

# Persistent High Utilization in a Privately Insured Population

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A small percentage of patients are responsible for the majority of healthcare spending in the United States. This trend has remained extremely stable over the years, with only slight fluctuations in the amount of healthcare spending attributable to the top users. Between 1970 and 1996, approximately 66% to 72% of annual healthcare costs were attributable to the top 10% of healthcare users; 50% to 58% were attributable to the top 5%, and 26% to 30% were attributable to the top 1%.<sup>1</sup> Health insurance is designed to provide protection from financial ruin due to unexpected illness or random events. However, the basic principles of risk-sharing, fundamental to health insurance, are undermined when a concentrated group of users spend a large amount of annual healthcare dollars for multiple years. Gaining a better understanding of individuals with persistent high costs is critical for effective interventions to be designed to meet their needs.

Despite the impact that this small group of high users has on overall healthcare spending, little work has been done to describe this population in detail. The majority of the work conducted to evaluate the persistence of high users has utilized the Medicaid and Medicare populations.<sup>2,3</sup> One such study found that of those Medicaid enrollees in the top 1% of spenders in the first year, approximately 46.4% remained in this position in the following 2 years.<sup>2</sup> It should be noted that these costs included institutional long-term care services such as nursing facility care. Individuals receiving long-term care coverage represent a unique population, and their spending patterns may have limited generalizability.

Studies of the general population also demonstrate persistence in high users, though not at the level seen in the Medicaid population. Using a working age sample, Monheit and colleagues found that of the top 5% of spenders in 1 year, approximately 30% remained in this position the following year.<sup>4</sup> However, it should be noted that this study focused on only 2 years of data. Another study, by Naessens and col-

## ABSTRACT

**Objectives:** To describe individuals characterized as persistent high users—that is, individuals who are in the top 10% of users every year over the 3-year study period.

**Study Design:** Retrospective cohort study of 4 groups in a privately insured population. Groups were defined by the number of years an enrollee was in the top 10% of the spending group (top decile) for the period from 2009 to 2011: persistent high-user group (3 out of 3 years in the top decile spending group); frequent high-user group (2 out of 3 years in top decile); incidental high-user group (1 out of 3 years in top decile); and never high-user group (0 out of 3 years in top decile).

**Methods:** This study used insurance claims data to examine enrollees with persistently high health service utilization. Data for the year 2008 were utilized to assess baseline individual characteristics. Annual data for 2009 to 2011 were used to examine healthcare expenditures, utilization patterns, and specific clinical conditions among the 4 groups of the study sample.

**Results:** Among 42,038 enrollees, 1216 (2.9%) met the criteria as persistent high users. Over a 3-year period, this group accounted for 21% of total healthcare expenditure. Compared with the other groups, persistent high users had higher overall disease burden due to multiple chronic conditions and incurred significantly higher expenses in medication and professional services (including primary and specialty care).

**Conclusions:** This study highlights the need to proactively engage employees and their dependents for primary and secondary prevention of common chronic diseases before an individual's health status, healthcare utilization, and medical cost become difficult to manage.

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### Take-Away Points

Persistent high-use individuals are identified as those in the top 10% spending category every year in a 3-year period.

- These individuals represent 2.9% of total enrollees but account for 21% of total healthcare spending. This group also had higher overall disease burden due to multiple chronic conditions.
- Compared with those who are never in the top 10% in any year, the persistent high-user group incurred 17 times higher total healthcare expenditure and 17 times higher medication expenditure.
- Innovative interventions focusing on prevention and management of common chronic diseases have great potential to affect costs for this group.

leagues, found that among adults aged 18 to 64 years, of those in the top 5% in the first year, approximately 26%, 21%, and 20% remained in this position in the second, third, and fourth years, respectively.<sup>5</sup> However, this study did not thoroughly characterize the population beyond its expenditures.

Despite the fact that approximately 55% of Americans are covered by employer-based insurance,<sup>6</sup> previous work on persistent high users has focused on Medicare and Medicaid populations and has done little to describe individuals enrolled in an employer-based health insurance plan. This study aims to describe individuals with persistent high utilization in an employer-based health insurance plan through basic demographics, the types of conditions they have, and the types of services they utilized. A more thorough understanding of what makes these individuals a more expensive population may assist in the strategic reorganization of a healthcare system that will address these health needs in an effective and timely manner.

## METHODS

### Study Design and Setting

The study samples were drawn from employees of a large employer in Pennsylvania and the employees' dependents. The employer has several locations across the state of Pennsylvania and employs more than 30,000 blue- and white-collar employees—the majority of whom reside in urban locations. Until 2011, the employer offered only a traditional preferred provider organization plan without any deductible to its employees. In 2011, the plan implemented a small annual deductible, which ranged from \$250 to \$500.

### Data Analysis

This study used Highmark insurance claims data to examine enrollees with persistently high health service utilization. We limited the population to those continu-

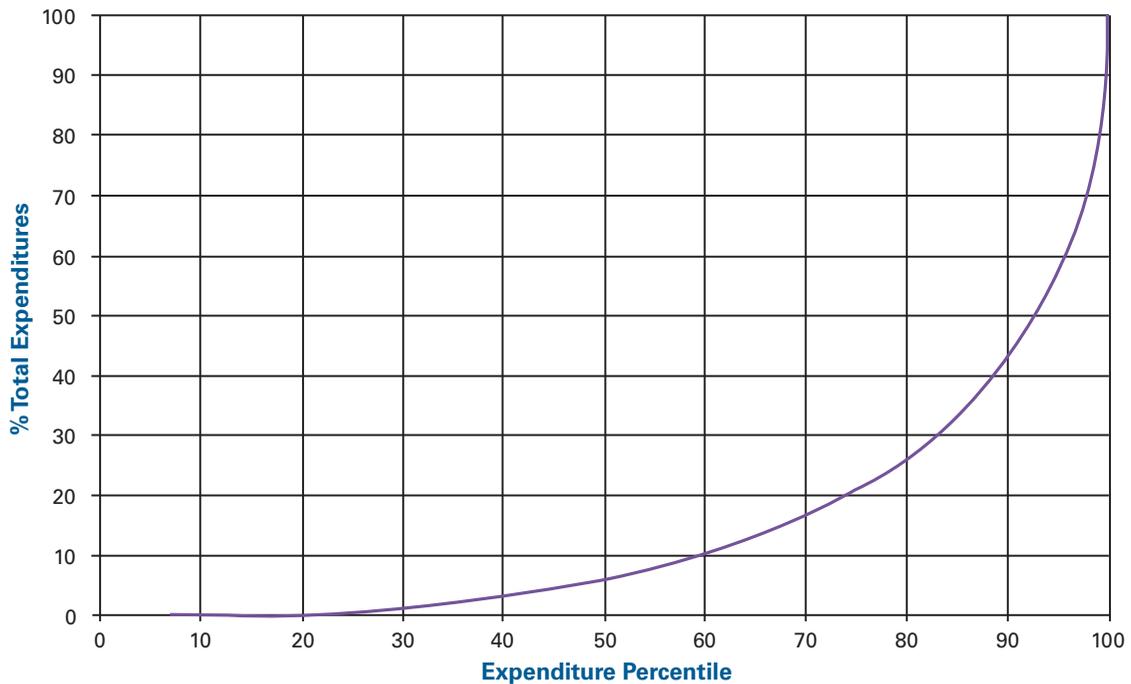
ously enrolled for the period of 2008 to 2011. By doing so, we minimized potential selection bias that could result from the population changing over time due to noncontinuous enrollment. We were thus able to look at the annual healthcare expenditure and utilization of the same population for 4 years. Data for the year 2008 were utilized to assess baseline individual characteristics, including gender, age, and area of residence. Data for 2009 to 2011 were used to examine healthcare expenditures, utilization patterns, and specific clinical conditions among the 4 user groups of the study sample, as defined below. Rural-Urban Commuting Area Codes (version 2.0) were calculated for each enrollee residence and categorized into 3 levels: urban, large rural/town, and small rural/isolated.

Healthcare costs include the amount paid by the insurer and the amount of cost sharing paid by individuals. Costs were examined in expense categories and by the type and frequency of utilizations. The 4 user groups referred to in this study were defined by the number of years an enrollee was in the top 10% (top decile) spending group from 2009 to 2011: persistent high-user group (3 out of 3 years in the top decile), frequent high-user group (2 out of 3 years in the top decile), incidental high-user group (1 year out of 3 years in the top decile), and never high-user group (0 out of 3 years in the top decile).

The Adult Comorbidity Evaluation-27 (ACE-27)<sup>7</sup> is an administrative claims-based comorbidity index originally developed to predict cancer patient survival. The index is able to capture a broad array of 26 common patient conditions, and it scores the conditions according to 4 levels of severity. For the purposes of this study, the ACE-27 algorithm was used to assess each of the 26 conditions per patient-year during 2008 to 2011. This information was used to conservatively identify common patient conditions and characterize individual comorbidity severity.

Two measures were used to examine the strength of association among persistent high-user groups, expenditures, service utilization, demographics, and comorbidity. Omega squared ( $\omega^2$ ) measure of effect size was used to detect the association between a categorical variable (eg, persistent high-user groups) and continuous variables (eg, healthcare expenditure, health service utilization). Cramer's V ( $\varphi_c$ ) was used to examine the association between a categorical variable (eg, persistent high-user groups) and other categorical variables including specific medical

■ **Figure.** Percent of Total Expenditures Versus Expenditure Percentile (2008)



conditions, number of comorbidities, and severity of comorbidity. For both indices, values exceeding 0.25 were interpreted as moderate to strong associations.

As a secondary objective, we developed an exploratory predictive model of the persistent high-user group. Using logistic regression, relevant 2008 variables were used to predict patients belonging to the persistent high-user group in 2009 to 2011. Candidate predictors for inclusion in the model included 2008 age category; patient gender; rurality of residence; logarithms of total, inpatient, medication, outpatient, and professional expenditures; number and overall severity of patient conditions defined by the ACE-27 score; and each of the 26 individual comorbidities in the ACE-27. To reduce collinearity and unstable estimates, service utilization variables were not included. Stepwise regression with an entry and stay alpha of 0.15 was used to retain the best predictive variables. The best model search was conducted on a randomly sampled training data set consisting of 75% of the total data. The final model was evaluated on the remaining 25% of the data.

## RESULTS

### Demographics

In 2008, the top 2% of costliest enrollees accounted for nearly 30% of total healthcare dollars, while the top

10% of enrollees accounted for more than 55% of the total healthcare expenditure (Figure). On the other hand, 60% of all enrollees consumed only about 10% of total healthcare resources.

We defined high users as the top decile spending group in each year. Of the 4203 high users in 2009, 1216 remained high users in 2010 and 2011; these 1216 enrollees formed the persistent high-user group. The frequent high-user group consisted of 1766 enrollees who were defined as high users 2 out of 3 years. The incidental high-user group consisted of 5429 enrollees who were defined as high users 1 out of 3 years. Finally, the never high-user group consisted of 33,627 enrollees who were never classified as high users during the study period.

In the baseline year (2008), the average age of the population was 41.9 years (SD = 21.8). The mean age of persistent high users was the highest of all user groups, at 59.0 years (Table 1). The mean ages of groups of frequent high users, incidental high users, and never high users were 56.8 years, 51.8 years, and 38.9 years, respectively. Most patients (88%) had residence in urban areas; urban status, however, was not found to vary by persistence level. The Cramer’s V measure of association suggests weak to no association between the persistent user group and the characteristics of gender ( $\phi_c = 0.04$ ), age category ( $\phi_c = 0.16$ ), and patient residence ( $\phi_c = 0.02$ ).

■ **Table 1.** Demographics (2008)

	Persistent High Users	Frequent High Users	Incidental High Users	Never High Users	Cramer's V <sup>a</sup>
<b>N</b>	1216	1766	5429	33,627	
<b>Prevalence % [Predictive Probability]</b>					
<b>Gender</b>					0.04
Female	58.0 [3.2]	58.0 [4.6]	57.6 [14.0]	52.2 [78.3]	
Male	42.0 [2.6]	42.0 [3.8]	42.4 [11.7]	47.8 [81.9]	
<b>Age</b>					0.16
Mean, years	59.0	56.8	51.8	38.9	
0-18	4.3 [0.5]	5.0 [0.9]	7.6 [4.3]	26.7 [94.2]	
19-24	1.2 [1.0]	1.4 [1.7]	2.2 [8.0]	3.9 [89.3]	
25-34	3.2 [1.3]	5.3 [3.2]	7.6 [14.0]	7.2 [81.6]	
35-44	8.8 [1.7]	10.0 [2.8]	13.0 [11.3]	15.6 [84.1]	
45-54	18.9 [2.6]	20.2 [4.0]	23.3 [14.3]	21.0 [79.2]	
55-64	23.0 [4.1]	22.8 [5.9]	21.3 [17.0]	14.8 [73.0]	
65+	40.5 [8.1]	35.2 [10.2]	24.9 [22.2]	10.8 [59.5]	
<b>Patient residence</b>					0.02
Urban	87.7 [2.9]	87.2 [4.2]	88.8 [13.0]	89.3 [80.0]	
Large rural/town	9.3 [3.5]	8.3 [4.6]	8.1 [13.8]	7.5 [78.1]	
Small rural/isolated	3.0 [2.7]	4.5 [6.0]	3.1 [12.5]	3.2 [78.8]	

<sup>a</sup>Values exceeding 0.25 were interpreted as moderate to strong associations.

### Service Utilization and Expenditure

In our sample, the average healthcare expenditure per enrollee was greater in persistent high users than in all other user groups combined. In a 3-year period, the persistent high-user group represents just over 1200 enrollees (2.9% of the total population) while accounting for more than \$46.5 million in spending (21% of the total expenditure).

Persistent high users had average annual healthcare expenditures of more than \$38,000 (Table 2). This was more than 17 times the average annual healthcare expenditure of never high users (\$2201). This trend of increasing expenditure as persistence increased was consistent for expenditures of all service types, including medication, inpatient, outpatient, and professional services. Persistent high users spent approximately 17 times more than never high users on medication, 13 times more on outpatient services, and 11 times more on professional services. Most strikingly, persistent high users spent nearly 200 times more on inpatient services than did never high users. Expenditure variables most strongly associated with persistent high utilization included total ( $\omega^2 = 0.44$ ), medication ( $\omega^2 = 0.33$ ), and professional expenditures ( $\omega^2 = 0.35$ ).

The average annual service utilization frequency also increased as persistence increased. This was most

apparent for medical specialty visits. Persistent high users saw a medical specialist an average of 14.5 times per year, compared with 0.3 medical specialist visits per year for never high users. The average annual utilization of inpatient services, primary care visits, and surgical specialty visits was 0.8, 5.2, and 2.9 visits per year, respectively, for persistent high users. Mean frequencies of use for these services were much lower for the group of never high users at 0.01, 0.2, and 0.3 visits per year, respectively. Most utilization variables had moderate association with the persistent high-user group: inpatient admissions ( $\omega^2 = 0.27$ ), outpatient primary care ( $\omega^2 = 0.29$ ), surgical ( $\omega^2 = 0.28$ ), and medical specialty visits ( $\omega^2 = 0.32$ ).

The frequency of emergency department (ED) use also increased as persistency increased. This was true for ED visits resulting in subsequent hospital admissions, as well as ED visits resulting in outpatient discharge. For ED visits resulting in outpatient discharge—indicative of potentially avoidable ED visits—the frequency of use for persistent high users (0.8 visits per enrollee per year) was more than 5 times higher than for never high users (0.1 visits per enrollee per year). However, the  $\omega^2$  associated with both categories of ED visits indicated that neither were strong predictors of persistent high users.

■ **Table 2.** Service Utilization and Expenditure (2009-2011)

	Persistent High Users	Frequent High Users	Incidental High Users	Never High Users	Ratio (persistent/never)	Omega Squared <sup>a</sup>
Average annual healthcare expenditure per enrollee, \$	38,288	21,961	11,423	2201	17.4	0.44
<b>Average annual healthcare expenditure per enrollee by service type, \$</b>						
Medication	9851	3482	1696	551	17.9	0.33
Inpatient	8760	6587	3033	44	199.1	0.13
Outpatient	9048	5987	3437	654	13.8	0.03
Professional	10,628	5904	3255	951	11.2	0.35
<b>Average annual service utilization frequency per enrollee</b>						
Inpatient admissions	0.8	0.5	0.2	0.01	8.0	0.27
Outpatient primary care visits	5.2	4.1	2.4	0.2	26.0	0.29
Outpatient surgical specialty visits	2.9	2.2	1.1	0.3	3.2	0.28
Outpatient medical specialty visits	14.5	10.4	5.0	0.3	48.3	0.32
ED → inpatient admissions	0.3	0.2	0.08	0.0	—	0.18
ED → outpatient discharges	0.8	0.5	0.3	0.1	8.0	0.06

ED indicates emergency department.  
<sup>a</sup>Values exceeding 0.25 were interpreted as moderate to strong associations.

### Comorbidity

The comorbidity conditions of each group were characterized using ACE-27 to determine the types of conditions present (Table 3). Comorbidities with moderate association with persistence were: hypertension ( $\varphi_c = 0.36$ ), respiratory disorders ( $\varphi_c = 0.31$ ), diabetes ( $\varphi_c = 0.28$ ), congestive heart failure ( $\varphi_c = 0.27$ ), and arrhythmia ( $\varphi_c = 0.25$ ). The number of comorbidities from 2008 to 2011 ( $\varphi_c = 0.36$ ) and comorbidity severity from 2008 to 2011 ( $\varphi_c = 0.30$ ) were also associated with the persistent high-user group. The presence of at least 2 conditions significantly increased the likelihood of being in the persistent high-user group when compared with having only 1 condition, no condition, or if any conditions present have mild overall severity.

The variations in comorbidities across the 4 groups of users exhibit a consistent dose-response pattern. The most common conditions in all user groups, in decreasing order, were hypertension, diabetes, and respiratory illnesses. The prevalence of these 3 conditions among persistent high users was 67%, 36%, and 31%, respectively; additionally, the prevalence was much lower in the never high-user group, at 14%, 4%, and 2%, respectively. Notably, there was also high prevalence of renal disease (17%), arrhythmia (17%), congestive heart failure (17%), neuromuscular disorder (17%), and solid tumor (14%) among persistent high users. A trend of higher prevalence of conditions with increasing persistence was consistent

across nearly all conditions. Among never high users, 4% of enrollees were classified as having moderate to severe comorbidity burden, compared with incidental high users (25%), frequent high users (45%), and persistent high users (55%).

### Exploratory Predictive Model

A multivariate logistic regression model was employed to explore the predictive power of using year 1 data (2008) to determine if an individual would be classified into the persistent high-user group for the following 3 years (2009-2011). In the test sample, the area under curve statistic (*c*-value), a measure of classification accuracy, was 0.923; this indicates a very high level of accuracy, with 1.00 being the highest possible level. An optimal sensitivity and specificity can be chosen by selecting a point along the receiver operating characteristic curve for the logistic model. In this case, the sensitivity, specificity, and positive predictive value results in values of 0.80, 0.90, and 0.19, respectively.

## DISCUSSION

The persistent high-user group in this study had a high prevalence of several common chronic conditions (eg, the aforementioned hypertension, diabetes, and respiratory illness), and members of this group were also more likely to have multiple conditions than other groups. The highest expenditure categories for persistent high users were

■ **Table 3.** Comorbidity by User Group (2008-2011)

Condition, %	Persistent High Users	Frequent High Users	Incidental High Users	Never High Users	Cramer's V <sup>a</sup>
	Prevalence % [Predictive Probability]				
Hypertension	66.6 [8.94]	60.5 [11.8]	42.8 [25.7]	14.4 [53.5]	0.36
Respiratory	31.1 [19.0]	21.0 [18.6]	10.9 [29.8]	1.9 [32.6]	0.31
Diabetes	35.8 [14.0]	25.0 [14.2]	15.5 [27.1]	4.1 [44.8]	0.28
CHF	16.7 [30.8]	9.4 [25.2]	3.8 [31.5]	0.2 [12.5]	0.27
Arrhythmia	17.3 [17.5]	14.6 [21.5]	7.2 [32.8]	1.0 [28.3]	0.25
Renal disease	17.0 [23.9]	10.4 [21.4]	4.0 [25.3]	0.7 [29.4]	0.24
Solid tumor	14.1 [14.0]	14.0 [20.2]	7.6 [34.0]	1.1 [31.7]	0.22
AMI	9.7 [20.5]	8.3 [25.3]	3.9 [36.9]	0.2 [17.2]	0.21
Neuromuscular	16.5 [20.9]	8.6 [15.8]	4.3 [24.3]	1.1 [39.1]	0.20
CAD	8.8 [20.8]	6.6 [22.6]	3.9 [41.7]	0.2 [14.9]	0.20
Stomach/intestine	11.9 [21.9]	6.6 [17.6]	3.4 [28.2]	0.6 [32.3]	0.19
Venous disease	8.7 [27.9]	4.7 [22.1]	2.3 [33.2]	0.1 [16.8]	0.18
Obesity	6.0 [14.0]	6.9 [23.2]	3.3 [34.0]	0.4 [28.9]	0.16
PAD	5.0 [28.7]	2.9 [24.1]	1.5 [38.0]	0.0 [9.3]	0.15
Dementia	4.3 [32.9]	2.1 [23.6]	0.7 [26.1]	0.0 [17.4]	0.13
Hepatic	5.3 [17.1]	3.6 [16.8]	2.4 [34.7]	0.3 [31.3]	0.13
Stroke	3.2 [19.3]	2.4 [21.8]	1.4 [38.6]	0.1 [20.3]	0.11
Paralysis	2.4 [26.8]	1.4 [23.2]	0.7 [38.4]	0.0 [11.6]	0.10
Leukemia	2.7 [22.9]	2.0 [25.7]	0.6 [24.3]	0.1 [27.1]	0.10
Psychiatric	1.6 [35.7]	0.9 [30.4]	0.2 [28.6]	0.0 [5.4]	0.09
Pancreas	1.0 [30.2]	1.0 [44.2]	0.1 [18.6]	0.0 [7.0]	0.09
Alcohol abuse	1.8 [19.8]	1.0 [15.5]	0.6 [31.9]	0.1 [32.8]	0.07
Illicit drugs	1.0 [33.3]	0.5 [25.6]	0.1 [23.1]	0.0 [17.9]	0.07
Rheumatologic	1.4 [19.8]	0.6 [13.2]	0.3 [22.0]	0.1 [45.1]	0.05
AIDS	0.2 [10.0]	0.0 [0.0]	0.0 [0.0]	0.0 [0.0]	0.05
Lymphoma	0.4 [29.4]	0.2 [23.5]	0.1 [35.3]	0.0 [11.8]	0.04
<b>Number of comorbidities</b>					0.36
0	15.8 [0.6]	20.1 [1.2]	41.1 [7.4]	80.9 [90.7]	
1	15.7 [3.0]	22.3 [6.2]	26.0 [22.4]	12.8 [68.4]	
2+	68.5 [14.4]	57.7 [17.7]	33.0 [31.0]	6.3 [36.9]	
<b>Comorbidity severity</b>					0.30
None	15.8 [0.6]	20.1 [1.2]	41.1 [7.4]	80.9 [90.7]	
Mild	29.6 [4.5]	35.1 [7.8]	34.2 [23.4]	15.2 [64.3]	
Moderate	14.8 [10.3]	17.6 [17.8]	10.7 [33.2]	2.0 [38.6]	
Severe	39.8 [20.4]	27.3 [20.4]	14.0 [32.1]	1.9 [27.1]	

AMI indicates acute myocardial infarction; CHF, congestive heart failure; PAD, peripheral artery disease.

<sup>a</sup>Values exceeding 0.25 were interpreted as moderate to strong associations.

professional services and medication; they also had many more outpatient primary and specialty care visits than any other group. Collectively, this indicates that persistent high users have multiple common chronic conditions and, compared with other groups, a higher overall disease burden, more frequent visits to outpatient primary and specialty care, and they also take multiple medications at a cost nearly 18 times that of never high users.

The predictive model suggests the expenditure and comorbidity data in prior years may be sufficient to predict membership in a high-user group in later years with a high degree of accuracy, indicating a real potential for an organization to project persistent high-cost enrollees based on prior data captured in this study. However, high accuracy did not translate into high model performance in some aspects. For example, the positive predictive val-

ue of the best model was close to 20%, indicating that only 1 in 5 patients identified as persistent high users will actually fall in the high persistence group. Whether any other classifier may be able to improve on this baseline positive predictive value is an open question. Total expenditure may be a main determinant of future persistence, or a strong surrogate for its underlying drivers.

Due to the limitations of working with insurance claims data, this study was not able to include certain data that might have been valuable to this analysis, such as socioeconomic variables and location of services. Without such information, it is impossible to determine if certain enrollees utilize more or less expensive locations for services. Additionally, the study data set only includes data from a single employer in Pennsylvania, limiting generalizability of results. However, the time frame (4 years) and large enrollee population (employer-insured population) provide unique insight into understanding persistent high users of healthcare. This insight will benefit those seeking ways to improve the health and utilization patterns of persistent high users in employer-based populations.

One method to improve outcomes for high-cost patients is to address the prevention and care of chronic conditions. Charlson and colleagues found that patients with multiple chronic conditions incurred significantly more healthcare costs than those with just 1 chronic condition.<sup>8</sup> In the employer-based insurance population in this study, having chronic conditions and having multiple conditions were much more prevalent among persistent high users. Provision of medical home care has been shown to be an effective approach to address such conditions.<sup>9,10</sup> The use of nurses for a home telecare intervention for congestive heart failure patients has also shown positive results.<sup>11</sup> In recent years, the use of paramedics for such home visits has also been considered. Community paramedicine has the potential to fill in many roles, including patient education, patient adherence to care plans, and patient self-care.<sup>12</sup>

Value-based insurance design (V-BID) is another potential option for improving outcomes of patients with persistent high cost. V-BID has gained increasing popularity among employers and is included as an allowable form of coverage by the Affordable Care Act.<sup>13</sup> The hope is that improved patterns of care will increase the quality of care received, indirectly decreasing healthcare costs. V-BIDs can focus on common chronic conditions, such as those prevalent in the persistent high-user group in our study population, in an attempt to improve outcomes and control costs. Evidence-based treatment guidelines exist for managing these chronic conditions. One study assessing

the effectiveness of a V-BID that adjusted cost-sharing for chronic medications showed an increase in medication adherence and increased participation in a care management program.<sup>14</sup> Another study focused on a V-BID that targeted high users of care by incentivizing enrollment in a disease management program,<sup>15</sup> which resulted in an increase in medication adherence and a decrease in total healthcare costs. Other studies utilizing various V-BIDs have shown improved medication adherence, but little change in healthcare expenditures.<sup>16</sup> While these benefit designs may not always result in immediate cost savings, they often show an improvement in outcomes for the patients enrolled. This may be an effective way to address the needs of patients with persistent high utilization and costs, with the potential for cost savings in the long term.

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## CONCLUSION

This study highlights the need to proactively engage employees and their dependents for primary and secondary prevention of common chronic diseases before an individual's health status, healthcare utilization, and medical cost become difficult to manage.

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**Authorship Information:** Concept and design (WH, ML, FC, HP); acquisition of data (WH); analysis and interpretation of data (WH, ML, FC, HP); drafting of the manuscript (WH, ML); critical revision of the manuscript for important intellectual content (WH, ML, FC, HP); statistical analysis (WH, FC); administrative, technical, or logistic support (ML); and supervision (WH, HP).

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