C")	100	-0.04	-188.57	0.021	0.137	(-0.25 to 0.29)	0.858
EXTAVIA** (interferon beta-1b "E")	224	-0.05	-199.13	0.004	0.029	(-0.05 to 0.06)	0.870
GILENYA~ (fingolimod)	798	-0.07	-118.39	0.004	0.026	(-0.05 to 0.05)	0.853
GLATOPA**† (glatiramer acetate "G")	470	-0.03	-140.35	0.004	0.032	(-0.06 to 0.07)	0.882
PLEGRIDY (peginterferon beta-1a)	6	-0.02	-24.88	0.004	0.050	(-0.09 to 0.1)	0.912
REBIF** (interferon beta-1a "R")	345	-0.07	-172.78	0.004	0.027	(-0.05 to 0.06)	0.855
TECFIDERA (dimethyl fumerate)	731	-0.05	-204.34	0.004	0.023	(-0.04 to 0.05)	0.845

PAP= Patient assistance program; PED= Price elasticity of demand; SD= Standard deviation; CI= Confidence interval;
All cost data in 2018 USD
Rows divide data by branded drug name with name of generic active ingredient and the first initial of the branded name as an identifier in parentheses to reflect KPWA's formulary designations.
Total number of claims excludes imputed data (months with no claim) and claims without patient assistance (no price variation).
~ KP Considers "highly effective" in formulary designations
** KP preferred brand in formulary designations
† Generic
^Standardized to a 30-day supply

VITA

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