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Health Care Cost Trends

Reimagining Pharmacy Financing

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Reimagining Pharmacy Financing

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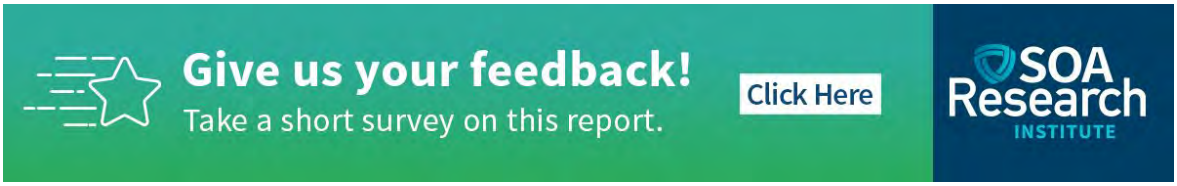

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Reimagining Pharmacy Financing

Section 1. Executive Summary

The cost of prescription drugs is top of mind for consumers, payers and policymakers. Despite legislative efforts, such as the Inflation Reduction Act,[1] the problem remains. More than 30% of all Americans say they have not taken prescription drugs as prescribed in the last 12 months because of the expense.[2] The purpose of this paper is to discuss an alternative to policy solutions: reimagining pharmacy financing in the commercial space using a value-based reimbursement methodology that increases transparency, encourages competition, aligns stakeholder incentives and mitigates total cost of care (TCOC) increases. This paper will demonstrate that it is possible to implement such a methodology under the current infrastructure, but there are limitations.

1.1. DEFINING VALUE

INTRODUCTION

Historically, most discussions about health care focus on hospital and physician costs. That is changing rapidly as more and more expensive gene-therapy drugs enter the market. Although very few patients require these drugs, the costs of the drugs, some of which exceed $2 million, can be devastating to the payer, especially if the payer is a small employer.

To respond to this risk, the Society of Actuaries (SOA) sponsored two projects. The first was a multidisciplinary Pharmacy Partnership Forum. This pharmacy forum was held in early 2023 with a conference report published later that year.[3] A key take-away was the need for a new pharmacy financing methodology and the need for this report to establish a baseline for further discussion. This report includes sections on defining value, measuring value and rewarding value.

DEFINING VALUE

The starting point for developing a value-based pharmacy financing methodology is to understand how stakeholders define value. In this report, stakeholders include anyone directly impacted in the day-to-day operations related to pharmacy financing, including consumers, payers, providers, government entities and organizations in the supply chain such as manufacturers and pharmacy benefit managers. Staff and consultants are not considered direct stakeholders in this paper.

In any situation each stakeholder has its own objectives and values. Some stakeholders define value in terms of the ISPOR (International Society of Pharmacoeconomic and Outcomes Research) value flower. The value flower has two core petals: quality-adjusted life years (QALYs) and net costs. A QALY measures how an intervention, such as taking a new drug, improves the patient's quality and length of life. The quality adjustment is a number between 0 and 1, with 1 representing full health. The quality adjustment is multiplied by the expected extension of life due to the drug. Some national health systems use QALYs to determine whether a drug is cost-effective, which informs their decision whether or not to cover the drug. For example, the system may cover a drug if the cost per QALY is under $50,000, but it will not cover a drug if the cost per QALY exceeds $50,000. The other core value, net costs, may or may not reflect elements of costs such as

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cost share and rebates. Other value elements may include more qualitative factors, like caregiver time and emotional strain, reflect the impact of a drug on caregivers and the time to recovery.

CASE STUDIES

One of the goals of this report is to focus on the impact of certain drugs on TCOC for two disease states: diabetes and hypercholesterolemia. Diabetes is a disease characterized by the body's inability to regulate and use glucose, a type of sugar in the body. Although many drugs are used to treat diabetes, this report will focus on three types of drugs:

- *Insulin:* Insulin is the hormone that delivers glucose to the cells to create energy. Insulin drugs, such as Humalog and Lantus, supplement the insulin produced by the body.
- *GLP-1 (glucagon-like peptide-1) receptors:* This class of drugs, which includes Ozempic and Trulicity, slows digestion and increases insulin secretion.
- *SGLT2 (sodium-glucose cotransporter-2) inhibitors:* This class of drug, which includes Farxiga and Jardiance, removes glucose through urine.

Hypercholesterolemia is often referred to as high cholesterol. Cholesterol is a fatlike substance in the blood that performs many key functions, such as helping the liver produce bile necessary for the digestive process. If cholesterol levels are too high, however, this may lead to a buildup of plaque on artery walls, which can lead to cardiovascular diseases such as heart attacks and strokes. This report will focus on two drug classes used to control cholesterol levels:

- *Statins:* Statins, such as Lipitor and Crestor, block the substance used to create cholesterol.
- *PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors:* This drug class, which includes Praluent and Repatha, helps the liver absorb more of the so-called "bad cholesterol."

1.2. MEASURING VALUE

Pharmacy financing is complex. Numerous types of stakeholders are involved, and each stakeholder has to make several types of decisions. For example, when a new drug is introduced, the payer must decide whether or not to cover the drug, negotiate the price of the drug with the manufacturer, and determine where to place the drug on its formulary. Although the analytics behind each of these decisions is important, this paper focuses on examining the scalability and usefulness of methods determining the impact of a drug on TCOC for the two disease states mentioned above: diabetes and hypercholesterolemia. Only these drug classes were included in the analysis.

DATA AND METHODS

The data source for this analysis is the Health Care Cost Institute commercial claims data set for the years 2016–2021. The data set includes approximately one-third of all commercial members. The data set includes the same types of information that most managed care organizations have. To perform the analysis, the authors included only groups where medical, pharmacy and mental health claims were available.

The impact on TCOC for each drug class was analyzed using the following three methodologies:

- *Pre-Post Index Methodology:* This methodology compares TCOC before and after an index event such as a hospitalization or diagnosis. This study was based on a related list of hospital admissions and TCOC for the six months before the event and the 12 months after the event. The advantage of this method is that it provides a clear, logical framework for the analysis. That said, not enough members with an index event may be available to provide a statistically reliable analysis.

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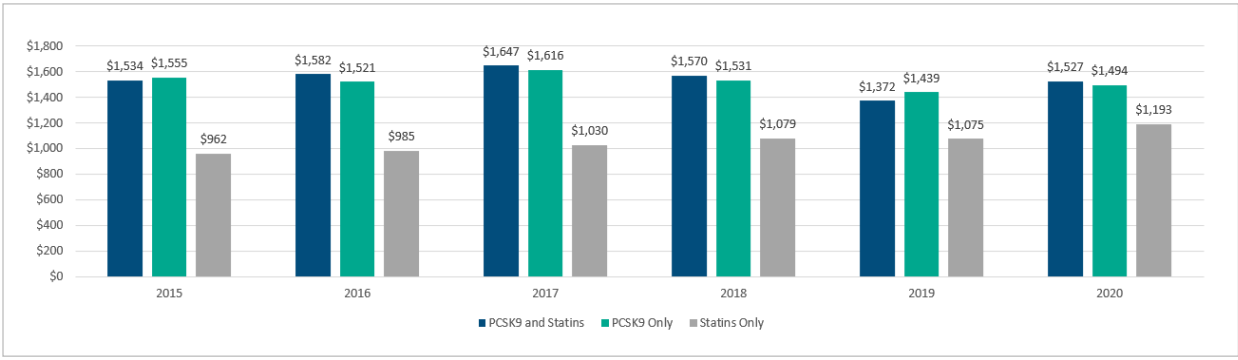
- *Propensity-Matching Methodology:* The purpose of this methodology is to compare TCOC with patients taking the drug to those who do not on an "all other things being equal" basis. This is done by matching members taking the drug and those who do not using itemized criteria such as age and gender. This methodology not only provides a clear framework but also reduces the impact of confounding factors. Like the pre-post methodology, the matching process may result in too few patients to conduct a statistically reliable study.
- *Risk-Adjustment Methodology:* Under this methodology, each member in the data set is assigned a risk score, based on their risk factors, such as age and gender. The scoring methodology is based on some industry standard, such as the Centers for Medicare and Medicaid Services hierarchical condition categories (CMS-HCC) risk score model used in this report. The risk adjusted TCOC for any subgroup is the unadjusted TCOC divided by the sum of the risk scores. The advantages of this methodology are that every member in the data set is included in the analysis, it is easy to administer, and the methodology is widely accepted and understood. The disadvantage is that the methodology was developed for other purposes, so it may or may not adequately reflect the risk associated with the specific members in these specific groups.

THE RESULTS

Overall, the analysis showed that TCOC was higher for newer drugs than for more established drugs. For example, as shown in Figure 1.1, TCOC for PCSK9 drugs is higher than TCOC for statins under the risk-adjustment methodology. In interpreting these results it is important to consider not only the advantages and disadvantages of the methodologies discussed above, but also the fact that measuring TCOC does not reflect other value elements, such as the clinical benefits of the drug and quality of life. It is also important to consider the timeframes over which the results are measured. A 12-month analysis may not reflect all the value realized by patients of the various drugs being compared.

Figure 1.1
TOTAL RISK-ADJUSTED ALLOWED COSTS



1.3. REWARDING VALUE

It is possible today for two stakeholders to sit down and hammer out a value-based financing agreement that aligns the objectives of both stakeholders. That said, the process is still not scalable and not widely accepted. This section addresses the potential barriers and opportunities moving forward.

MEASURES OF SUCCESS

The first step in expanding the use of value-based pharmacy financing is to define success. The criteria the authors have used in this report and their previous work include the following:

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- *Increasing Transparency:* In any negotiations, transparency is a source of potential conflict. In pharmacy financing, rebates and pricing spreads are two such sources of conflict that need to be considered in developing a methodology.
- *Encouraging Competition:* Any new financing methodology needs to encourage competition, which should in turn lead to lower costs and higher value.
- *Mitigating Total Cost of Care Increases:* Although one can certainly identify nonfinancial elements of value, mitigating TCOC increases generally benefits everyone.
- *Aligning Stakeholder Incentives:* Although each stakeholder has specific values based on their goals and objectives, from a societal perspective these goals and objectives need to result in a system that provides access to affordable drugs. On the other hand, stakeholders will not participate in a system where their objectives and goals are not sufficiently met.

APPLYING THE CONCEPTS

Many types of negotiations take place in a pharmacy financing system, including the price a manufacturer charges a wholesaler for a drug, the price the wholesaler charges the pharmacy for a drug, and the rebates manufacturer pays a pharmacy benefit manager (PBM) and/or a payer for formulary access and preferred tier placement. Numerous ways are used to incorporate value-based reimbursement into this process. The starting point is always setting the point-of-sale costs, that is, the agreed upon amount to be paid for each drug at the time the prescription is filled. Like all negotiations, those negotiations are based on the perceived value of a drug at the time. Another step in the process is related to measuring the actual net value of a drug after the fact. This part of the process can be done through some type of guarantee. The guarantee usually has several caveats, such as the period in question and how far actual experience deviates from the expected amount set in the upfront negotiations.

A key question in developing a value-based reimbursement system is how to measure the net value. Value-based reimbursement methodologies for physicians and hospitals rely heavily on scorecards. Measures in the scorecard may include financial elements of value such as net costs and nonfinancial measures such as provider accreditation. An alternative to the scorecard for pharmacy financing is a value stack. A value stack is like a scorecard, but each element of value can be monetized either directly or indirectly through proxy measures. For example, the value of pain relief can be monetized by the reduction in spend on pain medications. The monetized incremental value can then be compared to the monetized incremental cost in a return-on-investment (ROI) ratio, and the incremental values and incremental costs can be further itemized to the stakeholders to whom they accrue, thereby also creating stakeholder-level ROIs.

ENHANCING THE INFRASTRUCTURE

Although the value-based concept can be implemented today, it would be helpful to enhance the current infrastructure to make the system more scalable. One example is closing the analytical loop. Currently, pharmacy analytics is done in silos. When a new drug is introduced, extensive analysis is done using the data from clinical trials. As time goes by, this initial information needs to be replaced with real-world experience. Techniques have to be further developed to incorporate emerging data into the financing analytics in the most appropriate way.

Similarly, during the negotiation process, each stakeholder will want to understand how much risk they are really undertaking and how much opportunity really exists. This will require a deeper understanding of the concept of total risk analysis, which allows analysts to answer questions such as “What are the chances we will lose more than $1 million?”[4]

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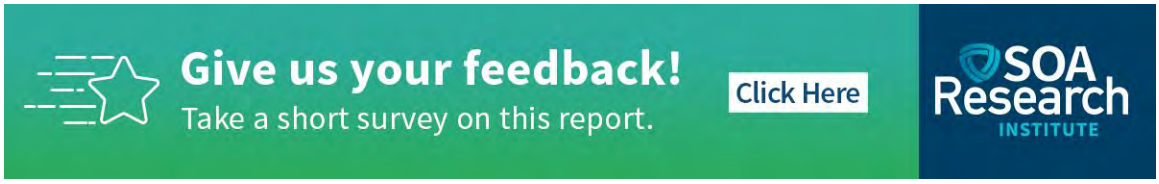
NEXT STEPS

Although the authors have determined that it is possible to develop a more scalable and more meaningful value-based reimbursement methodology using the current infrastructure, it will take greater cross-disciplinary collaboration to bring forward the best innovation and ensure wide-spread utilization of "reimagined pharmacy financing" advances. Experts such as policy analysts, health economists, clinical pharmacists, health actuaries, benefits brokers and consultants, consumer advocates and financial analysts working with all types of stakeholders must share innovative ideas and valuable learnings as they emerge to ensure the best of each discipline is incorporated into the greatest common solutions for all. The authors look forward to participating in these efforts as we "reimagine pharmacy financing" together so we can transform our pharmacy ecosystem for the benefit of all.



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Section 2: Defining Value

2.1. INTRODUCTION

The cost of prescription drugs is top of mind for consumers, payers and policymakers. Although many efforts have been made to reduce pharmacy costs over the years, the problem remains. One potential solution is to reimagine pharmacy financing in the commercial space using a value-based reimbursement methodology that aligns stakeholder objectives, mitigates the total cost of care (TCOC), increases transparency and increases competition. The purpose of this report is to demonstrate that it is possible for stakeholders to implement such a methodology now using the current infrastructure. That said, the process faces several limitations, which will be discussed throughout this report.

BACKGROUND

In 2017 the SOA launched "Initiative 18|11: What Can We Do about the Cost of Healthcare?" in partnership with the Kaiser Family Foundation (KFF). The term "18|11" is derived from the fact that at the time the U.S. was spending 18% of its gross domestic product (GDP) on health care compared to other developed nations, which were spending 11%. The purpose of Initiative 18|11 was to have a multidisciplinary discussion about the cost of health care in the U.S. That discussion occurred in March 2018, and the results were summarized in a conference report.[5] As part of that process, several topics were prioritized for a deeper dive, including pharmacy.

Lessons Learned from Initiative 18|11

Although a wide range of topics were covered in the original Initiative 18|11 work, three specific takeaways stood out as general considerations in thinking through any solution to reduce the cost of health care.

The Health Care Identity

The health care identity states that one person's cost is another person's income. As a result, for any cost-reduction solution to be truly effective, the impact on the other stakeholders must be considered. In some cases, this might mean tighter controls over the process. In other cases, this might mean demanding more value. This report will focus on defining and measuring the value of prescription drugs.

Long Pocket/Wrong Pocket

In the U.S. most financial transactions are primarily based on annual accounting periods. Treatment for a disease, on the other hand, often requires an upfront investment, recognizing that the benefits may not fully materialize for several years. Because patients can switch payers each year, this sometimes means that the party making the investment may not be the party realizing the benefit. This may or may not even out over time. This is one of the many challenges associated with pharmacy financing that will be addressed in Section 4 of this report.

The 5/50 Principle

About 50% of health care costs are attributed to roughly 5% of the population.[6] Apart from a small number of persistent spenders, the composition of the 5% changes each year. This poses a budget risk for payers, especially smaller ones with less tolerance for variation. Managing pharmacy spend risk considering the 5/50 principle will be discussed in this report.

Pharmacy Deep Dive

As part of the Initiative 18|11 discussions, it became clear that the pharmacy ecosystem is complex. Hence, a logical first step was documenting the ecosystem to provide a foundation for further study. The result was two article series published in *The Actuary* magazine:

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- *Actuarial Perspectives on Prescription Drug Financing:*[7] This series includes articles on the drug development process, the economic impact of prescription drugs and the consumer impact.
- *Additional Actuarial Perspectives on Prescription Drug Financing.*[8] This series includes additional articles on the drug development process, the regulatory process and the economic impact of prescription drugs.

The themes from those publications were to increase transparency, encourage competition, align stakeholder incentives and mitigate TCOC increases as noted above.

ABOUT THIS REPORT

Historically, most health care discussions and research focused on hospital and physician costs. After all, retail prescription drugs are currently 11% of total health care costs.[9] But retail prescription drugs do not tell the entire story. In 2021 the total health care spending for drugs was $603 billion before rebates, costing $421 billion for retail prescription drugs and $182 billion for facility-dispensed drugs.[10] Although few people use high-cost specialty drugs, the high cost per drug means these medications account for more than half of overall drug spend, and new high-cost gene therapies are emerging. For example, Zolgensma, a gene therapy used to treat spinal muscular atrophy, costs more than $2 million.[11] For some employer groups, a claim of this size can be devastating financially. Only a handful of gene therapies are on the market today, but one forecast predicts about 60 by 2030.[12]

The SOA Response

To address this situation, the SOA has sponsored two pharmacy projects. The first was a conference similar to the Initiative 18|11 conference. The SOA's Pharmacy Partnership Forum was held in March 2023, and a conference report has been published.[13] The second project is this research project.

The explicit purpose of this project is to conduct quantitative research to determine whether the patient populations of different drugs treating the same disease have different results on TCOC and, if so, to discuss a potential framework for pharmacy financing methodologies that includes a methodology for determining the impact of a specific drug on TCOC. The target audience for this report is multidisciplinary (e.g., health actuaries, clinical pharmacists, health economics outcomes researchers, medical doctors, and benefits consultants and brokers). The authors have assumed that readers understand the basics of the pharmacy ecosystem as laid out in the two series of articles in *The Actuary* referenced above.

Report Structure

One of the two purposes of this report is to discuss potential frameworks for value-based reimbursement, and so this section ("Defining Value") focuses on value definitions for diabetes and high cholesterol in the context of various stakeholders' strategic goals.

The third section ("Measuring Value") focuses on quantitative research regarding the impact of specific drugs on TCOC, including descriptions of the data and methods used in the research.

Section 4 ("Rewarding Value") discusses applying our findings to determine a scalable and meaningful way to reward results. This will include a focus on potential reimbursement strategies that increasing transparency, encouraging competition, aligning stakeholder incentives and mitigating TCOC increases. Section 4 closes with a discussion of areas for further study.

2.2. VALUE DEFINITIONS FOR DIABETES AND HIGH CHOLESTEROL

The first step in reimagining pharmacy financing is to define value. The definition of value depends on the stakeholders' goals and the specific types of analysis being performed. This section discusses key

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considerations a stakeholder might contemplate in defining the value of a specific drug in a given context. Some health economists use the ISPOR value flower as a framework for defining health care value, because it can help guide discussions about many types and sources of value that prescription drugs deliver. However, the authors expect each stakeholder to use the framework that best meets their goals.

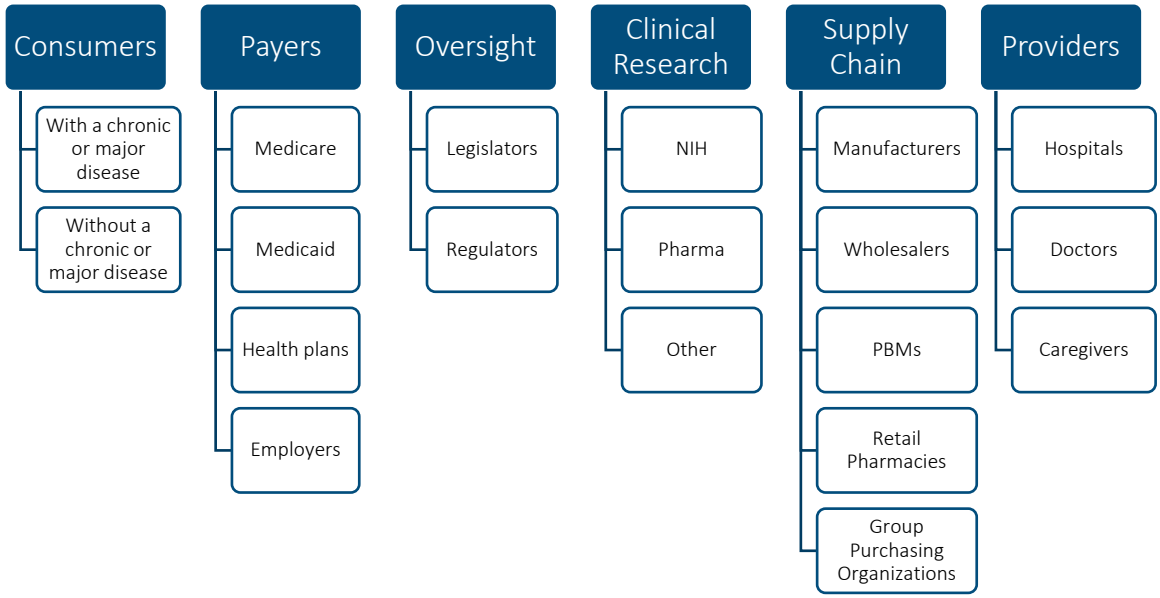
STAKEHOLDERS

One way to view stakeholders in the pharmacy ecosystem is through a single lens: that of the consumer. After all, the ultimate purpose of the ecosystem is to provide consumers with the prescription drugs needed to maintain and/or improve their health. Similarly, another way to view value is through the lens of the whole of society. In this view, money and resources spent on prescription drugs must be weighed against other possible uses, such as education and military readiness.

The Framework

This report focuses on pharmacy financing, thus, the stakeholder framework will be defined on a transactional basis, such as the one shown in Figure 2.1.

Figure 2.1
DIRECT STAKEHOLDERS



The direct stakeholders shown in Figure 2.1 receive indirect support from others. For example, regulators and legislators receive support from researchers and policy analysts. In addition, each stakeholder receives support from employees, brokers and consultants to perform their duties. From a financial perspective, taxpayers and investors are also a necessary part of the process.

Strategic Considerations

Each stakeholder wants to optimize their financial position, which can mean different things for different stakeholders. With a few exceptions, organizations also tend to have several nonfinancial objectives, which will influence the value framework used by the stakeholder. Nonfinancial objectives could include patient well-being, equity and diversity, product excellence, consumer and provider accountability, sustainability and innovation.

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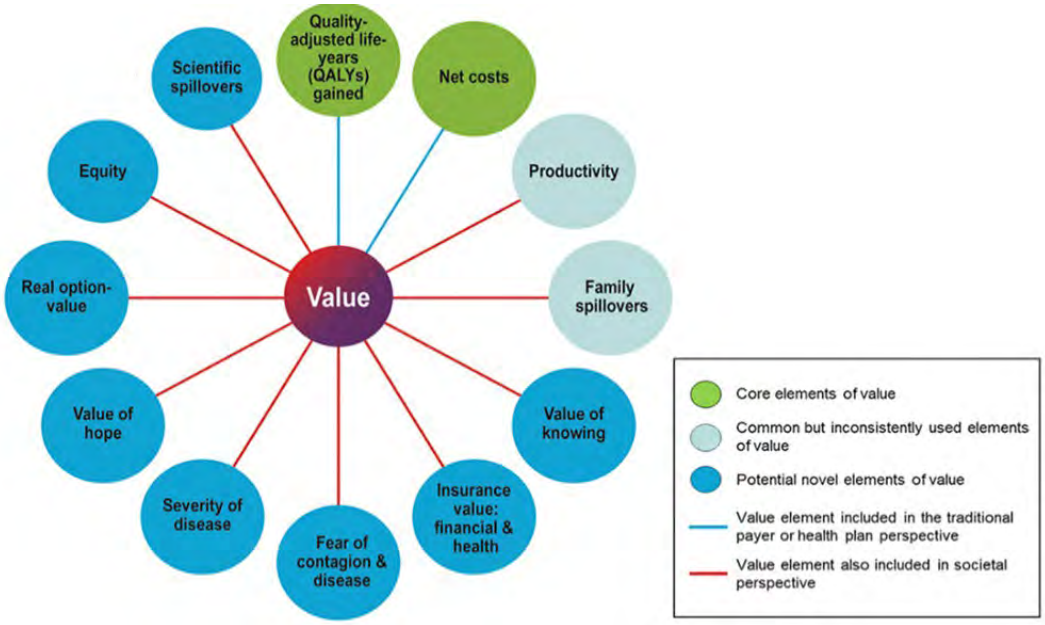
VALUE DEFINITION FRAMEWORKS

The value flower is an example of a formal framework for defining value developed by the International Society of Pharmacoeconomic and Outcomes Research (ISPOR).[14] The value flower is often the starting point for health economists and others performing cost-effectiveness research.[15] Given the level of research associated with the value flower, it often serves as a good starting point for developing a framework to meet the specific needs of a specific stakeholder, as long as the benefits and limitations of this framework are considered. In this report we will discuss the benefits and limitations around meeting stakeholders' needs and the ability to meaningfully measure the value of each element in a scalable manner.

About the ISPOR Value Flower

The ISPOR value flower was introduced in 2018 as part of a report by the 2018 ISPOR Special Task Force on U.S. value assessments. The task force's purpose was to review previous work and spur new research in additional elements of value. This framework is illustrated in Figure 2.2.[16]

Figure 2.2
THE ISPOR VALUE FLOWER



Source: Peter J. Neumann, Louis P. Garrison, and Richard J. Wilke, "The History and Future of the 'ISPOR Value Flower': Addressing Limitations of Conventional Cost-Effectiveness Analysis."

The Core Values (The Green Petals)

Core values are elements that are consistently included in analyses performed from a payer's perspective. The cost per quality-adjusted life year (QALY), a measure of cost effectiveness, is frequently used in deciding coverage, especially in other countries. For example, a payer may choose to cover a new drug that costs $50,000 per QALY but not one that costs $100,000 per QALY. In such contexts, QALY thresholds are used primarily in coverage determinations for new drugs. The definition of net costs can vary based on the decision maker's need at the time.

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QALYs

QALYs measure how an intervention, such as taking a new drug, improves the patient's quality and length of life. A QALY has two components: survival expressed as life years (LYs) and the quality adjustment, which ranges from 0 to 1. The QALY therefore is the quality adjustment (0 to 1) multiplied by the survival (LYs). A QALY of 1.0 represents an additional year of life in perfect health.[17]

A survey such as the EQ-5D often determines the numeric value assigned to a QALY.[18] This instrument measures quality of life across six dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety and depression. Although many researchers consider these surveys valid, reliable and responsive, some inherent limitations are always present in using any survey. Most notably, the population surveyed may or may not be the stakeholder's target population.[19]

Also, the concept of QALYs has been criticized. Some observers have expressed concerns that the concept discriminates against patients with disabilities[20] and that the results do not adequately reflect differences in patients' goals and values. One alternative is to base assessments on survival measures.[21]

Net Costs

In the context of the "value flower," net costs are defined as follows: "Future cost savings resulting from a treatment today should be subtracted from the direct treatment cost to yield the net incremental cost of treatment. When relevant, future net costs should be appropriately adjusted for uncertainty and discounted from the year of occurrence." The specifics of how to apply this principle depend on the situation of the key decision maker for the problem at hand.[22]

For example, a PBM or payer might define net costs as the claim cost of the drug net of discounts from the pharmacy, cost share amounts from the patient, and formulary rebates from the pharmaceutical manufacturer.

A payer may also find it helpful to consider TCOC associated with the treatment, which could include physician administration costs or costs of hospitalization associated with the treatment, all net of provider and pharmacy discounts and pharmaceutical manufacturer rebates. Another option is the overall change in TCOC associated with a patient's change in the course of therapy or the overall change in TCOC for a payer's portfolio of patients with the introduction of a new drug in the therapy class could be evaluated.

The focus for this report will be the net TCOC, which will be discussed in more detail in below. This analysis will compare the relative TCOC between drugs within a disease state.

Common but Inconsistent Values (The Light Blue Petals)

Two elements of value shown in Figure 2.2 are often used to measure value but are done inconsistently: productivity and family spillover.

Productivity

For a working-age population, productivity can be measured as total compensation lost because of absenteeism or presenteeism attributed to the disease. Although it is possible to measure this directly for a relatively small population, such as an employer group, significant volatility may be seen in results from one group to another because of the variance from the mean often associated with smaller sample sizes. Efficiently measuring or projecting productivity results for a larger population may require assumptions about average compensation for various positions, which can be less precise but still useful if efficiency is essential to the stakeholder.[23]

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Family Spillover

Family spillover refers to the impact of a drug on the financial and overall well-being of the patient's family. Caregivers may spend significant time assisting patients with their care and/or with their activities of daily living, which may represent a significant opportunity cost or direct expense to the family. Variations in methodology have made scalable and consistent use of this concept challenging.[24]

Novel Elements of Value (The Dark Blue Petals)

Novel elements of value include elements that are often overlooked or underappreciated in defining value. Although some progress has been made in measuring these elements, more research is needed. The novel elements of value include the following:[25]

- *The Value of Knowing:* This element of value captures the additional value associated with a drug when a test can accurately predict who will respond. Care must be taken in measuring this value to avoid double counting between the test and the drug.
- *Insurance Value: Financial and Health:* This value element reflects that an insured person is more likely to receive the care they need than those who do not.
- *Fear of Contagion or Disease:* The fear of a disease, especially an infectious one, can lead to anxiety and other potentially harmful effects. On the other hand, fear of contagion may be beneficial in dealing with pandemics.
- *Severity of Disease:* This value measure focuses on how the severity of a disease might impact the value placed on a drug. For example, a slight gain in health may be more valuable to a person with a poor prognosis than the same gain is to a person with a good prognosis.
- *The Value of Hope:* This element reflects the patient's willingness to undergo treatment in hopes of a desirable outcome.
- *Real Option Value:* This is the value that accrues when a treatment extends a patient's life in the hope that a future improvement in medical technology may fully cure the patient.
- *Equity:* This element reflects the benefit to society derived from the altruism or sense of fair play of others.
- *Scientific Spillovers:* This value element is associated with a medical technology that leads to other discoveries that add value.

Other Elements of Value

Although the value flower is widely accepted, some elements of value for a drug are not captured in Figure 2.2.

Adherence-Improving Factors

This element of value is included in some versions of the value flower but not in others. This element is usually defined in terms of advances in medical technology that result in greater adherence to the course of treatment. For example, administering a drug as a pill rather than an injection may increase adherence.

Adherence is usually measured in terms of the medication possession ratio (MPR), or proportion of days covered (PDC), which are measures of the percentage of days for which a drug is dispensed or covered over a given period. Adherence measures are key in managing chronic diseases.

Long-Term Clinical Effectiveness

When a new drug is introduced, the determination of the clinical effectiveness of the drug is based on a series of well-designed, expensive clinical trials that are conducted over a defined period. Some Phase III trials can last three to five years. This period may or may not be sufficient to determine long-term clinical effectiveness for some stakeholders. For example, a patient may be cancer-free after three years but suffer

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a recurrence five years later. Similarly, it may take several years before a drug's long-term impact on disease progression can be fully measured.

Time to Recovery

For many consumers and their families and employers, the time it takes to recover and return to normal activities is crucial.[26]

Side Effects

The value of a drug can be either positive or negative. Side effects are one example of a negative value. Side effects result in adverse medical events that typically lead to higher TCOC due to increased emergency room visits, hospitalizations or lengths of stay, more diagnostics and/or increased physician visits, and medication prescription and utilization. Death is also a possible undesirable side effect, though it does not always lead to increased TCOC.

Risk Management

It is easy to think of financial value in terms of net costs. Indeed, that is a critical value element for every stakeholder. If the term "net costs" is interpreted as just an average, then it overlooks an essential element of value: risk management. One element of risk management includes the ability to reasonably predict the impact of outliers in advance and to take precautionary measures, such as a stop-loss policy. Risk management also includes managing an outlier once it becomes known. Techniques to manage an outlier often take the form of a disease management program that provides education and services to the patient.

TYPE 2 DIABETES CASE STUDY

Once a framework is in place, the next step is to apply that framework to a specific drug or class of drugs. This step requires understanding the underlying disease state and the expected course of treatment.

Overview

Diabetes Type 2 is often called adult-onset diabetes, even though prevalence of the disease among children is increasing. Diabetes is a disease characterized by the inability of the body to regulate and use glucose, a type of sugar. The liver produces glucose, and glucose also comes from food. When someone eats, that signals the pancreas to produce insulin. Insulin is the hormone that delivers glucose to the cells. The cells then use glucose to produce energy. Two things can go wrong here. First, the pancreas may create too little or too much insulin. Second, the cells may not respond to insulin and take in less sugar. There are two immediate consequences to this process. If the blood sugar level is too low, the person may become weak and dizzy, resulting in falls, car accidents and other undesirable incidents. If the blood sugar level is so high that it cannot be converted to energy, the body stores the excess sugar, resulting in weight gain.[27]

For many diabetic patients, it is necessary to monitor and regulate their glucose levels throughout the day. This can be done by performing a "finger stick" test or using a glucose monitor. With the finger stick test, the patient sticks their finger, draws blood using a test strip, and inserts it into the reader. A glucose monitor is a wearable device, so all the patient has to do is scan the monitor using their smartphone or scanning device. The patient can adjust their food and insulin intake accordingly with this information. However, most clinicians rely on an A1C (glycated hemoglobin) test to measure clinical effectiveness. This fasting blood test measures the average blood sugar level over the past three months.

Diabetes is a chronic disease that impacts many major organs, including the heart, eyes and kidneys. Diabetes also has a negative effect on the nervous system, which can lead to strokes, cardiovascular diseases and amputation of the feet or limbs.[28]

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Treatment

Regardless of the severity of the diabetes or the time since onset, diet and exercise are always key elements in a patient's treatment plan. The physician may prescribe a drug regimen to supplement the diet and exercise. Key drugs are shown in Table 2.1.

Table 2.1
TYPE 2 DIABETES DRUGS

Type of Drug	Brand Names: Examples	Clinical Benefit	Administration	Clinical Risks
Metformins	Axpinet, Diagemet, Glucient, Glucophage, Metabet	Lowers glucose production in the liver, which improves sensitivity to the liver	Tablets, solutions	B-12 deficiency, nausea, diarrhea, renal impairment, hypoglycemia
Sulfonylureas	Glynase, DiaBeta, Amaryl, Glucotrol	Helps the body secrete more insulin	Tablets	Hypoglycemia, weight gain, beta-cell exhaustion
Thiazolidinediones	Actos, Avandia	Increases the body's sensitivity to insulin	Tablets	Heart failure, bladder cancer, bone fractures, weight gain
DPP-4 inhibitors	Januvia, Onglyza, Tradjenta, Nesina	Stimulates insulin release and suppresses glucagon secretion	Tablets	Pancreatitis, joint pain, respiratory tract infection
GLP-1 receptor agonists	Trulicity, Ozempic, Rybelsus, Byetta, Victoza, Saxenda, Adlyxin	Slows digestion and increases insulin secretion	Tablets, injections	Pancreatitis, nausea, diarrhea
SGLT2 inhibitors	Farxiga, Jardiance, Invokana, Steglatro	Removes glucose in the urine	Tablets	Ketoacidosis, urinary tract infections
Insulin	Lantus, Humalog, Novolog, Apidra	Supplements insulin produced by the body	Injection, insulin pump	Hypoglycemia, weight gain, injection site reactions

Source: Mayo Clinic, "Diabetes: Diagnosis & Treatment."

Elements of Value for Type 2 Diabetes

For a patient with a mild case of diabetes, the value of a new drug would most likely be based on the drug's effectiveness as measured by their overall A1C level and the drug's side effects, especially weight loss or weight gain. Although patients with more advanced cases of diabetes would almost certainly share these values, other elements also come into play. For example, a patient on an insulin regimen would likely place

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value on a drug that maintains a steady glucose level daily to avoid the extreme highs and lows that can be disruptive to their daily life. Patients at a known risk of complications would value drugs that reduce that risk.

Other stakeholders, especially payers, would probably focus on many of the same value elements as a patient: net costs, short-term and long-term clinical effectiveness, and the impact of managing the disease on a patient's daily life. A stakeholder could map these values to a framework in several ways depending on their strategic objectives and the framework they typically use.

In the short term, clinical effectiveness is usually measured by changes in the patient's A1C levels. The short-term net costs of a Type 2 diabetes drug may include the cost of the drug itself, the cost of office visits and lab tests needed to monitor the patient's A1C level, and the cost of daily supplies. Daily supplies include testing supplies, such as a glucose monitor, and administration supplies, such as needles for insulin patients. In the longer term, clinical effectiveness can be measured in terms of complications and disease progression.

The impact of diabetes on the patient's daily life depends on the severity of the disease. Anxiety and depression, two key quality-of-life measures, are common among diabetics because of the chronic nature of the disease, and the diet and exercise requirements often represent a major lifestyle change. Insulin users could see a loss of productivity and/or a slowdown in performing their usual activities because of the need to monitor blood levels during the day. Patients with complications, especially an amputation, may see a loss of mobility. This could impact the patient and their family if additional care is needed.

HIGH-CHOLESTEROL CASE STUDY

This section provides a framework for understanding the value of cholesterol-lowering drugs similar to the framework described above for Type 2 diabetes.

Overview

Cholesterol is a waxy, fatlike substance found in the blood. Cholesterol is a type of lipid, meaning it does not dissolve in water and will not come apart in blood. This property means cholesterol can travel through the body, performing many valuable functions, such as helping cell membranes form protective layers, helping the liver create bile necessary for the digestive process, and producing certain hormones, such as vitamin D. The liver produces the cholesterol the body needs. Certain foods, such as saturated and trans (unsaturated) fats, can cause the liver to produce more cholesterol than needed. The small intestine absorbs the cholesterol from food and releases it into the bloodstream.

Lipoproteins, a combination of lipids and proteins, deliver cholesterol to the cells and collect excess cholesterol from the cells. LDL (low-density lipoprotein) cholesterol is a low-density lipoprotein that delivers cholesterol to the cells. It is often called "bad cholesterol" because it can combine with other substances to build up plaque on the artery walls. This buildup, which goes by the name atherosclerosis, is a disease that can lead to heart attacks, strokes and other serious diseases. HDL (high-density lipoprotein) cholesterol is high-density lipoproteins. It is often called "the good cholesterol" because it takes extra cholesterol out of the bloodstream and delivers it to the liver, where it is broken down and removed from the system.

Risk factors for high cholesterol include obesity, smoking, family history and the presence of other diseases such as chronic kidney disease, hypertriglyceridemia (caused by high triglycerides) and hypothyroidism. In many cases, no symptoms are associated with high cholesterol. As a result, most organizations recommend screening blood tests on a schedule determined by the patient's risk profile.[29]

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Treatment

Given the risk factors for high cholesterol, a treatment plan usually includes recommended lifestyle and dietary changes. If those changes are insufficient, the doctor may prescribe one or more of the drugs described in Table 2.2.

Table 2.2
CHOLESTEROL-LOWERING DRUGS

Type of Drug	Brand Names: Examples	Clinical Benefits	Administration	Clinical Risks
Statins	Lipitor, Crestor, Lescol, Mevacor, Pravachol, Zocor	Blocks substance the liver needs to make cholesterol, causing the liver to remove the cholesterol	Tablets	Muscle pain, muscle damage, memory loss, hyperglycemia
Cholesterol absorption inhibitors	Zetia	Limits the absorption of dietary cholesterol into the bloodstream	Tablets	Liver and muscle damage, headaches
Bempedoic acid	Nexletol	Inhibits cholesterol synthesis in the liver	Tablets	Pain, muscle spasms, gout
Bile acid binding resins	Welchol, Prevalite, Questran, Colestid	Prompts the liver to make more bile acids, which reduces cholesterol reabsorption	Tablets	Stomach problems, muscle pain, deficiencies in fat-soluble vitamins
PCSK9 inhibitors	Praluent, Repatha	Helps the liver absorb more LDL	Injectable	Respiratory infections, hyperglycemia

Source: Mayo Clinic, "High Cholesterol: Diagnosis & Treatment."

Comparison of Elements of Value

In many respects, the value elements of a cholesterol-lowering drug are like the value elements associated with a diabetes management drug: drug effectiveness and fewer complications. The impact on the patient's day-to-day life can be quite different. For many diabetes patients, managing their diabetes is a constant regimen of testing their glucose levels and adjusting their diet and insulin levels accordingly. Although high-cholesterol patients also must monitor their diet, daily testing and subsequent medication adjustments are currently unavailable. The accuracy of such kits is also known to vary greatly by brand. From the patient's perspective, this may make their daily routine a little easier, but the trade-off is less ability to adjust one's diet.

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APPLICATIONS OF VALUE DEFINITIONS

Now that we have reviewed various means of "defining value" for medications that treat diabetes and high cholesterol, we will turn to Section 3 and consider methods for "measuring value." If these value definitions can be quantified, then they can be measured. In Section 4 we will explore applications of these definitions and measures as we seek approaches to "rewarding results" in a scalable and meaningful manner.

Impact on TCOC will often be the central and greatest quantifiable impact for medications, including those that treat diabetes and high cholesterol. However, other types and sources of value should not be ignored. Productivity value and many other types and sources of value can be estimated or measured, even by proxy values, and aggregated into a cumulative value. Once the cumulative incremental value is identified it can be compared to the cumulative incremental cost in a comparison ratio commonly used across all society: return on investment. Then stakeholders can consider the types and sources of value that matter to them and their magnitudes when evaluating health care and business contractual decisions.

In Section 3 this research will focus on quantifying the impact of various diabetes and high-cholesterol drugs on the TCOC.

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Reimagining Pharmacy Financing

Section 3: Measuring Value

3.1. INTRODUCTION

When making a financial decision about a specific drug, most stakeholders consider net costs a key value. Depending on the decision, the net cost may mean just the direct costs associated with the drug itself, or it may include the impact of the drug on the total cost of care (TCOC). This section demonstrates techniques for measuring a specific drug's impact on TCOC and discusses how that can be used in decision making.

3.2. THE DECISION-MAKING PROCESS

The analytics a stakeholder uses in making a decision depend on the anticipated importance of the decision's impact on the plan sponsor's overall drug spend, its total cost of care, the availability of relevant data, and the resources available to do the analysis. In this section the emphasis will be on two types of decisions: benefit structure and financial implications. In any projection or analysis, more work can always be done. Still, a key consideration in determining whether or not to press on is how the additional work will impact the decision-making process. It is considered immaterial if the additional analysis is deemed to have little or no impact on the decision-making process. If the additional work is deemed material, the remedy in that case is to complete the additional work or disclose the analysis's limitations to the stakeholders.[30]

BENEFIT STRUCTURE

Once a drug is approved by the U.S. Food and Drug Administration (FDA) or a similar organization in another country, a payer must decide whether to cover the drug. In some countries, a drug may not be covered if it is not deemed cost-effective. In the U.S. many payers are required to cover all "medically necessary" benefits, so some drugs not covered in other countries may be covered under a U.S. plan to comply with the applicable legal standard. If so, the payer may impose stricter cost share requirements on the drug and/or require compliance with one or more utilization review programs to control costs. Cost share mechanisms include copays, deductibles and coinsurance.

In the U.S. the specifics regarding cost share and utilization programs depend on whether the drug is covered under the prescription or medical benefits. Although many ways can be used to make that determination, a convenient way to think about it is that if the drug can be self-administered, then it usually falls under the prescription drug benefit. If the drug administration usually requires clinical assistance, it more often falls under the medical benefit.

- *Prescription Drug Benefits:* For administrative ease, prescription drug benefit plans rely on a formulary. A formulary is a list of covered drugs and the cost-share tier for the drug and applicable clinical programs. Most plans have between two and five tiers, with the lowest tiers, typically comprising generic medications, having the lowest cost share amounts, and the highest tiers, typically comprising brands without available generics and specialty drugs, having the costliest cost share amounts. Similarly, clinical programs, such as preauthorization and step therapy, more often apply to designated drugs in the upper tiers.

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- *Medical Benefits:* If a drug is administered in a medical setting, such as a provider's office, it may fall within the medical benefit. In this case the cost share for the drug is treated the same as any other medical benefit. Some clinical programs may also apply to drugs covered under the medical benefit.

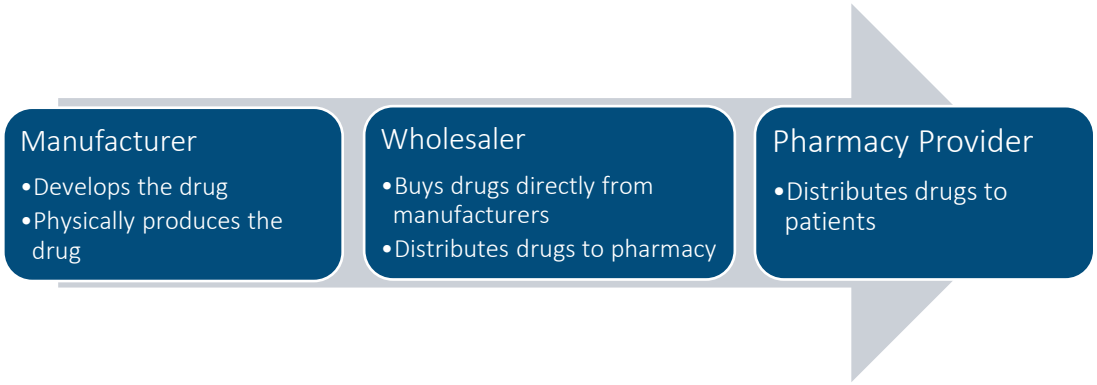
FINANCIAL DECISIONS

In some countries, pharmacy financing is a relatively simple process. A national board determines the price of a drug, and once that price is set, it applies to all. The U.S. systems sees multiple payers, each with a say in the final price, which greatly complicates the process. The focus of this report is on the process the U.S.

Consumer Price

A drug seldom goes directly from a manufacturer to a patient. Instead, many intermediaries assist along the way. Each step of this process impacts the amounts paid by the payer and the consumer. Delivering a drug to a patient follows several steps, as illustrated in Figure 3.1.

Figure 3.1
THE DELIVERY PROCESS



Of course, money changes hands at each point in this process, and the amount of money is determined through negotiation. The negotiations start with the list price set by the manufacturer, referred to as the wholesale acquisition cost (WAC). The manufacturer and the wholesaler negotiate adjustments such as bulk purchasing discounts, prompt payment discounts and distribution fees. The wholesaler then charges the pharmacy provider a marked-up price. Pharmacy providers include retail, mail and specialty pharmacies, hospitals and clinics. National databases publish average wholesale prices (AWPs), which for brand drugs are equal to WAC × 1.2. Payers and pharmacy benefit managers (PBMs) negotiate discounts from AWPs from pharmacy providers and rebates (usually based on a percentage of WAC) from manufacturers. These negotiations impact the direct cost of the drug. The final negotiated price is the average manufacturer price (AMP). The Centers for Medicare and Medicaid Services (CMS) require publication of the AMP.

Role of Pharmacy Benefit Managers

Ultimately, payers and consumers finance the cost of drugs. PBMs act as third-party administrators on behalf of payers to handle the day-to-day operations associated with a pharmacy benefit. The functions a PBM may perform include the following:[31]

- Administrative services such as claims adjudication, eligibility management and benefit plan management.
- Negotiation services such as pharmacy network management and pharmaceutical manufacturer relations.

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- Clinical services such as utilization review, prior authorizations and step therapy edits, quantity limits, medication therapy management and specialty pharmacy patient services.
- Fulfillment services through mail, specialty and infusion pharmacies.

The financial analysis underlying PBMs' activities is usually done on a portfolio or book-of-business basis. The analysis consists of repricing the expected mix of drugs based on the new contract. Key elements of the contract include the following:

- *Allowed Costs:* The total or allowed cost per drug is usually expressed as a percentage discount off the AWP plus a dispensing fee. Although the name implies that AWP refers to the price a pharmacy pays the wholesaler for a drug, it usually contains a substantial markup over the price the wholesaler pays to the manufacturer (AMP). One benefit of using AWP is that it can be used as a benchmark because third-party drug price database organizations publish the values. The dispensing fee is a per-script fee often applied to each retail prescription (mail and specialty pharmacy prescriptions often do not have a dispensing fee applied). Note that although terminology may vary by context, the term "allowed costs" usually means the total cost at the point of sale, including both the amount the payer reimburses for the drug and the patient's cost share.
- *Minimum Rebates:* Rebates are the amounts the manufacturer reimburses the payer for putting their drugs on the formulary and sometimes also on a favorable benefit tier. Rebates are based on completed financial periods, so they are not usually included in the allowed cost at the point of sale. The term "net costs" may or may not include the impact of cost share and rebates.
- *Administrative Fees:* Administrative fees are other per-prescription, per-member-per-month or fee-for-service amounts the payer reimburses the PBM for various services.

The negotiations often involve the PBM's guaranteeing the payer a minimum level of discounts and rebates. The PBM reimburses the difference between the actual and minimum guaranteed amounts if that level is unmet. Incorporating a TCOC guarantee into the current process would require contractual language describing the data and methods used to determine the amount to be transferred among the parties. Techniques for developing the appropriate measures underlying the transfer are discussed below.

TCOC Budgetary and Pricing Projections

Health care in the U.S. is operated mostly on an annual basis. Every year, insurers set premiums based on projected TCOC for the upcoming year, self-insured employer groups budget how much they will spend on health care benefits in the following year, and PBMs negotiate contractual terms with payers, manufacturers, wholesalers and network pharmacies. If no new blockbuster drugs, such as a new cancer biologic, are on the horizon, then the analytical process is done on a portfolio basis. If, however, a new blockbuster drug has recently been introduced or is about to be introduced, then the portfolio analysis has to be supplemented with an in-depth look at the projected impact of that drug on TCOC.

Portfolio Pricing

In the absence of a blockbuster drug, TCOC, in its simplest form, can be projected to a future period by trending the numbers and adjusting for future changes, as illustrated in the hypothetical example in Table 3.1. Key considerations in developing the trend assumptions include past trends and adjustments for future experience, such as changes in provider or PBM contracts, shifting demographics, new laws and, when applicable, the results of an in-depth analysis of TCOC.

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Table 3.1
HYPOTHETICAL PROJECTION PORTFOLIO METHODOLOGY.

	Year 1 PMPM (1)	Core Trend (2)	Subtotal Year 2 PMPM (3)	Drug Impact PMPM (4)	Year 2 PMPM (5)
Medical	$ 450.00	10%	**$ 495.00**	$ –	**$ 495.00**
Pharmacy	$ 50.00	20%	**$ 60.00**	$ 5.00	**$ 65.00**
Total	**$ 500.00**	**12%**	**$ 555.00**	**$ 5.00**	**$ 560.00**

In-Depth Analysis

In considering the impact of a new drug (shown in column 4), the stakeholder will likely analyze not only the impact of the drug itself but also the impact the introduction of the drug has on other drugs in the therapeutic class. The impact on drugs in adjacent therapeutic classes may also be considered. If thorough and reliable information about the new drug's likely impact on TCOC is available, then its projected impact on medical benefit costs could also be incorporated in the "Medical" row of column 4.

Since 1997 the FDA has approved between 18 and 59 new drugs each year.[32] The approval process focuses on clinical effectiveness and the drug's safety. This process includes little or no information about cost and savings. A stakeholder requiring cost and value information will have to develop it themselves or rely on an organization that specializes in that type of analysis, such as the Institute for Clinical and Economic Review in the U.S. or the National Institute for Health and Care Excellence in the U.K. Both organizations produce health technology assessments (HTAs), which include an in-depth review of the clinical considerations about the drug in question and a projection of future incremental costs and value attributable to the drug.

At the launch of a new product, the only information available about the new drug is often the information developed as part of the approval process, including the findings from the clinical trials. This information could include items such as the number of inpatient admissions and the relative adverse effects of the new drug relative to comparator drug(s). The researcher can use this information to construct a decision tree to determine the relative costs of the drugs.

One drawback to relying solely on information from clinical trials is that limited cost and utilization data may be limited at that time. That said, using the information available from the clinical trials, information derived from analyzing what happened when similar drugs were introduced, and other information available on the internet, the in-depth analysis needs to consider the following:

- *Approval Date:* If the effective date of the approval is not known at the time the projection is made, then the stakeholder must estimate that date. After all, a drug expected to be approved in January is more likely to significantly impact a calendar year budget than a drug expected to be approved in December. Further, PBMs typically need time after a drug's approval date to review the drug and determine formulary placement before it is available through the PBM's formulary.

- *Target Population:* Every drug is specifically designed to treat one or more conditions. This population is the starting point for determining the expected utilization of the drug. This information may be available for payers in administrative data, such as the claims and eligibility files. However, clinical and laboratory measures that may not be available to the payer often define whether or not the drug is appropriate for the patient.

- *Take-up Rate:* The take-up rate is the percentage of the target population that begins taking the drug. The take-up rate often follows the technology curve. When a new drug or technology is

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approved, the percentage of the target population using that drug or technology tends to be very low. It takes time for doctors and patients to read about the drug, become comfortable with it, make doctor's appointments and so on. After a while, often a rapid increase is seen in the number of patients willing to try the new drug or technology as doctors and patients "catch up" with the new technology. After the catch-up phase, the rate of increase in utilization slowly decreases until it reaches a steady state. This can be estimated by examining patterns from the take-up rates of similar previously launched drugs.

- *Adherence:* Once a patient has a prescription filled, it is impossible to know if they adhered to the recommended dosage schedule. Proxy measures such as the medication possession ratio (MPR) and proportion of days covered compare the number of days' supply filled or covered versus the number of calendar days. These numbers can be estimated using information from similar drugs. This report considers a patient with an MPR greater than or equal to 80% adherent. Otherwise, the patient is considered nonadherent. Of course, patients who receive a prescription but never get the first prescription filled are also nonadherent but will not be included in our measures of adherence (and nonadherence) because our primary data sources are pharmacy and medical claims databases.

- *Drug Costs:* This item is the best estimate of the unit costs for the drug based on whatever information is available at the time of the projection.

- *TCOC Impact:* At the very least, the budget projection should reflect the impact of services related to prescribing the drug and monitoring its impact. This may include increased office visits, lab tests and home monitoring equipment. If other reliable information is available about the total cost of care, such as an expected reduction in inpatient admits, emergency department visits, lengths of stay, adverse events or complications, that information could also be reflected in that analysis. If sufficient information is available, then it could be helpful to measure the impact of a drug over the course of treatment for a patient. For example, it may take several months for a patient with Type 2 diabetes to see a reduction in their A1C after being prescribed a new medication.

The initial projection used to set objectives is always based on limited information and requires many assumptions. Additional information, such as the actual take-up rate and the medication possession ratio, becomes available each year. Eventually, with rare exceptions, the drug will be analyzed as part of a portfolio rather than as a single new drug. The process of incorporating new data into the process is represented by the actuarial control cycle illustrated in Figure 3.2.

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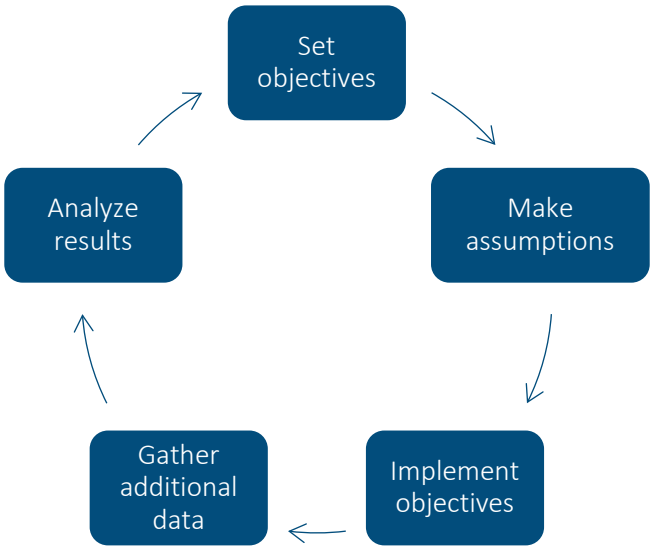
Figure 3.2
THE ACTUARIAL CONTROL CYCLE



3.3. THE DATA

The primary data source for this research is the Health Care Cost Institute commercial claims data set for calendar years 2016–2021. This data set includes approximately one-third of all commercial members in the U.S. Only adults (ages 18–65) in groups with medical, pharmacy and behavioral health claim data were included in the study to ensure complete and accurate data. The study also excluded members with Type 1 diabetes, pregnancy, cancer or autoimmune disease diagnoses to reduce potential confounding factors.[33]

Table 3.1
DATA SUMMARY

Member Count (in millions)	2016	2017	2018	2019	2020	2021
Total Unique Members	55.5	55.3	53.8	53.7	51.0	46.6
With Pharmacy Claims Available	33.3	32.1	30.7	28.4	26.7	27.0
With Mental Health Claims Available	33.0	31.7	30.3	28.0	26.3	26.8
Under 65	31.9	30.6	29.4	27.2	25.5	26.2
Nonstandard Product	31.7	30.4	29.2	27.0	25.3	26.0
Full Year Eligibility	19.5	19.0	18.1	17.1	16.6	16.1

Percent of Total	2016	2017	2018	2019	2020	2021
With Pharmacy Claims Available	60%	58%	57%	53%	52%	58%
With Mental Health Claims Available	59%	57%	56%	52%	52%	58%
Under 65	57%	55%	55%	51%	50%	56%
Nonstandard Product	57%	55%	54%	50%	50%	56%
Full Year Eligibility	35%	34%	34%	32%	33%	34%

This data set aggregates data received from several large carriers, so the available data include the information shown in Figure 3.3, which is commonly available in carrier claims data sets.

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Figure 3.3
KEY DATA ELEMENTS IN HCCI DATABASE

Eligibility Data	Inpatient, Outpatient and Professional Data	Pharmacy Data
• Patient identifier (encrypted) • Enrollment calendar month and year • Age band and gender • Product type (EPO, PPO, HDHP etc.) • Member ZIP code • Funding (self-insured vs. fully insured)	• Patient identifier (encrypted) • Medical claim identifier (encrypted) • Service dates • Diagnosis codes • Procedure, revenue and DRG codes • National Provider Identifier • Network indicator (in network or out of network) • Dollar chain amounts (allowed, copay, deductible, coinsurance, net paid)	• Patient identifier (encrypted) • Claim ID (encrypted) • Incurred date • Quantity in metric units • Dollar chain amounts • Dispensing fee • Prescriber ID • Days supply • National drug code • Multisource indicator • Specialty pharmacy flag

The HCCI database does not include descriptions of standard codes, but the researchers were able to download the necessary files from another source. Similarly, the medical and pharmacy claims database does not include information such as electronic health record data or lab results.

3.4. METHODOLOGIES

As noted above, the ability to measure the impact of a specific drug depends on the data available to do the analysis. The research underlying this report demonstrates methodologies for measuring the impact of a specific drug on TCOC. This information can be used directly in the negotiation process for the drug in question, and it can be used to inform actuaries and other researchers about patterns and observations that may be useful in measuring the impact of a drug on TCOC.

METHODOLOGY OVERVIEW

In this report the authors measured the impact of different drugs treating two disease states on the total cost of care, as noted in Section 2. The first disease state is Type 2 diabetes. For this disease state, the authors compared SGLT2s, such as Jardiance and Farxiga, and GLP1s, such as Trulicity and Ozempic, taken individually and in combination, to insulin. The second disease state is hypercholesterolemia (high cholesterol). For this disease state, the authors compared PCSK9s, such as Repatha and Praluent, to statins, such as Crestor and Lipitor.

The research was conducted using three methodologies, as shown in Figure 3.4. The goal is to understand each methodology's broader applicability and compare similarities and differences in results to understand the implications of each methodology more deeply.

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Figure 3.4
METHODOLOGY OVERVIEW

Pre-Post Index Event	Propensity Match	Concurrent Risk Adjustment
•Evaluate impact of initiating medication following an index event •An inpatient admission is an example of an index event	•Match study populations on clinical and demographic characteristics	•Compare costs in a 12-month period using industry standard risk-adjustment model

The key items to be considered in evaluating the specifics of each methodology include the following:

- Does the methodology adequately account for confounding factors that may unduly influence the results?
- Can statistical testing be done to ensure that the results are not due to random variation?
- Is the methodology scalable for use in the decision-making process?

PRE-POST INDEX EVENT METHODOLOGY

This methodology compares TCOC before and after a major event, such as a hospital admission. This methodology seeks to normalize populations because all populations experienced the index event clinically. For example, in this study Type 2 diabetes or hypercholesterolemia that is clinically severe enough to result in an inpatient admission is significantly clinically different from less clinically severe manifestations of those conditions. The effect of the intervention can be evaluated by comparing the post event period costs to the pre-event period costs: a more successful intervention should result in a greater decrease (or smaller increase) in TCOC in the post event period than other interventions. The pre-post index event timeline is illustrated in Figure 3.5.

Figure 3.5
PRE-POST INDEX EVENT TIMELINE

Pre-Event: 6 Months						Wash-Out Period	Evaluation Period: 12 Months											
1	2	3	4	5	6	Index Event + 1 Month	1	2	3	4	5	6	7	8	9	10	11	12

A few comments about the timeline:

- *The Pre-Event Period:* The pre-event period establishes a baseline so different populations can be normalized on their pre-index event TCOC.
- *The Wash-Out Period:* A one-month "wash-out" period that starts on the date of the index event is used to ensure that the costs of the index event itself are not included in the pre- and post-event comparison.
- *The Post event Period:* The post event period consists of the 12 months after the wash-out period concludes and is compared to the pre-event period to assess the intervention.

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This paper compares the average TCOC in the pre-event period to the average TCOC in the post event evaluation period because that is most relevant to pharmacy financing. The study parameters are shown in Appendix A.

This methodology can be useful to approximate narrowly defined clinical scenarios from claims data without clinical or lab information. This could inform prior authorization or step therapy guidelines and inform clinical programs. The method could also be useful in developing pharmacy reimbursements based on an episode of care. Once the evaluation period for an episode is complete, the savings or risk can be measured and then shared among the stakeholders.

Although this method is useful in determining the impact of a drug on TCOC, if the specified clinical protocols are followed, patients taking the drug that did not experience an index event are excluded from the study. This means a complete picture of the value of the drug is not available, and the methodology can suffer from limited sample sizes.

PROPENSITY-MATCHING METHODOLOGY

The purpose of using this method in this study is to compare TCOC between patients who take a drug and patients who do not on an "all other things being equal basis," where "all other things being equal" reflects similar comorbidities and demographics. This analysis can also provide insights into whether drug utilization increases over time and whether patients are adherent. Basically, this method matches individuals taking the drug to individuals not taking the drugs based on specified criteria.

In this research individuals were matched using more than 180 characteristics based on the World Health Organization's ICD-10-CM diagnosis codes and National Drug Code (NDC) pharmacy utilization (documented in Appendix B). The propensity match algorithm matched individuals on a subset of characteristics most predictive of using the drug being analyzed. The subset of 25 characteristics was developed using a loosely fit XGBoost model. This decision tree–based machine learning algorithm was useful for handling the high-dimensional, highly heterogeneous ICD/NDC data. It provided an efficient method for reducing the 180 variables to a more manageable subset to improve the matching algorithm's efficiency. The matching model used a covariate balancing propensity score, a method for maximizing the information the propensity score provides for both covariate balancing and conditional probability of treatment assignment.

This methodology provides significant flexibility in creating clinically similar populations for comparison and precisely matches the populations on the study topic (namely, the drugs patients are utilizing). This method can also assess variability in study results by redoing the matching and evaluating if the results remain similar.

However, this technique can be very computationally intensive and may require implementing the models on limited sample sizes because of system constraints. The ability to assess variability through repeated iterations of matching and bootstrapped sampling can allow for assessing the variability present due to limited sample sizes.

RISK ADJUSTMENT

Under this methodology, every member of a population is assigned a risk score using a standard industry methodology. This study uses the CMS-HCC concurrent risk scores model, which uses each member's demographic profile, diagnosis and pharmacy utilization to develop a risk score; this is documented in Appendix C. Once the risk score has been assigned, the risk-adjusted total cost of care can be compared between groups. The risk-adjusted costs can then be determined by dividing the cost for a group of people by their risk score. For example, suppose the unadjusted allowed costs per member per month (PMPM) for a group of people is $550, and the average risk score is 1.10 (indicating the group is predicted to be 10%

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more expensive than average based on their demographic, diagnosis and pharmacy information). Then the adjusted risk score would be $500 = $550 ÷ 1.10. This group could then be compared to a group with a $476 average PMPM and a risk score of 0.95 on an "all other things being equal basis."

This is the most scalable method for comparing TCOC because it can be automated easily for all drug classes, uses all members taking a drug, and is widely used by payers for other purposes.

However, the risk-adjustment process was designed for other purposes, so one may find some model risk; that is, the design of the process may not adequately reflect the true risk being measured. This may occur if the model is trained on a general population (as the CMS-HCC model is), but the study population is very narrowly tailored. Additionally, the accuracy of individual risk scores (measured in terms of mean squared error [MSE]) tends to be low compared to other statistical measures. However, MSE converges to 0 for the population means as the population size grows.

3.5. RESULTS AND COMMENTARY

Results for each method are presented in each condition category studied, hypercholesterolemia (PCSK9s and statins) and Type 2 diabetes (GLP1s, SGLT2s and insulin). The results are accompanied by commentary on the findings. Section 3.6 is devoted to a higher-level summary, lessons learned, insights and suggestions for future studies.

HYPERCHOLESTEROLEMIA: INDEX METHOD

The hypercholesterolemia group of models analyzed PCSK9s and statins. In the index method model, we compared the costs six months before and 12 months after an inpatient admission for a list of hypercholesterolemia diagnosis-related groups (DRGs). A more detailed description of the index method is contained in Appendix A.

Statin use has been consistent since 2016, with about 60% of patients filling at least one prescription in the 12 months following the index event; see Figure 3.6. PCSK9 utilization has been much lower for a combination of reasons. The two products in this class entered the market in mid-2015. Additionally, the higher cost of these drugs can sometimes serve as a deterrent to filling a prescription. When first launched, the annual cost (pre-rebate) of PCSK9s was over $14,000. However, significant price declines have occurred recently (Praluent and Repatha have pre-rebate annual costs of around $6,000 in late 2023. Finally, the clinical indications for PCSK9s are much narrower than those for statins. So, even following an inpatient admission for a hypercholesterolemia-related condition, a patient may not be indicated (or successfully navigate a payer prior authorization process) for PCSK9 therapy.

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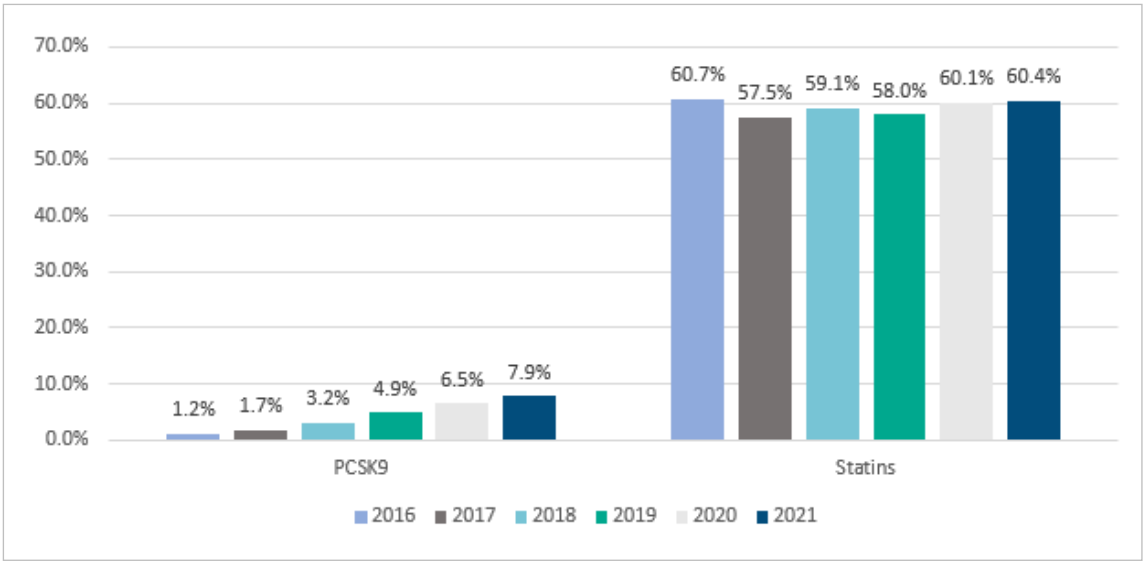
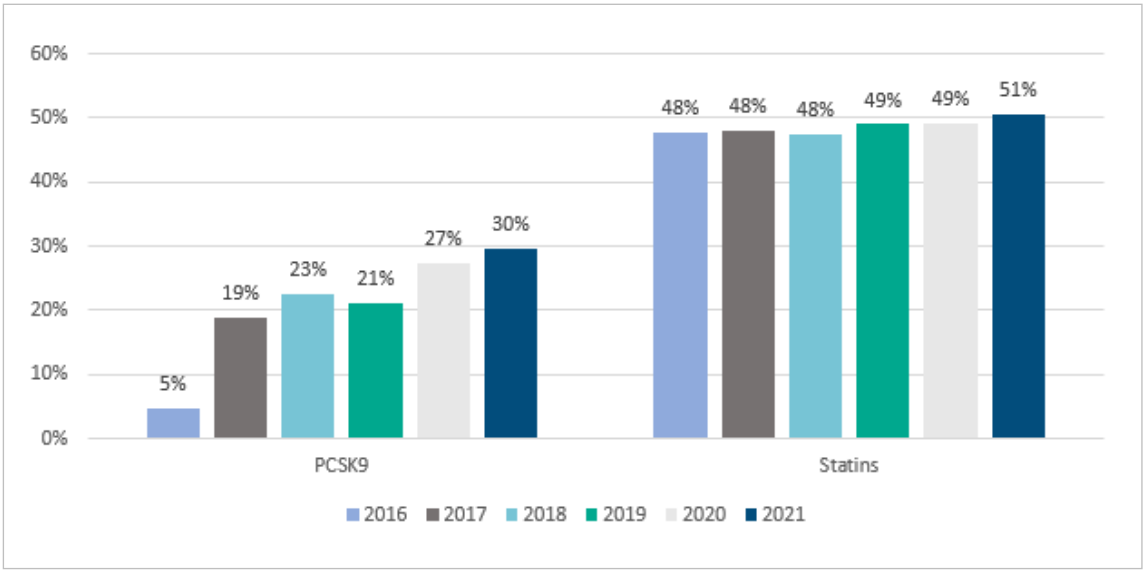
Figure 3.6
PERCENT OF PATIENTS TAKING DRUGS IN THE POSTEVENT PERIOD



Cost is also a key concern with continued adherence, and the data exhibited much lower adherence to PCSK9s than statins. However, adherence to PCSK9s increased following the 2018 price decline of a key product in this class; see Figure 3.7. Recall that adherence in the post event period is defined as filling prescriptions that supply medication for 80% of this 12-month period.

Figure 3.7
ADHERENCE TO DRUG IN POSTEVENT PERIOD



Four groups were analyzed: those newly taking a PCSK9 (adherently or not) in the post event period (that is, initiating therapy after the index event), those not taking a PCSK9 in either the pre- or post-event period, those newly taking a statin (adherently or not) in the post event period, and those not taking a statin in the pre- or post-event period. The groups who were taking the drugs in both periods or who ceased therapy

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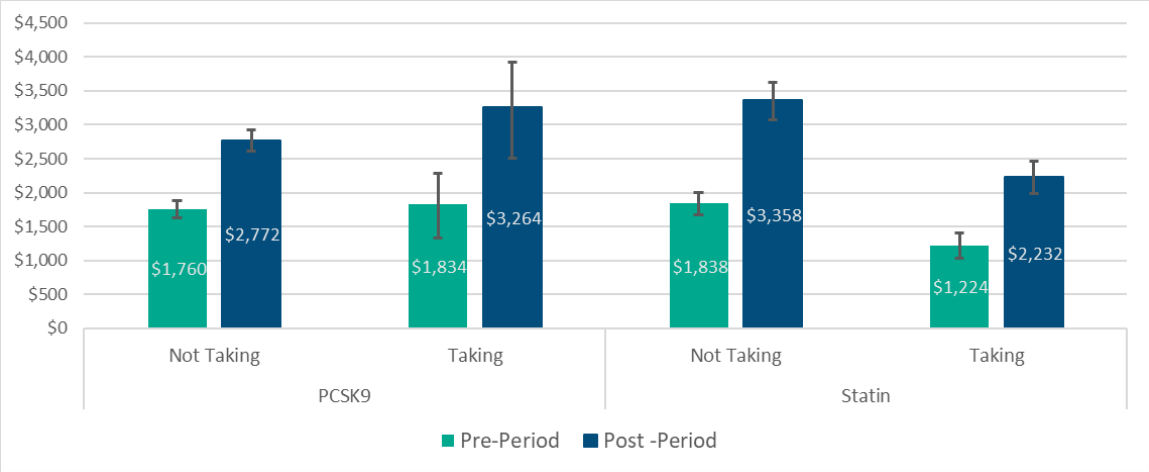
after the index event had few patients and so were excluded for simplicity of interpretation. Individuals taking both PCSK9s, and statins are included in both groups.

Allowed costs for the four groups were similar in the pre-event period, except for the group newly taking statins. All four groups saw an increase in allowed costs in the post event period. However, allowed costs increased significantly for the group initiating PCSK9 therapy (a 78% increase, or $1,430 PMPM) compared to those who did not (a 57.4% increase, or $1,012 PMPM). In contrast, costs for the groups initiating or not initiating statin therapy increased the most (82.7% and 82.4%, or $1,008 and $1,520 PMPM, respectively) but did so nearly uniformly. This is summarized in Figure 3.8 for admits that occurred in 2020 and whose index periods were in 2021.

Figure 3.8
2021 INDEX PERIOD ALLOWED COST PMPM COMPARISON



Two potential comparisons result in understanding the TCOC impact of PCSK9s, both pointing in a similar direction. One possible conclusion from this data focuses on the PCSK9 numbers and observes that although costs were roughly equal in the pre-event period ($1,760 and $1,834), the costs for the group initiating PCSK9 therapy increased significantly more ($418 PMPM or $5,016 per year) than the group that did not initiate PCSK9 therapy. The $418 increased cost per month represents a pre-rebate allowed cost. PCSK9s may offer a rebate in excess of 50% of WAC; however, the increased costs calculated by this method would require a rebate of over 85% of WAC to achieve neutral TCOC impact over the 12-month post event period. Longer evaluation periods may produce a different break-even rebate amount as some value accumulates and compounds over time.

Another potential comparator to the PCSK9-taking group is the statin-taking group. Costs for the statin-taking group increased $1,008 PMPM, compared to the $1,430 for the PCSK9-taking group, a difference of $422 PMPM, or an implied rebate of 88% to achieve neutral TCOC impact over the 12-month post event period. A different projection period might have a different "breakeven" rebate determination.

HYPERCHOLESTEROLEMIA: PROPENSITY SCORE METHOD

In the propensity score method model, we compared the costs over 12 months for individuals in a control group and a treatment group with similar diagnosis codes and pharmacy utilization histories. A more detailed description of the propensity score method is contained in Appendix B.

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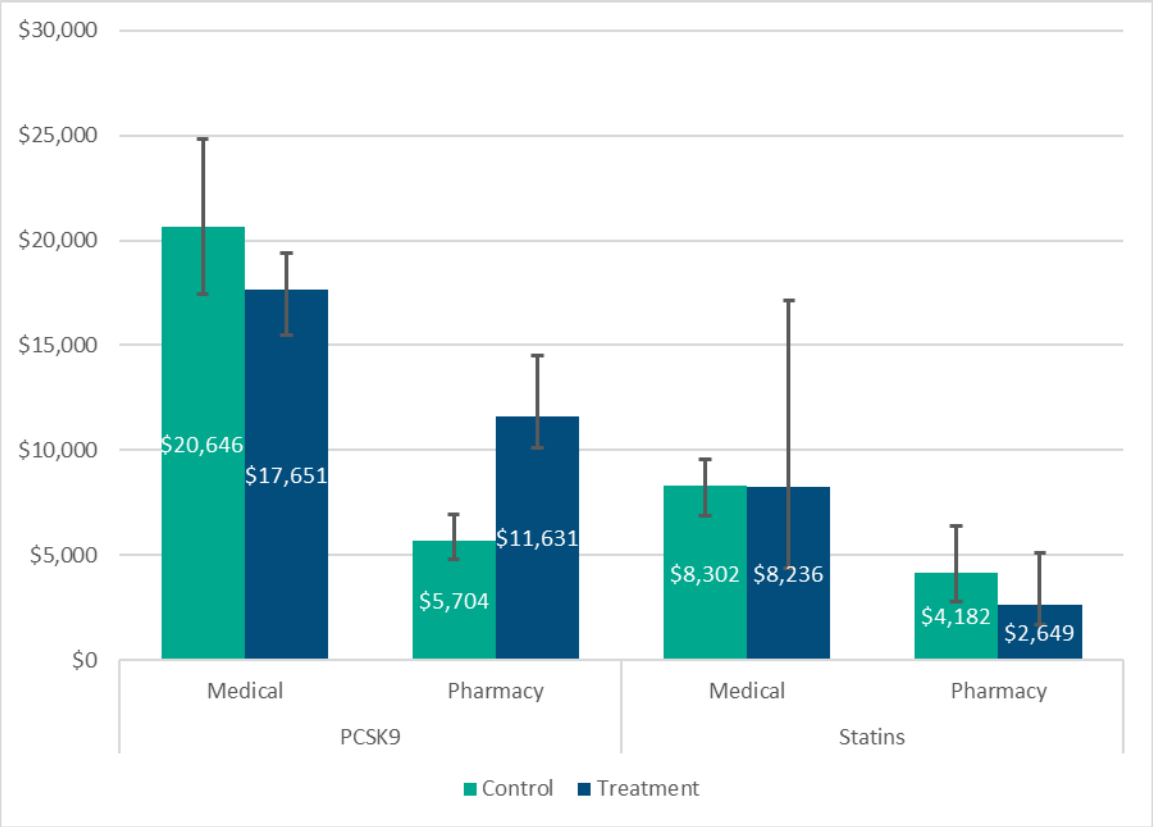
Annual cost results from this model for 2021 are shown in Figure 3.9. Medical and pharmacy costs are broken out for the control (not taking the drug) and treatment (taking the drug) populations.

Figure 3.9
2021 TOTAL COSTS PMPY BY DRUG AND STATUS



In 2021 allowed costs for the PCSK9 treatment group were $2,932 higher per member per year (PMPY) than the PCSK9 control group. That implies a rebate of 51% of WAC for a PCSK9 to achieve a break-even TCOC impact over a one-year period. The breakeven rebate might be different over a longer projection period.

Annual costs with medical and pharmacy spending combined for all years studied (2016–2021) are shown in Figure 3.10.

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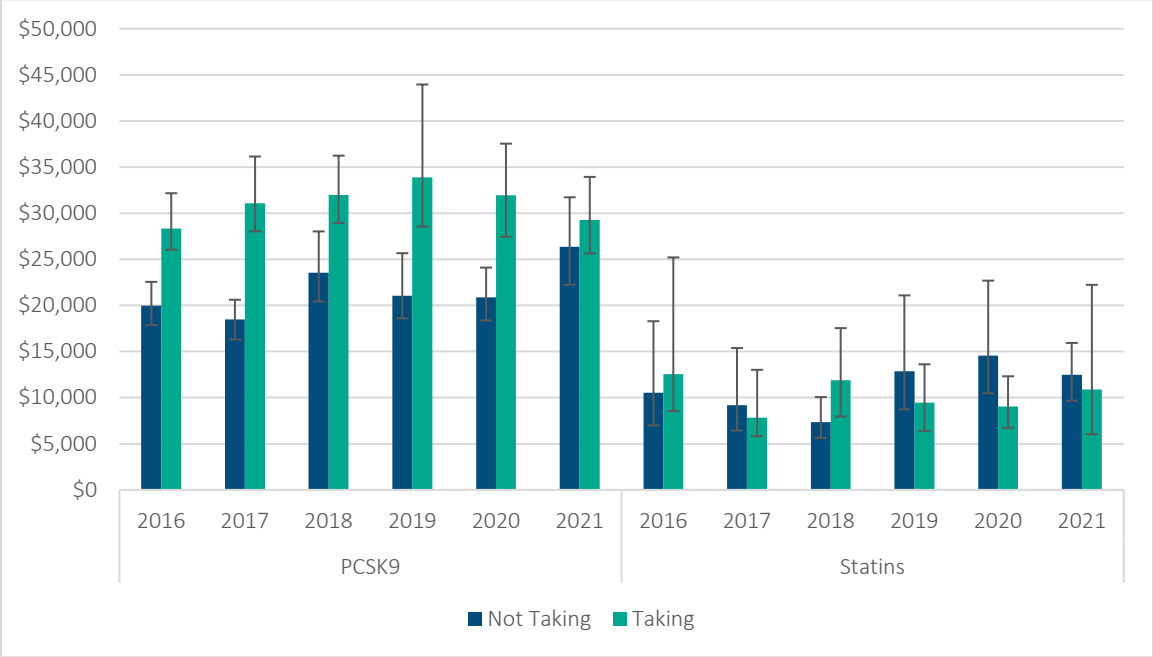
Figure 3.10
2021 TOTAL ALLOWED COST PMPY BY DRUG AND YEAR



These models suggest that PCSK9s may not reduce TCOC: although medical costs are reduced, the added pharmacy costs are greater than the medical cost reduction. The error bars represent a 90% bootstrapped confidence interval using a bias-corrected and accelerated (BCA) interval appropriate for these skewed and small sample sizes. The difference in TCOC between the populations taking and not taking PCSK9s is significant at this level for each year other than 2021.

These error bars for the statin models are too wide to make definitive statements, and the means are similarly volatile, with the not-taking population having higher costs in 2017, 2019, 2020 and 2021, and the taking population having higher costs in 2016 and 2018. It would be necessary to narrow these confidence intervals to make definitive statements about the impact of statins. However, these results may suggest that statins result in a marginal improvement in the total cost of care.

HYPERCHOLESTEROLEMIA: RISK ADJUSTMENT METHODOLOGY

In the risk-adjustment method model, we compared the costs over 12 months for individuals taking each drug, controlling for population differences by adjusting costs with a risk score. A more detailed description of the risk-adjustment methodology is contained in Appendix C.

The risk scores for the two groups taking PCSK9s were significantly higher than those of the statin group; see Figure 3.11. The statin group is also much larger than these two groups combined, so normalizing the risk score among the combined population to 1.0 results in the statin group's having a risk score close to exactly 1.0. The 1.6 to 1.7 risk scores for the PCSK9 groups suggest that the known additional expected cost of these individuals based on their diagnosis and pharmacy utilization could be 60% to 70% more than the statin population.

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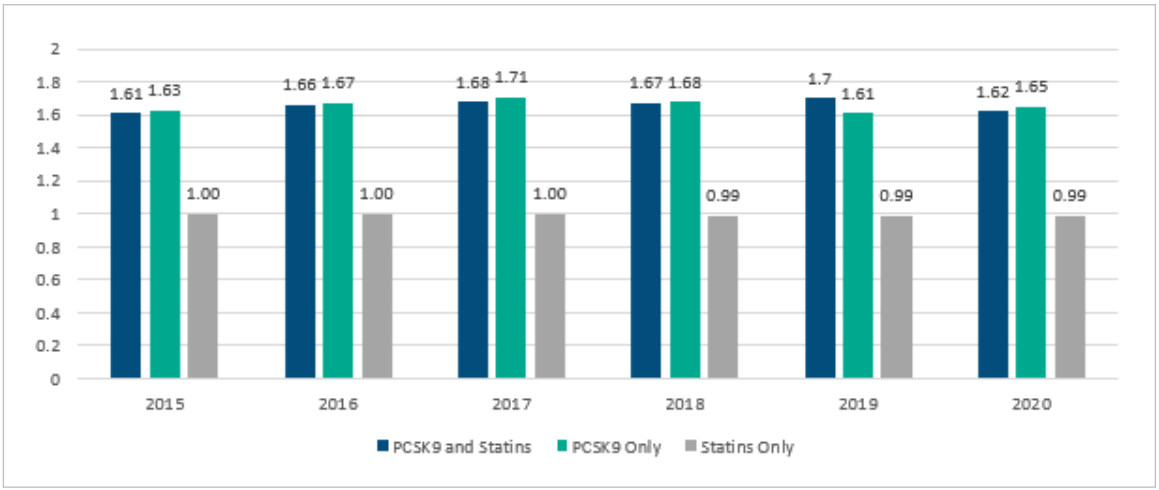
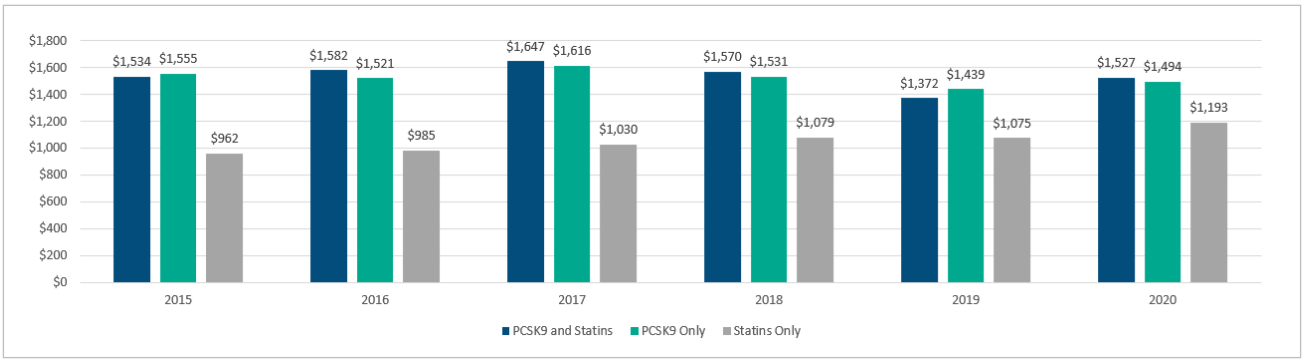
Figure 3.11
RISK SCORES FOR PCSK9 AND STATIN GROUPS, 2015–2020



Risk-adjusted total allowed costs for the individuals taking statins only are significantly lower than for the two groups taking PCSK9s; see Figure 3.12. The PCSK9 and statin groups have allowed costs similar to the PCSK9-only group, suggesting that combining the two therapies does not significantly impact medical costs (as low-cost generic statins are widely available and do not contribute much to pharmacy costs). This suggests that although we would expect the PCSK9 groups to cost 60% to 70% more based on risk scores (discussed above). TCOC may cost an additional 30% to 60% above that. Pre-rebate risk-adjusted allowed costs for the two PCSK9-taking groups exceeds the statin-only group by about $300 PMPM. This implies a needed rebate of 63% of WAC to achieve a neutral TCOC impact over the 12-month projection period. Different projection periods may produce different break-even rebate amounts as some TCOC savings increase over time.

Figure 3.12
TOTAL RISK-ADJUSTED ALLOWED PMPM COSTS FOR PCSK9 AND STATIN GROUPS, 2015–2020



TYPE 2 DIABETES: INDEX METHOD

The Type 2 diabetes group of models analyzed GLP1s, SGLT2s and insulin. In the index method model, we compared the costs six months before and 12 months after an inpatient admission for a list of Type 2 diabetes related DRGs. A more detailed description of the index method is contained in Appendix A.

Insulin use has grown slightly each year, with over 60% of patients taking insulin after the index event in 2020. SGLT2 and GLP1 utilization has been much lower because of similar factors discussed with PCSK9s; these are newer products on the market, and they have a higher price, which can act as a deterrent to a

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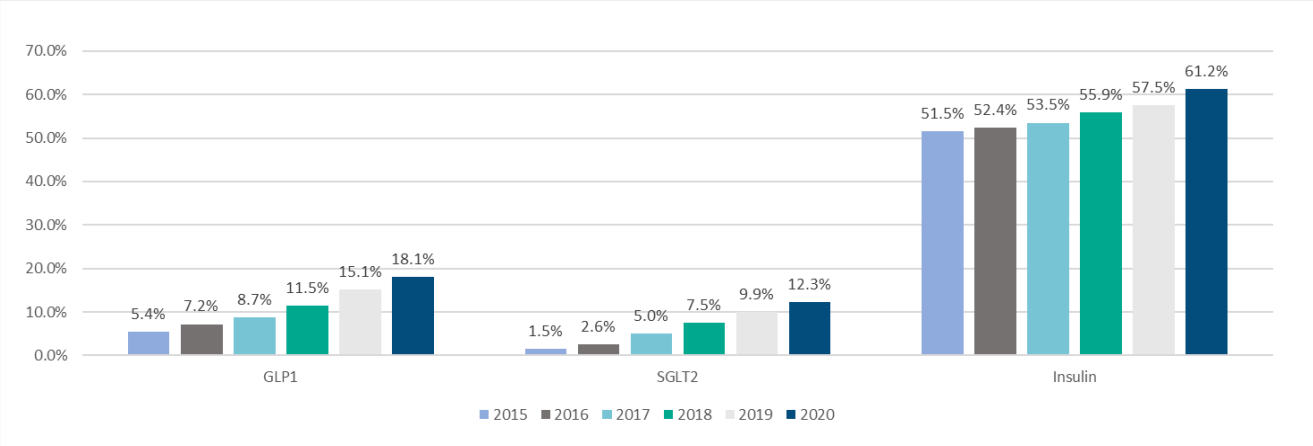
member's filling their prescription. They are also more tightly controlled by prior authorizations and other clinical management programs. Adherence for all three medications averaged between 40% and 50%; see Figure 3.13.

Figure 3.13
PERCENT OF PATIENTS TAKING PRESCRIPTION IN THE POSTEVENT PERIOD



All three of these drugs can (and are) used in combination, so to consolidate the analysis, we looked at each of the three drugs individually, separating those taking or not taking the drugs (regardless of which other drugs they were taking). These results are summarized in Figure 3.14.

Allowed costs increased in the post event period for all six groups, and all three drugs also exhibited the behavior that the group taking the drug in the post event period had lower TCOC in the pre-event period, often statistically credibly, so based on the 90% BCA bootstrapped intervals. Similarly, for all three drugs, the costs in the taking group increased at a greater period-over-period rate than the not-taking group.

Focusing on GLP1s, post event period allowed costs increase by 84.2% in the taking group versus 54.2% in the not-taking group. This means that the additional TCOC for the taking group is $262. The GLP1 products vary in pre-rebate cost from approximately $7,500 to $10,500 PMPM, which is much more than the extra period-over-period costs for the taking population ($3,144 annually), suggesting that the GLP1s may be moderately cost-effective while not necessarily seeing TCOC reductions that offset their prices when taken by these populations. This suggests a needed rebate of 30% to 41% of WAC, depending on the WAC cost of the drug, to achieve neutral TCOC impact over the 12-month projection period. Different projection periods might produce different break-even rebate amounts.

The SGLT2 post event period costs rose faster for the "taking" group at 136.2% versus 51.1% for the "not-taking" group. This additional period-over-period allowed cost increase is similar in magnitude to the allowed cost of SGLT2s, which implies that a rebate of over 100% of WAC would be needed to achieve neutral TCOC impact over the one-year projection period. Longer projection periods may result in a larger accumulation of savings.

Similarly, with the insulin groups, allowed cost increased by 139.6% in the "taking" group, compared with 50.4% in the "not-taking" group, with an unexplained period-over-period increase of $758. The annual cost of insulin varies significantly by patient because dosage levels can differ.

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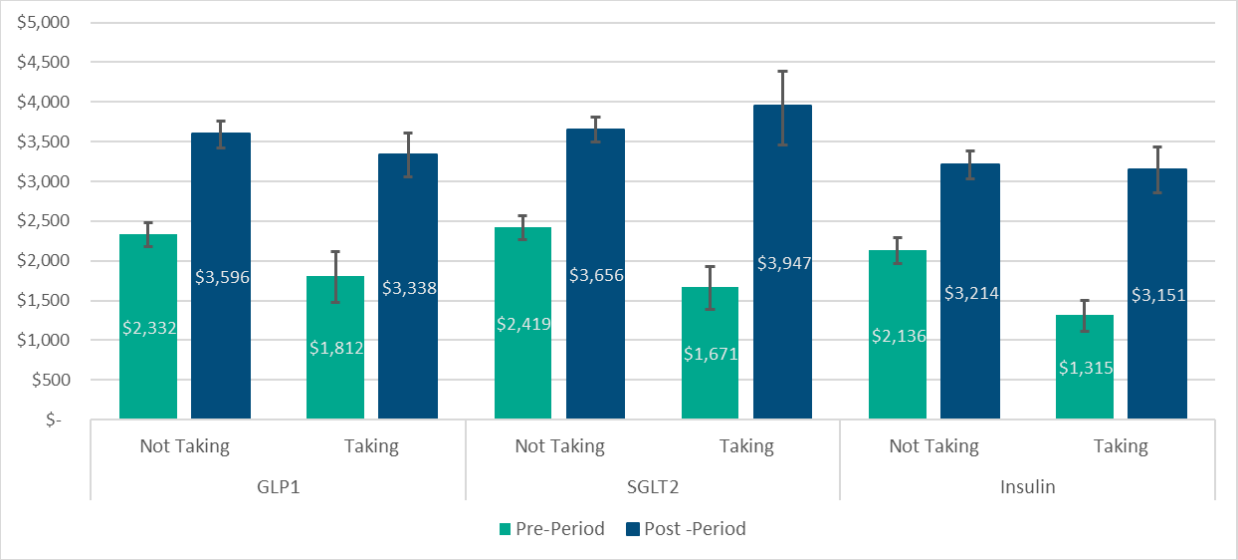
Figure 3.14
2021 INDEX PERIOD ALLOWED COST PMPM COMPARISONS

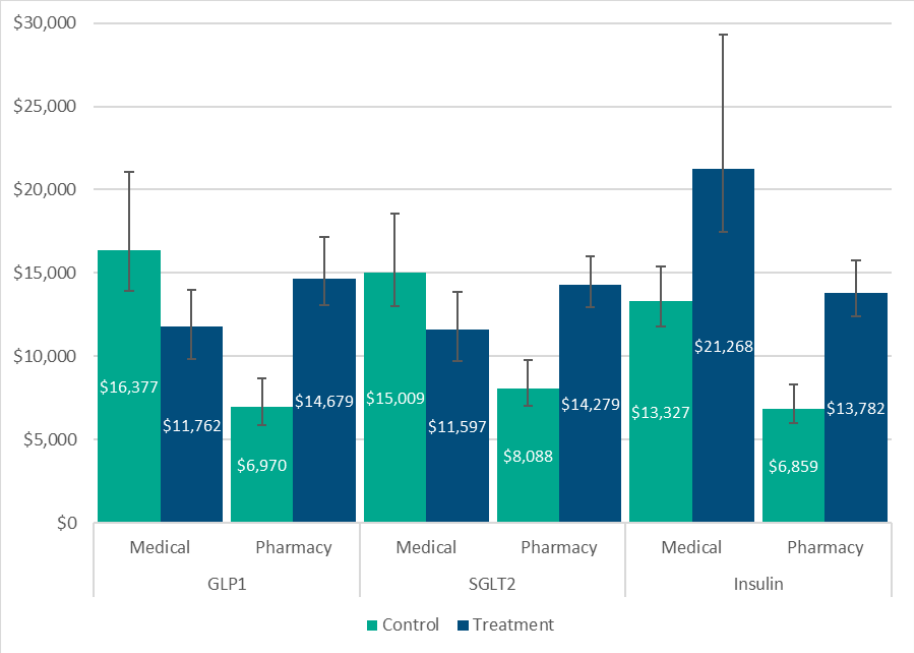


TYPE 2 DIABETES: PROPENSITY METHOD

In the propensity score method model, we compared the costs over 12 months for individuals in a control group and a treatment group with similar diagnosis codes and pharmacy utilization histories. A more detailed description of the propensity score method is contained in Appendix B.

Annual allowed cost results from this model for 2021 are shown in Figure 3.15. Medical and pharmacy costs are broken out for the control (not taking the drug) and treatment (taking the drug) populations.

Figure 3.15
2021 TOTAL PMPY COSTS BY DRUG AND STATUS



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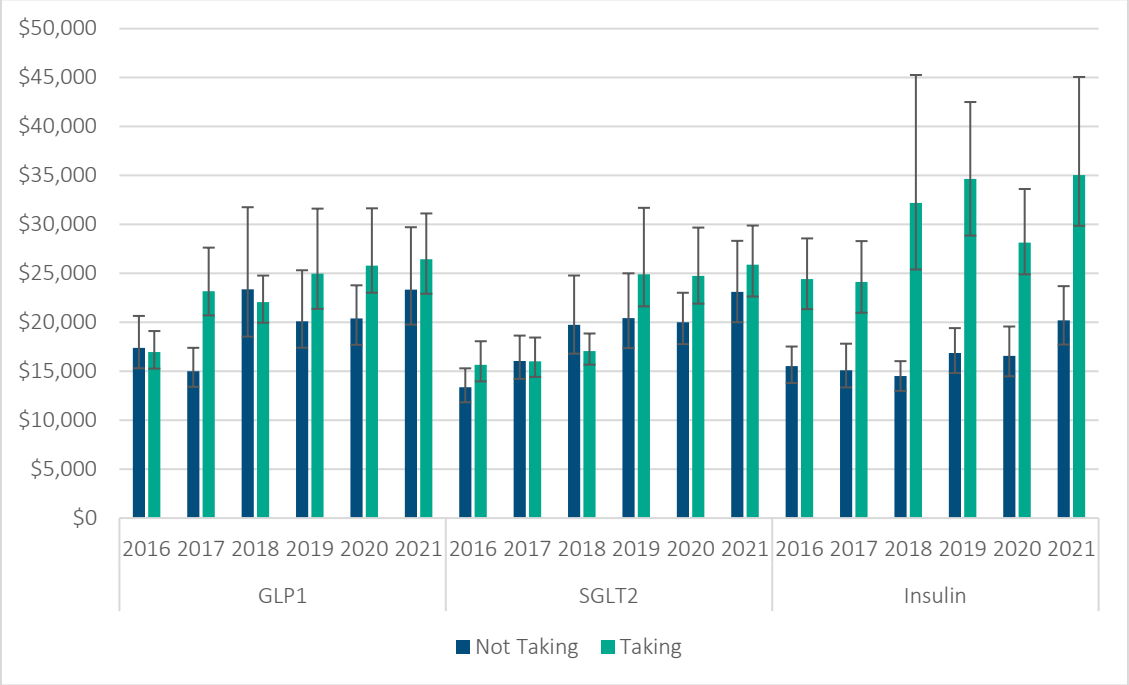
Annual allowed costs with medical and pharmacy spending combined for all years studied (2016–2021) are shown in Figure 3.16.

Figure 3.16
2021 TOTAL ALLOWED PMPY COST BY DRUG AND YEAR



These models suggest that GLP1s and SGLT2s both result in a reduction in medical TCOC that partially offsets the increase in prescription costs. The 2021 results suggest GLP1s and SGLTs result in an extra $258 and $232 per member per month (PMPM), respectively. These are the amounts needed for TCOC neutrality. However, the error bars are wide and do not allow a definitive conclusion. The modeling appears to suggest that taking insulin costs significantly more than not. But this is because of a lack of information in the claims data, resulting in a poor match of clinical severity. Although the match is good from an analytical perspective (described in more detail in Appendix B), the diagnosis code and pharmacy utilization data do not provide enough specificity to differentiate between the wide range of clinical severity of Type 2 diabetes. In other applications, taking insulin is exactly the data element that would help differentiate Type 2 diabetes clinical severity; however, we cannot use that because insulin usage is the measure we are comparing. As a result, even though their diagnosis and pharmacy utilization look similar in the claims data, the group not taking insulin is less clinically severe than the insulin group, resulting in significantly lower costs.

TYPE 2 DIABETES: RISK ADJUSTMENT

In the risk-adjustment method model, we compared the costs over 12 months for individuals taking each drug, controlling for population differences by adjusting costs with a risk score. A more detailed description of the risk-adjustment method is contained in Appendix C.

The Affordable Care Act (ACA) risk-adjustment model contains risk scores for a history of using SGLT2s/GLP1s, combined in a “hypertension medication” measure with a 0.706 coefficient. It also contains risk scores for a history of using insulin, which has a coefficient of 1.34. Additional combination coefficients are used when either of these medications is used in an individual with Type 2 diabetes. The combination coefficients

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subtract 0.253 and add 0.447, respectively, from the hypertension medications and insulin groups, further widening the gap.

By bundling all hypertension medications into one group, the ACA model's coefficient is more indicative of the cost of low-cost generics, which comprise most hypertension prescriptions. The model would need to be retrained without these coefficients to adjust for this appropriately. We attempted to exclude these coefficients from this existing model. However, that also produced unreasonable results. Because of this, the results below are included for the sake of completeness; however, they do not provide valuable insights into the impact of these drugs on TCOC.

As expected, the risk scores for the insulin groups are much higher than the non-insulin groups; see Figure 3.17. Another interesting result is that the SGLT2 and GLP1 group risk scores are not significantly different from the SGLT2 only or GLP1 only groups. This suggests that the slightly different indications of these two drugs are either not being implemented in clinical practice or are more nuanced than ICD-10 diagnosis codes allow.

Figure 3.17
RISK SCORES

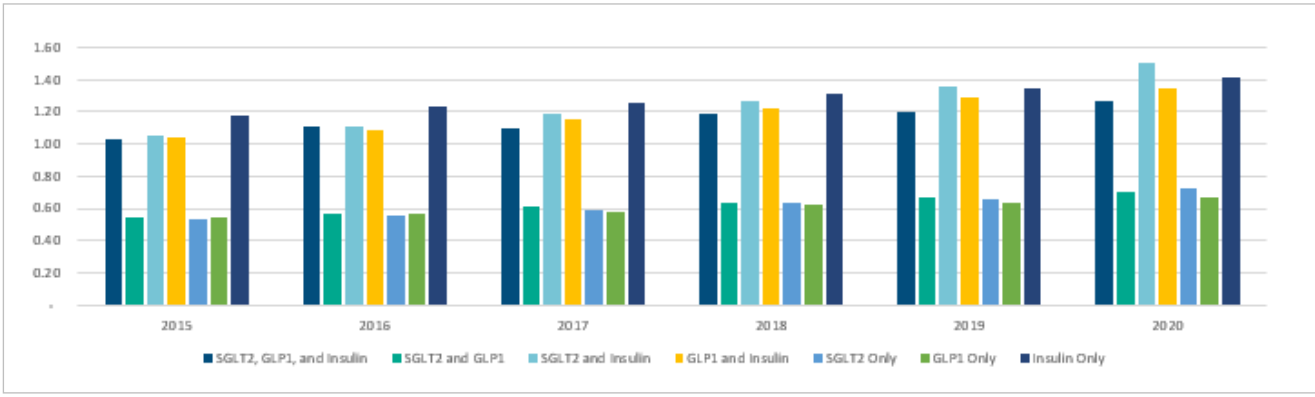
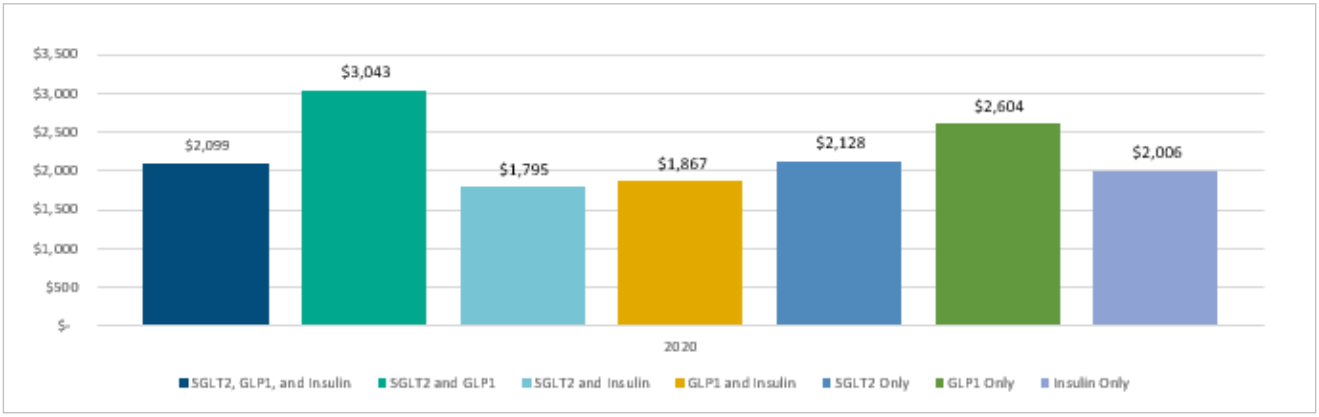


Figure 3.18
TOTAL 2020RISK-ADJUSTED ALLOWED PMPM COSTS



Risk-adjusted total PMPM costs are shown in Figure 3.18, although they are largely features of the risk scores shown above (a high-risk score results in a low risk-adjusted PMPM). Although the results of this model do not provide useful insights into the drugs and their impact on TCOC, they do provide insights into lessons

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learned about the pros and cons of risk-adjustment models that need to be considered when contemplating using them more broadly.

3.6. LESSONS LEARNED

This research aimed to understand which methodologies may be used to provide a scalable framework for quantifying the value provided by pharmaceutical products. In addition to (and perhaps more important than) the numeric results shown above about the various drugs' impact on TCOC, many lessons were learned about the pros and cons of the three study methodologies we applied.

General observations include the following:

- *Limited Claims Data Information:* Claims data are a very rich data set in that they track all medical interventions provided to individuals over their entire tenure with a payer. They do so with standardized code sets that can be analyzed much more easily than text or other information in other data sets. At the same time, this standardization results in a necessary limitation in the information contained, for two reasons. First, diagnosis codes that appropriately describe an individual's medical condition are often not coded. Second, a diagnosis code is included on a claim only if it impacts the medical treatment provided.[34]

- *Incomplete Diagnosis Code Information:* Provider practices often have limited financial incentives to supply complete diagnosis code information for codes not included in government risk-adjustment models. In addition, one has a finite number of diagnosis codes; chronic kidney disease, hypercholesterolemia and chronic obesity have only five to 10 diagnosis codes describing them, despite the broad range of clinical complexity of these diseases. For example, each has a single ICD-10-CM code that can be used despite these conditions' wide range of clinical manifestations.

- *Tradeoff between Control and Sample Size:* Two of the methods used (the index event and propensity-matching methods) resulted in small sample sizes partly because of the rigorous matching processes. For the index event method, for example, although an inpatient admission is a useful normalizer of clinical severity, it severely limits the available sample size. Even among chronically ill populations, inpatient admissions are rare.

- *Computational Intensity:* When conducting research on a large data set but with limited computational capacities, these methodologies may require significant tradeoffs. For example, simplified service category descriptions (simple medical and pharmacy splits) may be required even if more detailed service category descriptions could be of interest. Additionally, smaller sample sizes may be required in the propensity-matching method, which may lead to wider error bars in the results.

- *Evaluation Periods:* One-year projections of impact on TCOC may not provide a complete picture. Some drugs have compounding effect over time on patients' health, causing savings to increase over longer periods.

Specific observations regarding the index event method include the following:

- *Clear Framework/Methodology:* This methodology allows for a clear comparison of costs to assess TCOC effectiveness, is easy to explain and understand, and provides multiple ways to assess TCOC effectiveness by triangulating a range of plausible results from the several comparison points. At the same time, a challenge with this method is that those multiple modes of assessment may result in conflicting or contradictory results.

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- *Choice of Index Event:* This model used an inpatient admission for the index event. However, other events could be used, such as the first prescription filled, the first time a diagnosis was coded, or an outpatient or inpatient event for a condition. The inpatient admission had the benefit of being a significantly clinically severe event and so tightly controlled the population. However, a downside of using an inpatient admission was that deciding the list of DRGs that would qualify as the index event involved too much judgment. Especially for the PCSK9s, drug utilization was unexpectedly low in the post event period for many DRGs, so utilization of PCSK9s was prioritized in selecting this list. Still, a wide range of final DRG lists would be reasonable.

- *Pre-event Period Variation:* Variation in the pre-period can be difficult to explain and can make the period-over-period comparison less reliable. Further, the model does not allow any way to create similarity in pre-event period costs to make an appropriate comparison.

Specific observations regarding the propensity-matching method include the following:

- *Wide Use, Reliable Methodology:* This methodology is widely used in epidemiology and clinical research, has a significant background in statistical research, and is very reliable. Although the analytical complexities of this model can leverage more advanced data science and statistical methods, the concept of matching individuals on similar diagnoses and pharmacy history is easily accessible to a wide audience. At the same time, the nuances of this method can be opaque, and significant judgment can be needed when designing the model, opening the opportunity for different stakeholders to have differing views of the "correct" result.

- *Computationally Intensive:* This methodology was extremely computationally intensive, with total run time for the limited sample sizes exceeding 30 hours. This may not be a significant issue for a rare disease with a limited population, but it can require the exclusion of significant portions of the available data for the more common conditions included in this research study.

- *Limits in Claims Data:* This method can highlight limitations in claims data, as discussed above in the general observations. An example of this occurred with the insulin model, where despite a good match from a statistical perspective, unreasonably higher TCOC was found in the insulin-using population because of underlying clinical differences that the claims data could not capture.

Observations regarding the risk-adjustment methodology include the following:

- *Scalable and Broadly Used:* This methodology is easily scalable, which, for this analysis, allowed for the use of the full data set with the available computational power. This methodology is also broadly used and publicly documented by the Department of Health and Human Services. At the same time, the broad use of this model may make it inappropriate for more specific applications.

- *Model-Specific Considerations:* The selection of which risk-adjustment model to use is crucial. Its design is also critical. For example, the characteristics of the ACA risk-adjustment model meant that the Type 2 diabetes results were unusable without retraining the risk-adjustment model to consider more levels of severity than were available. At the same time, for the hypercholesterolemia risk-adjustment model, the ACA model performed as expected and was consistent with the results in the other two models for that drug class. Any risk-adjustment model's appropriateness must be determined on a case-by-case basis.

- *Model Accuracy:* Risk-adjustment models are not highly predictive, even those based on state-of-the-art predictive analytics tools. They are more useful with large samples where the sample size

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can minimize the variance in any single risk score estimate. That may be an unreasonable methodology in situations where sample sizes are necessarily very small (such as a rare disease).

3.7. TCOC VALUE MEASURES

After analyses similar to the ones shown above are completed, several criteria must be considered to use techniques for "measuring value" as means for "rewarding value."

THE CRITERIA

The measures must meet the needs of the various stakeholders involved in the negotiations to be useful. This section assumes that the stakeholders involved are the payer (health plan, self-funded employer, government payer etc.) and the PBM representing the payer and the manufacturer.

Payer-Specific Projections

The general principles in projecting claims costs to a future period have already been discussed. Most payers want the projections to be as specific as possible to their own population and experience, but sometimes payer-specific data may not be statistically reliable. For example, using the index method, a TCOC guarantee for a PCSK9 drug would not be statistically reliable. The analysis above used only 163 patients in a broad covered population of millions of members. The chance of even one claim for a smaller payer, such as a 100-member population, is minuscule. Even if a claim was made for that group, the cost of care for that patient could be highly variable depending on the patient's circumstances.

In cases like that, a viable alternative could be to base the guarantee on the experience for the PBM's entire book of business and prorate the results across all payers or all payers covering the drug or those covering the drug and placing it on a preferred coverage tier.

Risk and Opportunity Measurement

The specifics of a TCOC guarantee are determined by a negotiation where both parties want to minimize their risk and optimize their financial position. This requires that each party be able to answer questions such as "What are the chances that I will lose/make more than $1 million if I accept the offer on the table?" A new analytical technique, total risk analysis, provides a framework for answering questions like this[35]. One of the key features of this methodology is that it reflects both the projection risk (the risk of overestimating or underestimating the key metric) and the random variation risk (the risk attributable to random variation because of large claims).

Scalability

As with any process, a tradeoff is always found between materiality and resources. A scalable process minimizes unnecessary work to spend more time on meaningful analytics. For TCOC guarantees, one of the keys to scalability is ensuring that the necessary data are readily available. Another important aspect of scalability is to avoid complex analytical techniques that add little value.

CONSTRUCTING A GUARANTEE

In its simplest form, a TCOC guarantee reads "If the TCOC exceeds *x*, then A pays B $*y* as determined on *z* date." There are many variations on this theme, however, as we discuss next.

TCOC Calculation

The TCOC calculation is specified in the contract as a percentage difference in TCOC between patients taking a drug and those not taking the drug, where the patients are on an all-other-things-equal basis. Similarly, an

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alternative is to compare TCOC for those taking a specific drug to those taking an alternative drug. Finally, the calculation can be done on a before and after basis.

The Trigger

The trigger is the breakpoint between a payment being made and a payment not being made. A key consideration in determining the trigger amount is the risk and opportunity for each stakeholder. In many cases, risk corridors may be designed to account for a reasonable level of random variation before payments are triggered.

Payer and Payee

If the guarantee includes a bonus, the payer pays the manufacturer if outcomes exceed predefined thresholds. The manufacturer reimburses the payer if the outcomes fail to meet the guaranteed amount. The payable amount could be reconciled as either a direct payment or a future offset.

Settlement Date

The settlement date is usually a few months after the end of the experience period. So, if a guarantee is applied to TCOC in calendar year 2023, the settlement would take place a few months into 2024 to allow time for run-out, reconciliation and processing.

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Reimagining Pharmacy Financing

Section 4: Rewarding Value

Over the years, important legislation aimed at making prescription drugs more affordable, such as the Inflation Reduction Act, has been passed in the U.S. Even so, one in four Americans still say they have difficulty affording the drugs prescribed to them.[36] This begs the question "Where should the U.S. go from here?" One approach would be to enact one or more of the many policy proposals currently on the table. Another approach would be to develop a pharmacy financing structure based on rewarding value using the current infrastructure. Here the focus will be on the latter approach.

4.1. DEFINING SUCCESS

Although many potential definitions of success for a pharmacy financing alternative exist, this section will focus on four key definitions. In evaluating a proposal, each stakeholder will have their view of the priorities within these four definitions.

INCREASING TRANSPARENCY

In any negotiation, transparency is a potential source of conflict. Each party wants to keep as much information about their position as confidential as possible while receiving as much information about the other parties as they can. In many situations, these issues can be resolved through good-faith negotiations.

In pharmacy financing, one issue that is troublesome to many stakeholders is rebates. A manufacturer offers rebates to payers who put their drugs on a favorable tier on their formulary. Rebates are not immaterial to understanding the cost of prescription drugs. A 2021 Colorado study showed that rebates accounted for 26% of total spend.[37] Although information about exact rebate amounts for specific drugs is often considered proprietary and confidential in most PBMs' and payers' contracts with pharmaceutical manufacturers, most payers are guaranteed a certain level of rebate overall by their PBM. This information is usually enough to compare formularies but not enough for a payer to negotiate an optimal rebate for a specific drug.

Many stakeholders, including policy analysts, find the lack of specific information about rebates for specific drugs to be frustrating because the net cost impact of individual prescription drugs is difficult to know. Although rebates receive the most attention regarding transparency, other factors such as coupons, alternative funding programs or specialty pharmacy carve-out programs can also confuse efforts to get a complete picture of the true net costs. Several policies have been proposed to increase the level of transparency in the system, including point-of-sale rebates[38] and reference-based .[39]

Often not complete transparency is also seen in pharmacy reimbursements. Sometimes, PBMs retain a positive or negative "spread" between the amounts paid to network pharmacies for a drug and the amount collected from the payer for the same prescription. Some states have passed transparency laws to require either that such network pharmacy "spreads" no longer are used or that their presence and/or magnitude be disclosed.

As we reimagine pharmacy financing and consider means of rewarding value, selecting means that increase transparency will be beneficial to increasing trust among stakeholders and throughout society.

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ENCOURAGING COMPETITION

An ideal world would see no impediments to manufacturers competing actively to develop new drugs at an affordable cost. Some would argue that this is the situation today and that the current patent system provides just enough protection to ensure that manufacturers are willing to invest in discovering new drugs and bringing them to market. Others would argue that current patent laws discourage competition and give undue advantage to the manufacturer. Since an in-depth discussion about the U.S. patent system is beyond the scope of this paper, the authors will focus on understanding how an alternative financing method might increase or decrease competition under the current patent framework Increasing competition is also generally expected to help with affordability. As we reimagine pharmacy financing, rewarding value in more scalable and meaningful ways with more comprehensible and broadly applicable measures across disease states should help encourage competition.

MITIGATING TOTAL COST OF CARE INCREASES

With health care spending at 18% of total GDP,[40] a key measure of success for pharmacy financing is the impact on the total cost of care across medical and pharmacy benefits. A key issue is how precise and detailed the estimate needs to be. It is common for the Congressional Budget Office to estimate the impact of a federal legislative proposal on the total cost of care for the nation as a whole or, possibly, by program. Other stakeholders are left to their own devices to estimate the impact on their bottom line. This is often no easy task for payers and other stakeholders with good data and plentiful resources.

Section 3 in this research project evaluated means of measuring the total cost of care impact of various drugs that treat two distinct disease states. Mitigating total cost of care increases is an important value and is sometimes the largest quantifiable value to reward.

ALIGNING STAKEHOLDER INCENTIVES

As noted earlier, each stakeholder has specific values based on their goals and objectives. From a societal perspective, however, these values need to result in a system that provides affordable and accessible drugs to consumers. Conversely, some stakeholders, such as manufacturers, health plans or pharmacy benefit managers, will not be inclined to fully participate in a system where their goals and objectives cannot be met.

One definition of success, then, is to align stakeholder incentives to encourage the optimal achievement of shared values. This will be imperfect because each stakeholder may have different ideas about the alignment. In analyzing a regulatory proposal, the optimal alignment will be defined primarily by the regulatory or legislative body proposing and/or enacting the policy change. Presumably that process will include input from other stakeholders through hearings, letters and similar techniques already in place. The key parties negotiate solutions not governed by regulation. These parties may or may not adequately represent the consumer's and other constituents' interests. The U.S. pharmacy ecosystem is currently viewed by many as being fraught with many misaligned incentives.

This project seeks to identify opportunities to align stakeholder incentives throughout the entire system better so that all stakeholders are increasingly motivated and aligned around increasing transparency, encouraging competition and reducing the total cost of care mitigation.

4.2. MEASURING VALUE

To recognize and reward value, it is critical to have the ability to measure it effectively, especially on a scalable level. Measuring the impact of a drug on TCOC was discussed in Section 3. In this section the emphasis is on monetizing the other value elements discussed in Section 2.

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THE CURRENT LANDSCAPE

Many HTAs measure the cost associated with increased value using QALYs. As discussed in Section 2, a QALY is determined by dividing the cost of the drug by the expected improvement in value, where the expected improvement in value is measured using a survey instrument.[41] In addition, several intensive studies have measured the value of certain value components, such as caregiver quality of life. Although some analysts consider this the optimal method at the current time, several limitations face using this method for ongoing pharmacy financing negotiations:

- QALYs are based on information known at launch, which may or may not play out over time.
- The methods used to perform the analytics are often not scalable because they are time-consuming and resource intensive.
- QALYs are based on a weighted composite of the value elements, and those weights may or may not be consistent with stakeholder objectives.
- The underlying studies may not reflect the stakeholder's population. For example, if the stakeholder is a payer for a large commercial population, then a study based on a large Medicare population may be misleading.

Many doctors and hospitals are reimbursed to some extent using the alternate payment method (APM) framework developed by the Health Care Payment and Learning Action Network to reward providers for quality and efficiency and encourage providers to take some of the risk associated with the care provided. A common technique to measure quality in this context is using a scorecard. Under this approach, a provider is paid on a fee-for-service basis during the year with a penalty or bonus at the end of the year. The bonus or penalty is based on a scorecard, which is the weighted average of specified measures. Measures may be based on TCOC, credentials, customer service goals, consumer surveys or compliance with evidence-based medicine, such as A1C testing. The advantages of this approach include the fact that the measures used are more likely to relate to the stakeholder's objectives, and the outcomes are current. Even so, several limitations exist, including the fact that the value of the measures is still based on intense studies with all the related drawbacks.

THE VALUE STACK CONCEPT

For any value-related process to work, each component of the scorecard has to be easily measurable, which means that data must be readily available to the payer, and the calculation has to be programmable. For a pharmacy, the problem is that many elements of value, such as pain relief, are not currently easily measurable. Typically, pain relief is measured by a survey, which is not practical right now since there is no mechanism for collecting and distributing that information.

Another emerging form of scorecard is a stakeholder impact report, sometimes called a "value stack." With a value stack, proxy measures may be developed for some value elements that are not directly quantifiable in monetary measures. For example, if one value of a drug is that it reduces pain, a proxy measure of that could be a reduction in spend for pain relief medications. One advantage of the value stack approach is that each of a drug's incremental value components is measured or estimated (prospectively or retrospectively) in monetary terms that can be aggregated and compared to its incremental cost (commonly expressed as a return-on-investment [ROI] ratio). One disadvantage is that measured and estimated data may not be credible at the provider or manufacturer level. The value determined over a larger population can be used in that case. For example, if a payer has determined that using a drug reduces the pain management cost by $0.10 PMPM for its whole book of business, that number can be applied to the provider or manufacturer.

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4.3. APPLYING THE CONCEPTS

As noted above, each methodology for measuring value has its limitations. But, even if such a perfect methodology existed, it would still be challenging to incorporate them into a pharmacy financing structure that meets the definitions of success discussed earlier. Since this section assumes that the ultimate structure of an agreement is determined through negotiations between a payer and a manufacturer, this section will discuss considerations the stakeholders may consider during the process.

PRICE SETTING

Although drug prices are often set through a PBM or other intermediary, to keep things simple, this section assumes that the prices are set through negotiations between the payer (or a PBM on its behalf) and the manufacturer. During the negotiation process, it is safe to assume that the payer will want to keep costs as low as possible and to be reasonably certain that they will realize the value of the drug promised during the negotiations. On the other hand, the manufacturer will want to maximize their income and maintain their reputation as a reliable partner. The key factors to be considered during the negotiations include the following:

- *Portfolio or Single Drug:* As noted in Section 2, some drug prices are negotiated on a portfolio basis. This section focuses on individual drugs that require extra attention in the negotiation process.
- *Fee-for-Service or Shared Savings and Risk:* Most drug prices are applied on a fee-for-service basis. A discount from a benchmark is negotiated for pharmacy reimbursement purposes, and a rebate from a "list price" is negotiated with the manufacturer. If a manufacturer is touting the clinical benefits of a higher-priced drug, then the payer may want to ensure that the manufacturer backs up their claims with a shared risk and/or shared savings arrangement. Suppose the manufacturer is reasonably certain that the value of the drug will indeed materialize. In that case it may be worth it to them to agree to lower upfront reimbursement for the opportunity of higher overall reimbursement once the shared savings are realized. Alternatively, the manufacturer may insist on higher upfront reimbursement but agree on risk for financial penalties if its guaranteed clinical value is not achieved.
- *Shared Savings Determination:* To share savings, agreement must be found on how the amount of shared savings will be determined. This includes specifying the data, the methodology and the timing of the calculation. In some cases, shared savings will be determined annually; in other cases, they may be determined at the end of an episode of care.
- *Splitting the Savings:* Once the savings amount is determined, the next step is to decide how much is retained by the payer and how much is shared with the manufacturer.
- *Bonus or Penalty:* The risk may be shared as a penalty if guarantees are not met. Savings may be shared as a bonus for the manufacturer when guarantees are exceeded.
- *Provider Incentives:* Payers currently rely on cost-share tiers and clinical programs (such as prior authorization or step therapy edits) to manage utilization. Although that may be an effective way to encourage safer, more effective and lower-cost utilization, it is ultimately up to the provider to prescribe and the patient to choose the least costly option. The problem with this approach is that if the patient is seriously ill, they are likely to take whatever drug their doctor prescribes, especially if they will be hitting their out-of-pocket maximum regardless. An alternative is to provide doctors with information and/or financial incentives to prescribe the most cost-effective alternative whenever it is clinically appropriate.

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RISK MANAGEMENT AND AFFORDABILITY

When it comes to risk, not all payers are created equal. If a member in a large payer organization, such as the individual market for a large health plan with a million members, needs a $2 million drug, that cost is spread over a million members. Hence, the net increase in cost is $2 per member, which is negligible compared to the average cost per member per year. On the other hand, if the payer only has 100 members, then the average cost per member is $20,000, which is indeed material. Small payers have two primary options to manage this risk: move to a fully insured coverage or obtain stop-loss insurance. Either way, the resulting premiums will likely be experience-rated, which means the payer will probably not achieve any real cost savings.

One alternative is to reimburse manufacturers per capita instead of on a fee-for-service basis for low-frequency, high-cost drugs. From a payer's perspective, especially a smaller payer, this provides a mechanism for spreading risk over several payers. The risk is that the manufacturer may overcharge unless a year-end reconciliation process occurs and, possibly, an experience refund in the case of a low loss ratio. From the manufacturer's perspective, this arrangement guarantees a minimum income level. The risk is that the actual utilization may exceed what is expected by an unacceptable amount. In this case, some arrangement where the excess cost is shared by payers and the manufacturer could be implemented.

4.4. ENHANCING THE INFRASTRUCTURE

Based on the analysis above, a payer (and its PBM) could design and implement a value-based reimbursement agreement with a manufacturer that meets both stakeholders' objectives. The analytics would need to be carefully designed, and the methodology to calculate actual performance versus guarantees would have to be negotiated upfront until alignment on the details is reached. But it could be done.

A logical next step is to enhance the underlying infrastructure to make the process easier to implement and to provide more useful information. The authors recommend that the priorities for that effort be closing the analytical loop, building out the value stack concept, and expanding total risk analysis to include pharmacy value measurements. Each of these priorities has implications beyond just pharmacy financing, so it is anticipated that progress will be made on these priorities on a project-by-project basis. Most of the work will be completed by actuaries, health economists and other financial analysts with important contextual input from clinicians.

CLOSING THE ANALYTICAL LOOP

Today most pharmacy financing analytics are done in silos. Health economists and others develop health technology assessments (HTAs) based on the best available data and analytics at the time a new drug is introduced. Once it looks like a drug will be introduced, actuaries and others jump into the process by providing the analytics for pricing and negotiations using their best data and analytics. Right now, a gap exists between the information a health economist needs to produce an HTA and the information an actuary needs. This gap needs to be filled to make the process of moving from the information available at the time a drug is introduced to ongoing processes such as pricing and negotiations.

Health Technology Assessments

An HTA may be produced when a new drug comes on the market. An HTA may include some measure of net costs based on information available when the drug is introduced. Typically, this is primarily clinical efficacy and safety data and other value measures from the clinical trials and published or proprietary information about similar drugs. The manufacturer may also prepare budget impact models. Still, plan sponsors typically project the claims cost impact on their business using their population's characteristics and expected

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contractual pricing terms for pharmacy discounts and manufacturer rebates. After the drug is approved, real-world experience emerges from sources such as payer administrative data and electronic health records. Techniques need to be developed to incorporate information into a methodology to keep information about value up to date.

Clinical trials are often designed to focus on data on clinical efficacy and safety measures to facilitate review and potential approval by the FDA. Clinical trial data are often reviewed when payers consider inclusion on their formulary. Opportunities exist to design clinical trials to capture additional data useful for projecting real-world claim cost impact (including total cost of care impact) and any other measures likely to facilitate the design of scalable and meaningful value-based contracts between stakeholders. This could include data that enable stakeholder impact (value stack) projections and ROI projections for various stakeholders.

In addition, it could be useful for those who prepare HTAs to incorporate ROI projections from value stack models to help contextualize their findings for audiences beyond clinical and health economics experts who are involved in making coverage and formulary tier decisions and who are designing and negotiating value-based contracts.

Ongoing Measurement

Several new and/or enhanced analytical techniques (such as the value stack and others) must be developed to implement changes in pharmacy financing methods. Although each stakeholder could conceivably develop these on their own, there would be value in sharing the results to promote best practices that increase the scalability and meaningfulness of value-based contracts and other "reimagined pharmacy financing" methods that help promote transparency, encourage competition, mitigate total cost of care and align stakeholder incentives.

Technology Curves

As noted in Section 3, the take-up rate is an important consideration in modeling projected costs. The take-up rate, however, is not a single number. Instead, it changes over time. The four stages illustrated include the following:

- *Awareness and Acceptance:* When a new technology comes on the market, or a new drug is approved, it takes time for patients and doctors to become aware of the technology, accept the potential value and schedule appointments before the drug is available.
- *Catch-up:* Once the new drug or technology catches on, a rapid increase takes place as patients rush to meet unfulfilled needs.
- *Slowdown:* Once the unfulfilled needs are met, utilization begins to slow down.
- *Steady State:* At some point, utilization stabilizes as it reaches the normal level.

Although the exact shape of the technology curve will vary by drug, it may be helpful to compare the curve for several drugs to analyze similarities and differences.

Cost Effectiveness Curves

As discussed in Section 3, if a drug has been prescribed following an index event, a wash-out period occurs during which the underlying event is treated, and some trial and error takes place to adjust the dosage. In Section 3, the post event was of fixed length, but another way of doing that is to base the post event period on how long it takes to break even from the additional expenses incurred in the wash-out period. This would require studies on a drug-by-drug basis, but, again, similarities and differences by drug could provide valuable insights when a drug is first introduced.

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Data Credibility

Naturally, every payer wants the values used in pharmacy pricing to be based on their experience. Sometimes, however, we do not have enough data to be statistically valid. Techniques must be developed to determine the optimal way to incorporate payer-specific calculations into those calculations and reliable alternatives for when that is impossible.

Wrong Pocket/Long Pocket

One concern about pharmacy financing is that a payer will sometimes invest in a one-time treatment for a patient who leaves the group before the full value of the treatment (or before the breakeven point where the value exceeds the investment) is realized. It would be worthwhile to study whether payers with different population mixes find the "risk" of patients with treatments like this leaving the group is offset by other patients with treatments like this joining the group after other payers have "invested" in their treatments. Is this offsetting and balanced, or are there types of payers with certain types of populations where the risk is not balanced?

Member-Level Data

Most stakeholders have limited information on which to base decisions. For example, in most cases the only information a payer has available is the administrative data elements discussed in Section 3. Other information that would be helpful at the member level includes the following:

- Electronic health records, with lab results and prescribing information
- Death records to measure survival rates and
- Recorded side effects from a drug.

Historically, the ability to collect this information on a systematic basis has been challenging, to say the least. That may change with the implementation of the Trusted Exchange Framework and Common Agreement (TEFCA). TEFCA, which was mandated by the 21st Century Cures Act in 2016, provides the framework for exchanging member health information between stakeholders, including providers, regulators, and health insurers.[42]

VALUE STACK

The value stack is a stakeholder impact model that compares incremental value to incremental cost of a new drug as an ROI ratio. It seeks to incorporate all forms of incremental value driven by the drug, including prescription drug cost offsets, medical benefit cost offsets, productivity value and many other forms of societal value insofar as each of those values can be quantified and monetized either as they are measured or through proxy measures. The value stack assesses "how much" of the total incremental value comes from each of the various forms of value so that various stakeholders can focus on the various types of value that matter most to them. It also projects how much of the incremental value and how much of the incremental cost accrues to the various stakeholders involved in the supply chain (such as health plans, employers, PBMs, provider systems, government entities and patients) thereby calculating a separate ROI for each type of stakeholder. A value stack can be determined separately for different books of business (such as Commercial Fully Insured, Commercial Self-Funded, Medicare and Medicaid) taking into account the different population, utilization and cost dynamics of each.

The value stack provides the advantage of a common endpoint for many drugs (ROI) that is more comprehensible to the general public and that is already commonly used between PBMs and their payer clients for measurement and reconciliation of contractual guarantees for clinical programs.

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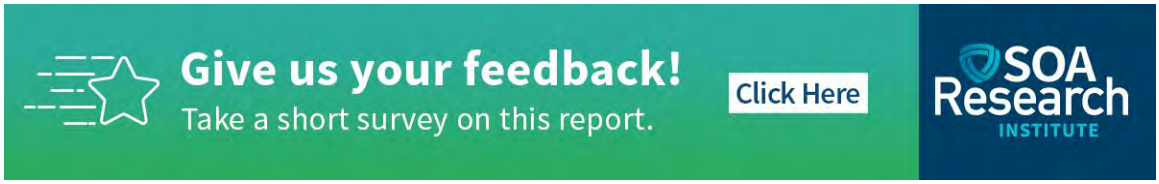
Each value stack for different drugs may require different proxy measures and different measurement techniques for capturing and analyzing the data on an ongoing basis. Although the endpoint (ROI) may be broadly scalable, the measurement methodologies may still require significant specialization.

TOTAL RISK ANALYSIS

Stakeholders rely on projections while making key decisions such as setting or negotiating a price for a drug. Inevitably, the projection will not be 100% accurate either because the underlying projection was wrong or because of random variation within the population. Total risk analysis provides a framework for answering questions such as "What is the probability we will lose more than $1 million if we go with this decision?" This concept is relatively new and requires further research to be useful for pharmacy financing.

4.5. NEXT STEPS

Although the authors have determined that it is possible to develop a more scalable and more meaningful value-based reimbursement methodology using the current infrastructure, it will take more than just enhancing the infrastructure to ensure widespread utilization of "reimagined pharmacy financing." Multidisciplinary experts such as policy analysts, health economists, clinical pharmacists, health actuaries, benefits brokers and consultants, consumer advocates and financial analysts working with all types of stakeholders must share innovative ideas and valuable learnings as they emerge. The authors look forward to participating in these efforts as we "reimagine pharmacy financing" together so we can transform our pharmacy ecosystem for the benefit of all.



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Appendix A: Index Method Technical Documentation

- Hypercholesterolemia Index Event Definition (MS-DRGs):
    - Coronary Bypass: 231–236
    - Percutaneous Cardiac Procedures: 246–249
    - Atherosclerosis: 302–303
    - DRGs are not included because of very low post-admit PCSK9 utilization.
        - Cardiac Valve Procedures: 216–221
        - Acute Myocardial Infarction: 280–282
        - Cardiac Disorders without AMI: 286–287
        - Heart Failure and Shock: 291–293
        - Percutaneous Vascular Disease: 299–301
        - Angina Pectoris: 311
- Type 2 Diabetes Index Event Definition (MS-DRGs):
    - Intracranial Hemorrhage or Cerebral Infarction: 064–066
    - Coronary Bypass: 231–236
    - Percutaneous Cardiac Procedures: 246–249
    - Circulatory Disorders without Acute Myocardial Infarction: 286, 287
    - Heart Failure and Shock: 291–293
    - Diabetes: 637–639
    - Renal Failure: 682–684

- Time Periods
    - Admits between January 1, 2015, to December 31, 2020 (allowing for 2021 to be a 12-month post-admit period).
    - Must have complete eligibility six months before the index event through 12 months after the index event.
    - Inpatient admits limitations:
        - Between 1- and 30-day lengths of stay
        - Discharged alive
        - Allowed > $1,000
    - Example:
        - Admit date: January 1, 2020
        - Pre-Period: July 1, 2019 to December 31, 2019
        - Wash-Out Period: January 1, 2020 to January 31, 2020
        - Evaluation Period: February 1, 2020 to January 31, 2021

- 90% confidence intervals were developed using 1,000 iterations of bootstrapped mean using the bias-corrected and accelerated bootstrap algorithm implemented in R's *boot* package.

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Appendix B: Propensity-Matching Technical Documentation

The ICD-10-CM-based matching characteristics were developed according to the listings in the following table. An asterisk indicates all valid ICD-10-CM codes with the indicated suffix preceding the asterisk.

Feature Definition	Diagnosis Code
Abnormal EKG	R94.31, R94.39
Abnormal Kidney Function	R94.5
Acidosis	E78.2*
Acute Bronchitis	J20.*
AFIB	I48.*
AKF	N17.*
AMI	I21.*
Aneurysm, Heart	I25.3
Angina	I20.*
Angioplasty	Z95.5, Z98.6*
Anxiety	F41.*
Asthma	J45.*
Atherosclerosis	I70.*
Atherosclerotic Heart Disease	I25.1*, I25.8*
Bariatric Surgery	Z98.84
Barrett's Esophagus	K22.7*
Bradycardia	R00.1
BPH	N40.*
Bypass Graft	Z95.1
Calculus, Kidney	N20.0
Cardiac Arrhythmia	I49.*
Cardiac Graft	Z95.8*
Cardiomyopathy	I25.5
Cardiomegaly	I51.7
Cataract	H25.*
Cellulitis	L03.*, L08.*
Cerebral Infarction	I63.*
Cerebral Occlusion	I65.*
Cholelithiasis	K80.*
CKD	N18.*
CKD, Anemia	D63.1
Colon Polyps	K63.5
Constipation	K59.0*
COPD	J44.*
CVI	I87.2

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Depression	F32.*, F33.*
Dermatitis	L30.*
Dermatophytosis	B35.*
Diarrhea	R17
Difficulty Walking	R26.2
Disc Disorder	M50.*, M51.*
Diverticulitis	K57.*
Dizziness	R42
Dry Eye	H04.12*
Dyspnea	R06.0*
Dysphagia	R13.1*
Dysuria	R30.0
Edema	R60.*
Elevated Blood Pressure	R03.0
Elevated Glucose	R73.*
Elevated White Blood Cells	D72.82*
Fatigue	R53.*
Fatty Liver	K76.0
Fibromyalgia	M79.7
Gastritis	K29.*
Gastroenteritis Colitis	K52.*
GERD	K21.*
Glaucoma	H40.*
Gout	M10.*
Headache	R51.*
Heart Failure	I50.*
Hematuria	R31.*
Hemorrhoids	K64.*
Hernia	K44.*
Hypercholesterolemia	E78.0*
Hyperglycemia	E10.65
Hyperglyceridemia	E78.1
Hyperkalemia	E87.79
Hyperlipidemia	E78.2, E78.3, E78.41, E78.49
Hypertension	I10
Hypertensive CKD	I12.*
Hypertensive Heart Disease	I11.*
Hypoglycemia	E16.2
Hypokalemia	E87.8
Hyponatremia	E78.5
Hypothyroidism	E03.*
Insomnia	G47.0*
Insulin Resistance	E88.8*

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Iron Anemia	D50.*
Join Stiffness	M25.6*
Joint Effusion	M25.4*
Muscle Spasm	M62.8*
Muscle Weakness	M62.81
Myalgia	M79.1*
Nicotine Dependence	F17.*
Nontoxic Goiter	E04.*
Obesity	E66.*, Z68.3*, Z68.4*
Old Myocardial Infarction	I25.2
Osteoarthritis	M16.*, M17.*, M18.*, M19.*
Osteoporosis	M80.*, M81.*
Other Anemia	D50.*
Pain, Abdomen	R10.*
Pain, Back	M54.*
Pain, Chest	R07.8*, R07.9*
Pain, Chronic	G89.2*, G89.4*
Pain, Joint	M25.5*
Pain, Limbs	M79.6*
Pain, Postprocedure	G89.18
Pain, Unspecified	R52.*
Palpitations	R00.2
Polycystic Ovary Syndrome	E28.2
Pharyngitis	J02.*
Plantar Fasciitis	M72.2
Pleural Effusion	J90.*
Pneumonia	J18.*
Polyneuropathy	G62.9
Polyuria	R35.*
Presbyopia	H52.4*
Proteinuria	R80.*
Pulmonary Collapse	J98.1*
Peripheral Vascular Disease	I73.*
Respiratory Failure	J96.*
Rhinitis	J30.*
Seborrheic Keratosis	L82.*
Sepsis	A41.89, A41.9
Sinusitis	J01.*, J32.*
Sleep Apnea	G47.3*
Somatic Dysfunction	M99.0*
Spinal Stenosis	M48.0*
Spondylosis	M47.*
Syncope	R55.*

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T1D	E10.*
T2D	E10.*
T2D with Circulatory	E11.5*
T2D with Hyperglycemia	E11.65*
T2D with Kidney	E11.2*
T2D with Neurological	E11.4*
T2D with Ophthalmic	E11.3*
T2D with Skin	E11.62*
Tachycardia	I47.*, R00.0
Testicular Hypofunction	E29.1
Urinary Tract Infection	N39.0
Valve Disorder	I34.*, I35.*
Viral Infection	B34.9
Vitamin B Deficit	E53.8
Vitamin D Deficit	E55.9
Weight Gain	R63.5

The pharmacy-based matching variables were developed using NDC code mappings in the MarketScan Redbook data. The roughly 30 most common drugs used by individuals also taking one of the five drugs included in this study were included, for example, metformin, sulfonylureas, DPP4s, proton-pump inhibitors and calcium channel blockers.

The prematching algorithm used an XGBoost model to fit 50 rounds (~25–75 rounds before the CV-validated optimal fitting round, depending on the model), predicting the utilization of the drug. The 25 most important variables (from standard variable importance measures) were fed into the matching algorithm. This preprocessing measure was necessary because the available computing resources could not efficiently run a matched cohort model with so many features. The AUC (area under the curve, a measure of goodness of fit for binary prediction models) was evaluated for the optimal fit model, the early-stopping model, and the limited feature model, and although a slight degradation was seen (<2% AUC), AUCs for all models were above 94%, indicating a very good fit.

The matching model used covariate balancing propensity matching, a statistical technique designed to address confounding in observational studies by ensuring balance in the distribution of covariates between treated and control groups. High-dimensional data sets often challenge traditional regression models because of multicollinearity and overfitting issues. Propensity matching, on the other hand, focuses specifically on achieving balance in covariates, making it particularly useful when dealing with numerous correlated features. Three variables were explicitly matched: age, sex and utilization of drugs in the same group as the one being studied (for example, the PCSK9 model exact matched on statin utilization).

A 2:1 control versus treated match was performed using nearest-neighbor matching. This was selected because of the low proportion of members in the treated population compared to the broader data set, so 2:1 matching provided a way to increase the sample size of the control population with relatively little additional computational overhead. The empirical cumulative distribution function (eCDF) for all matched criteria and results was consistently below 0.05 for most variables and below 0.1 for every variable, indicating a high-quality match.

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Appendix C: Risk-Adjustment Technical Documentation

The HHS-HCC risk-adjustment model (commonly called the ACA risk-adjustment model) was used for this analysis because it is broadly used by commercial payers for various purposes, especially the financial risk transfers between payers, a component of the Patient Protection and Affordable Care Act.

The 2023 model was used for all studied years and is available on the CMS website: https://www.cms.gov/medicare/health-plans/medicareadvtgspecratestats/risk-adjustors/2023-model-software/icd-10-mappings.

The 2023 model was used for all years to provide a consistent basis for comparison and to minimize the effect of model changes on the analysis.

There were some fields that the model required that were not present in the data, namely, the metal tier. We assumed that all plans were gold plans. Similarly, the age band granularity in the HCCI data was more aggregated than required by the ACA model, so some simplifying assumptions were made to align the two ranges. Neither of these assumptions had a significant impact on the model results.

The HHS-HCC model is a concurrent hierarchical condition category risk-adjustment model that predicts current-year costs based on current-year diagnosis code data. It groups diagnosis codes into categories. Then those categories are ranked hierarchically so that individuals with diagnosis codes in two or more categories within a hierarchy will receive a risk score only from the single highest category in the hierarchy group. The HHS-HCC model also has many combination features (a coefficient used when two different hierarchical groups are present, in addition to those two groups' coefficients).

Previous studies have quantified the R^2 and mean average error (MAE) of the HHS-HCC model as 45.2% and 85.5% for data censored at $250,000.[43] When looking at simulated groups of 1,000 and 10,000 individuals, MAE decreases significantly to 7.7% and 2.3%, respectively.

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