



Payment Policies to Manage Pharmaceutical Costs

Insights from other countries

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Overview

In recent years, the high cost of prescription drugs in the United States has been the subject of much public discussion. While attention has been focused on a few instances of what critics see as the most outrageous price increases, policymakers should also recognize that Americans spend twice as much per person on prescription drugs as do people in other high-income countries. Clearly, the problem of high drug costs in the U.S. extends far beyond a handful of extreme examples.

Outside the U.S., payers in many high-income countries have used various pharmaceutical policy tools to manage both drug prices and utilization. For example, payers in Europe, Canada, and Australia use various price benchmarks to establish maximum payment levels as well as policies to manage patient access to pharmaceuticals.

In contrast, the policies typically used by U.S. payers to manage the cost of prescription drugs have proved to be of limited effectiveness. Consumers and employers pay for the cost of pharmaceuticals. So, as drug costs continue to rise, payers—including public programs such as Medicare—may want to consider how policy approaches used in other countries might inform policies in the United States.

This report describes six types of payment policies employed in other high-income countries to manage the cost of pharmaceuticals; reviews evidence on the impact of these policies; and discusses the potential applicability of each approach to the United States.

The policies are detailed below:

- **External benchmarking**, the practice of determining how much to pay for a drug by using a formula that takes into account drug prices in other countries, is very common in European health systems. Evidence suggests that it results in lower drug prices, although how much lower depends greatly on which other countries are selected as a benchmark. Assessing the impact of this policy is challenging, because drugmakers have responded to widespread application of the practice by adapting their market launch and pricing strategies, utilizing techniques such as paying confidential discounts and rebates that conceal from outside observers the true prices paid.
- **Internal benchmarking**, or setting a payment level for a drug based on the payment level of clinically comparable products in the same market, has been shown to sharply reduce drug prices in many health systems. However, this approach cannot be applied to drugs for which there are no clinically comparable alternatives.
- **Value-based benchmarking** draws on various analytic tools and methods to determine the appropriate price for a drug based on its benefits. These analyses are intended to ensure that payers have a rational approach that considers a drug's value when they develop coverage and payment policies. Because U.S. payers, including Medicare, make no explicit linkage between costs and benefits, some drugs are likely to be priced at levels that substantially exceed the benefits they offer (including some specialty drugs), though others may also be underpriced.

- **Restrictions on off-label prescribing**, which is the use of medicines for purposes not approved by regulatory authorities, are used by health systems in several countries, including Australia, Germany, and Japan. Restricting payment for such off-label uses could have a significant impact on drug spending in the U.S., where some drugs, including those developed to treat cancer, are frequently prescribed for unapproved uses. The clinical impact of such a payment restriction policy would also need to be considered.
- **Payer-seller agreements (PSAs)** are negotiated between payers and pharmaceutical companies. Some PSAs reduce drug prices through discounts, rebates, or the provision of additional quantities of drugs at no extra charge. Others minimize the payer's risk of incurring higher-than-anticipated costs by adjusting prices according to volume of use, capping expenditures at an agreed-upon level, or limiting the number of doses of a drug for which a payer is liable. Some PSAs used in European countries have resulted in price discounts of up to 50 percent. Research suggests that a category of PSAs—known as performance-based agreements, which adjust the amount paid for a drug based on patient outcomes—have had little impact on drug spending to date.
- **Coverage denial** of drugs deemed to be unaffordable is used to manage costs by payers in some countries (including New Zealand and Australia). By rejecting coverage of drugs that may exceed an established budgetary threshold (or by delaying access to them), payers reduce spending and increase their leverage to negotiate discounts or rebates, especially for expensive drugs that have limited competition. Evidence on the health impact of such a policy is limited, and public and private insurers alike in the United States would face significant social, political, and legal barriers to rejecting drugs for coverage on the sole basis of cost.

Because health systems employ numerous policies at once, it can be difficult to isolate the effects of any one particular policy on pharmaceutical costs, patient access, and health outcomes. Furthermore, drug costs and utilization are affected by an array of other factors: a country's laws and regulations concerning intellectual property rights; direct-to-consumer advertising and similar efforts to increase demand for drugs; and other considerations beyond the purview of health care payers.

Nevertheless, evidence suggests that the six policies discussed in this report can, and do, support health systems in efforts to manage costs. Though research is sparse, there is no evidence suggesting that the reduced access to medicines that sometimes accompanies these policies has had adverse effects on patient health outcomes.

Similar practices could be evaluated to help foster more affordable access to medicines in the United States. To the extent that such policies are legally prohibited or politically unpalatable, a broad national consensus on the objectives and priorities of U.S. pharmaceutical policy will be needed.

Background

Comparing drug prices across countries can be complicated because of exchange rate fluctuations and differences in the purchasing power of local currencies, as well as differences in the dosing and package size for some drugs. It is also difficult to make international comparisons because countries purchase and use different amounts of various drugs as a consequence of variations in health across national populations. Finally, the prevalence of undisclosed rebates and discounts negotiated between drug companies and payers complicates cross-country comparisons of the actual prices paid for drugs—as opposed to the list prices, which are often publicly available. Even so, some comparisons are possible.

The U.S. accounts for more than a third of global pharmaceutical company revenue, and Americans spend substantially more on medicines than do their counterparts elsewhere in the developed world.¹ In 2013, per capita spending on outpatient drugs² in the U.S. was double the average per capita spending of countries in the Organization for Economic Cooperation and Development (OECD),³ with outpatient drug costs in the U.S. reaching \$1,026 per person compared with an average of \$515 across all the OECD countries.⁴

The relatively high U.S. drug spending reflects the higher prices paid for medicines while they are still under patent (referred to in the industry as “on-patent”), as well as high pharmaceutical utilization rates compared with other countries.⁵ Americans also tend to quickly adopt new and often costly medicines.⁶

Payers in the United States have a history of paying higher prices for on-patent medicines than do payers in countries of similar economic status, including Australia, France, and the United Kingdom. In fact, studies have concluded that U.S. prices for on-patent medicines exceed those in peer countries by 10 to 30 percent.⁷

Evidence suggests that this price gap is particularly large when it comes to so-called specialty drugs, which are distinguished by their relatively high prices.⁸ A survey of select health care services and products conducted in 2015 by the International Federation of Health Plans showed significant differences between the U.S. and other countries in the cost to payers for specialty drugs.⁹ For instance:

- Humira (adalimumab), a drug used to treat patients with rheumatoid arthritis, cost an average of \$2,669 for a 28-day supply in the U.S., compared with \$1,362 in the U.K. and \$822 in Switzerland.
- Harvoni (ledipasvir/sofosbuvir), a drug used to treat patients with hepatitis C, cost an average of \$32,114 for a 28-day supply in the U.S., compared with \$22,554 in the U.K. and \$16,861 in Switzerland.
- Tecfidera (dimethyl fumarate), a drug used to treat patients with multiple sclerosis, cost an average of \$5,089 for a 30-day supply in the U.S., compared with \$633 in the U.K. and \$1,855 in Switzerland.

Patient demand for medicines is inelastic, meaning that demand stays fairly constant regardless of changes in price.¹⁰ Patients not only assign great importance to products that they believe will extend or enhance their lives, but are insulated from actual costs by insurance coverage that significantly reduces out-of-pocket payments for prescription medicines. They also rely on physicians, who may not be aware of product prices, to prescribe their medicines.

To temper the monopoly power of drugmakers when it comes to on-patent drugs and to ensure affordable access to medicines, most high-income countries other than the U.S. regulate the price of on-patent pharmaceutical products, directly or otherwise.¹¹ In Japan, Australia, and virtually all the countries of Europe, this price regulation is accomplished through the concentration of market power in a single-payer health system or a national health service that purchases and/or defines the terms of payment for prescription drugs. In Canada, a country with diverse provincial-government and private sources of insurance coverage for prescription medicines, the federal government regulates on-patent pharmaceutical prices through an agency that operates independently from the provincial and private drug plans.¹²

In the United States, in contrast, purchasing power is spread among hundreds of independently operating public and private insurers and health systems, many of which rely on a pharmacy benefits manager to manage their drug benefits, design their formularies, and negotiate with drug companies to obtain rebates and discounts. Drug companies in the U.S. generally face no government involvement in the pricing of their products, with

some notable exceptions such as the mandatory rebates and discounts in the Medicaid, Veterans Health Administration, and 340B programs.¹³ In this environment, payers are largely reliant on their ability to take advantage of competition among therapeutic alternatives in order to obtain price concessions from drug companies.

Because on-patent drugs and biologics do not face competition from either generic or biosimilar drugs—sometimes there are not even therapeutically comparable branded alternatives¹⁴—the reimbursement practices typically used by payers in the U.S. can have a limited impact on the prices they pay.¹⁵ In this environment, U.S. payers and policymakers need to consider different strategies to manage the growing cost of pharmaceuticals.

New policy tools are especially needed to address the high cost of specialty drugs, which make up a growing share of total expenditures on medicines in the United States. In 2015, while spending on all drugs in the U.S. totaled \$310 billion (an increase of 8.5 percent from the year prior), specialty drug spending reached \$121 billion, up more than 15 percent from the previous year.¹⁶ And while specialty drugs are used by only 1-2 percent of the population, they account for more than one-third of U.S. pharmaceutical spending,¹⁷ reflecting the launch of increasingly expensive new products in oncology¹⁸ and other areas.

The challenge presented by rapidly growing drug spending and high prices has fueled a global debate on how pharmaceutical policy should evolve to better manage drug costs. In the United States, patient advocates and policy analysts are concerned about the impact of approaches currently used to manage costs and access to pharmaceuticals, including the use of tiered formularies with coinsurance rates as high as 33 percent in Medicare Part D¹⁹—and, in the case of new medications to treat hepatitis C, deferred or restricted coverage in some Medicaid programs.²⁰

The rapid rate of growth in pharmaceutical expenditures that predated the 2007 global economic crisis²¹ led to a period of experimentation and reform designed to better manage drug costs, particularly in Europe, where pharmaceutical spending makes up a considerably larger proportion of health care costs than in the United States.²² Notably, payers in Europe and other high-income countries make extensive use of different types of price benchmarks to assess drug prices, as well as of policies to manage utilization and moderate the rate of growth in drug spending.

Now, policymakers in all high-income countries are grappling with the challenge of a large number of new drugs coming onto the market with very high prices.²³ Consequently, the time is right in the United States to examine approaches used elsewhere to manage drug costs, and to assess their potential application.

Pharmaceutical cost-management policies used by payers

The six policies reviewed in this report have been adopted by payers in other high-income countries—including European nations, Australia, Canada, and Japan—to manage pharmaceutical prices, utilization, and costs. The policies—external benchmarking, internal benchmarking, value-based benchmarking, restrictions on off-label prescribing, payer-seller agreements, and coverage denial of medicines deemed unaffordable—were selected from among approaches identified through a review of policy and academic research literature. The selection criteria included their potential application in the U.S. health care system, with priority given to policies used to manage on-patent and high-priced specialty drugs.

Three of the six policies primarily affect the effective price paid for on-patent prescription medicines; one addresses utilization of medicines; and two target drug costs through both payment levels and utilization rates.

This report reviews experiences with the six policies in various countries; takes stock of evidence regarding their effects, strengths, and weaknesses; and discusses the potential impact of their use by payers in the U.S., including Medicare (summarized in Table 1).

External benchmarking

External benchmarking (also known as external reference pricing or international price referenc^{ing})—the practice of determining how much to pay for a drug by using a formula that takes into account what other health systems pay—is used in many high-income countries to limit the prices that sellers can charge (through price regulation) or payers will pay (through reimbursement policy). It is intended to limit the ability of drug companies to use their monopoly power when establishing prices for new products.

In countries using external benchmarking, the maximum price or payment level for a drug is typically defined based on prices for the same drug in other countries.²⁴ The number of countries taken into account and the formulas used to establish an external benchmark price or payment level for a drug vary from country to country.

An analysis published in 2015 found that 29 of 31 European health systems (Sweden and the U.K. were the exceptions) employed external benchmarking.²⁵ But the study revealed a great deal of diversity in the execution of this common practice. For example:

- Only Luxembourg reported applying external benchmarking to all medicines on the market, while most countries used it only for specific categories of medicines, such as those medicines accepted for coverage in the health system (16 countries); for prescription-only medicines; or for those medicines judged to be “innovative” (Estonia, France, and Germany).
- Twenty-three countries reported that external benchmarking was the main criterion used for price regulation or negotiations with drug companies, while six (Belgium, Finland, Germany, Italy, Poland, and Spain) reported that benchmarks were one factor among many in decision-making.
- Countries considered benchmark prices from as many as 31 other payers. Fifteen countries reported benchmarking their prices with prices from fewer than 10 other countries.
- Prices from France, Germany, and the U.K. were the most commonly used as benchmarks by other nations.
- Fifteen countries set their benchmark price based on the average price of the drug in other countries. Seven countries used the lowest price, and seven used other calculation methods.

It is common for a country to use the list price of a drug in other countries for external benchmarking purposes.²⁶ The list prices used are usually reported by drug companies as part of their application for coverage or market launch, and verified by authorities in the referenced countries. Neither price discounts nor rebates, whether negotiated or statutorily mandated, are typically taken into account when countries use external benchmarking.²⁷ As a result, the prices compiled from other countries overestimate the actual prices paid by health systems where discounts and/or rebates are applicable.

Another review of external benchmarking policies used by countries in Europe found an association between the per capita income of the referencing country and its benchmarks.²⁸ Of note, countries with lower per capita income used prices in higher-income countries as benchmarks more frequently than higher per capita income countries used prices from lower-income countries as benchmarks.

Recognizing the technical shortcomings of external benchmarking as commonly practiced, a recent European Commission study proposed potential avenues for improvement. Among these were use of a common price database; sharing of information on agreed-upon discounts and rebates (which would require changes to confidential contracts with manufacturers); incorporation of retrospective price reviews to account for the introduction of drugs in various countries at different times; and updates of price-comparison formulas to account for the purchasing power of different currencies.²⁹

External benchmarking is frequently used in combination with other pricing and reimbursement policies. For example, Canada's Patented Medicine Prices Review Board (PMPRB) limits on-patent medicine prices, by law, to a median list price calculated from prices of seven countries (France, Germany, Italy, Sweden, Switzerland, the United Kingdom, and the United States).³⁰ And Canada's provincial government drug plans and private health insurance plans use a variety of practices to obtain effective prices even lower than those established at the federal level.³¹

Impact of external benchmarking. The impact of external benchmarking on pharmaceutical prices depends on which countries are selected for benchmarking, the validity of data used in benchmarking, and how drug companies adapt their product launch sequence and pricing strategies to take into account this widespread practice. Actual evidence of impact on prices is limited. A 2012 study of 14 on-patent drugs³² in 14 countries, 11 of which used external benchmarking, found that the practice was associated with lower list prices.³³ However, because the researchers lacked information on the confidential rebates paid and discounts granted by drug companies, they were unable to assess the effect of the benchmarking policy on the effective prices paid. Furthermore, the precise impact of external benchmarking on prices could not be entirely disentangled from other policies employed by the countries. In addition, countries used different approaches in terms of the nations included in their respective lists of countries benchmarked against; the frequency of price updates; and the price calculation methods. Owing to this variability and the complications arising from the fact that countries often benchmark against each other's prices, some analysts have concluded that the impact of external benchmarking may be minimal or indirect.³⁴

What is more, the practice remains controversial because of its potential unintended effects. The Organization for Economic Cooperation and Development has criticized external benchmarking since it creates incentives for drugmakers to inflate list prices by launching products first in those countries that allow them to set higher prices.³⁵ Inflated list prices may reduce access in health systems where payers lack the leverage or authority to negotiate larger rebates and discounts.

Despite these challenges, external benchmarking maintains a prominent role among the tools used by health systems because of the belief that it provides payers with some indication of whether the prices they pay are in line with those of peer countries. The Netherlands attributed a 20 percent drop in its pharmaceutical prices to the adoption of external benchmarking in 1996.³⁶ Canada's PMPRB credits its policies (including external benchmarking) for keeping the rate of on-patent medicine price growth below the rate of inflation as well as for keeping prices below the median list price of the seven countries against which it benchmarks.³⁷

The World Health Organization also advocates use of external benchmarking to establish drug prices, in combination with transparent pricing and the application of differential pricing internationally to reflect differences in countries' ability to pay.³⁸ At the same time, owing to arbitrage risks (such as when a patient can purchase a pharmaceutical from a different country at a lower price) and the absence of international agreements to abide by income-related price differentials, drug manufacturers will probably seek to minimize differences in list prices among nations, and insist that effective prices remain confidential.

Applicability to the United States. While U.S. payers do not typically use external benchmarking, some federal programs set prices by using variations of the approach. For example, legally mandated rebates from drug companies to the Medicaid program are set based on a benchmark known as the average manufacturer price.³⁹ Some analysts have proposed that such rebates be extended to Medicare Part D in order to reduce Medicare costs.⁴⁰ Currently, the practice of price benchmarking is used elsewhere in the Medicare program. The payment rate for drugs reimbursed under Part B, which are typically administered by a physician, is set at 106 percent of another benchmark known as the average sales price.⁴¹

Because of the sizable gap between U.S. prices and those of other nations, international benchmarking by Medicare (in Parts B and/or D) could have a significant impact. If Medicare were to establish payment levels for designated high-priced specialty drugs (perhaps those lacking competition from therapeutic alternatives) using a formula that takes into account prices in select peer countries, there could be a sharp drop in prices paid, at least in the short term.⁴² However, if the approach were based solely on list prices, manufacturers would be likely to react by establishing higher list prices for new products in other countries and increasing the confidential rebates and discounts to payers there. Using this strategy, drugmakers could avoid accepting significantly lower payment levels in the United States, the nation whose contribution to the pharmaceutical industry's sales revenue is most significant.⁴³

For Medicare to apply such a policy, it would be necessary to select countries against which to benchmark and to establish a pricing formula. This in turn would require Medicare to develop an underlying policy on the payment level that is appropriate for Medicare relative to prices in other nations. Policymakers would also need to determine whether and how to account for the impact of confidential discounts and rebates.⁴⁴ Furthermore, because the U.S. tends to be among the first to approve and market new drugs, Medicare would face the problem of not yet having international benchmarks with which to guide its decisions at the time of a drug's launch in the United States. (An external benchmark price could be retrospectively adjusted once a product is launched elsewhere.)

Even in the absence of a Medicare policy change regarding external benchmarking, more information on the price of drugs in different countries could have a significant impact on drug pricing and expenditures in the U.S., if an entity decided to monitor, publish, and publicize list prices for drugs on an ongoing basis. More public attention to international price differentials could motivate pharmaceutical firms to modify their global pricing strategies to avoid negative attention and demands for policy change.

Internal benchmarking

Internal benchmarking—setting a payment level (or price) for a drug based on the payment level (or price) of one or more alternative products in the same market—is also widely used outside the United States. The purpose is to limit the amount paid for a medicine that does not offer clinically meaningful advantages over other available therapies. The price of a new product is based on that of clinically comparable products.⁴⁵

Some payers use a form of internal benchmarking—commonly referred to as reference pricing—to set the amount they will pay for a drug (known as the reference price). Drug companies can charge a higher price than the reference price, in which case patients are usually required to pay the difference between it and the reference price.⁴⁶ Depending on the degree of price sensitivity on the part of patients and prescribers, drug manufacturers have an incentive to align their prices with the reference price in order to avoid losing market share.

A 2012 study found that 16 of 20 European countries (all but Austria, Norway, Sweden, and the United Kingdom) used reference pricing.⁴⁷ Policymakers in the 16 countries assign drugs to reference groups based on:

- *active substance* or
- *pharmacologic class* or
- *therapeutic class*

Grouping drugs based on therapeutic class is the broadest approach, since it allows for the inclusion of more medicines. Conversely, grouping drugs based on active ingredient is the narrowest approach, since reference groups constructed in this manner will include only brand and generic versions of the same drug. Broader categories provide more effective price competition, particularly when they result in grouping a new brand with both older brands and generic versions of therapeutically similar products. Of the 16 countries using reference pricing in the 2012 study, eight defined reference groups based upon active substance only,⁴⁸ while eight had broader classification systems that included reference groups based upon pharmacological and/or therapeutic classes.⁴⁹

Some health systems set the reference price at the level of the lowest-cost drug included in the reference group. Others establish a reference price above the price of the generic products included in a group but below that of the most expensive branded product.

Reference pricing policies can take into account the situations in which patients do not benefit from lower-cost therapies in the reference group and must be treated with drugs that are more expensive. When this happens, payers can put caps in place to limit a patient's out-of-pocket cost. Payers may also create new reference groups or modify existing ones when new clinical evidence on the comparative effectiveness of different therapies becomes available.

Internal benchmarking can also be used for specialty drugs if therapeutically comparable products exist. In Australia, a new medicine that is significantly more costly than an existing therapy may only be listed on the national formulary, and thus covered by the government-subsidized drug plan, if it provides an incremental clinical benefit, when compared with the existing therapy, for at least some patients. If an incremental benefit is not demonstrated, but the evidence indicates that the new medicine is clinically comparable to other drugs

used to treat the same condition, then it may be added to the formulary only at the same price as the clinically comparable alternatives.⁵⁰

For example, the first TNF-inhibitor (a class of drugs used to treat rheumatoid arthritis and other autoimmune conditions) to be included on the Australian national formulary was etanercept (Enbrel).⁵¹ When other TNF-inhibitors became available—in particular, infliximab (Remicade) and adalimumab (Humira)—their prices were set based on the price of Enbrel. Australia also ties the price of biologic drugs, such as the above-mentioned TNF-inhibitors, to the price of lower-cost available biosimilar products.

In cases where a drug has no substitutes judged to be therapeutically comparable, internal benchmarking is infeasible—making the policy not appropriate for all drugs, including some high-priced specialty drugs.

Impact of internal benchmarking. When a drug is placed in a reference group of comparable products, the impact on payment level can be large, particularly if the group includes generics and/or biosimilars and if the reference price is linked to the price of the least expensive product included in the group. There is evidence from the experience of payers in other countries that use of internal benchmarking results in reductions in both prices and expenditures on drugs included in reference groups. Less information is available on the implications of reference pricing for patient access to drugs or for health outcomes. Three recent articles reviewed the findings from research studies:

A 2011 literature review on reference pricing in developed countries⁵² found that the practice was generally associated with a decrease in the price of drugs covered by the policy—with prices dropping in virtually every country that had implemented a policy of limiting payment for patent-expired medicines to the price of generic alternatives. The magnitude of price reductions varied widely, however, depending on the extent of generic competition and the pricing strategies employed by pharmaceutical companies.

The authors concluded that reference pricing—whether limited to products containing the same active ingredient or extended to include broader therapeutic groups—is associated with significant and consistent savings in the first years of application. They also found a few studies that examined the impact of reference pricing on patient outcomes and observed no association between the two, though more research is needed for a definitive conclusion.

A 2012 literature review identified 16 high-quality studies of nine reference-pricing policies used in six countries.⁵³ The authors found that the policies reduced the average price of drugs included in reference groups by 7 to 24 percent.⁵⁴ Reference pricing also encouraged consumers to switch from expensive products to alternatives that were available at or below the reference price, and improved patient adherence to prescribed medicines—presumably because of reduced costs. These trends were, in turn, associated with reduced payer expenditures for drugs in the affected drug classes by 7 to 18 percent, as well as significant reductions in out-of-pocket spending by patients. The rate of physician visits increased for a short period after policy implementation but did not persist in the long term.

And a 2014 review concluded that reference pricing may have reduced total expenditures in the short term by shifting utilization from more expensive drugs that required higher cost-sharing to drugs reimbursed at the reference price.⁵⁵ The authors were unable to draw conclusions about the long-term effect of reference pricing on health outcomes.

Applicability to the United States. Some analysts and stakeholders have proposed the use of reference pricing by Medicare and other payers in the United States, pointing to significant savings potential.⁵⁶ In fact, a form of internal benchmarking, known as the least-costly alternative (LCA) policy,⁵⁷ was used by Medicare until 2010 to limit its payment for Part B drugs for which lower-cost, clinically similar medicines were available. Some patients who used higher-priced drugs were required to pay the cost difference. The policy was rescinded following a court ruling that Medicare was not legally authorized to use it.

Policies based on internal benchmarking have the potential to yield cost savings for federal programs. An analysis by the inspector general of the U.S. Department of Health and Human Services found that reinstating an LCA policy in Medicare Part B⁵⁸ would have saved \$33.3 million in spending on drugs used for prostate cancer over the course of a single year.⁵⁹ Additionally, the inspector general found that when LCA policies for Part B drugs were stopped in 2010, providers chose to treat their patients with more expensive drugs. Similarly, establishment of a reference pricing policy for proton pump inhibitors (a class of drugs used to treat gastric reflux and to prevent ulcers) in an Arkansas state employee insurance plan yielded a drop in expenditures of \$2.5 million in the first year of implementation, \$2 million in the second year, and \$1.6 million in the third year.⁶⁰

A chief criticism of reference pricing in the United States is that its adoption by Medicare would drive down the price of on-patent pharmaceuticals that have therapeutic alternatives, and thus reduce the incentive to invest in research and development of new products.⁶¹ Because the price differential between on-patent brands and generic medicines in the U.S. is much larger than in other developed countries (in general, prices for on-patent medicines are higher in the U.S. than in other developed countries, while prices for generics are lower), use of reference groups that include on-patent medicines and generic therapeutic alternatives would lower payment for drugs still on patent, shrinking revenue for brand drug developers. And if Medicare were to adopt reference pricing, private payers might follow suit,⁶² creating even more pressure on drug companies to reduce their prices.

A second concern is the potential impact of reference pricing policies on the market share and price of generics. Some reference pricing approaches could discourage drug companies from lowering their prices below a reference price—for example, if generics and on-patent medicines are placed in the same reference group with a reference price that is greater than that of the generics. For this reason, some payers structure their reference pricing policies to counter this disincentive. In Germany, for example, patient copayments are waived for all products offered at 30 percent or more below the reference price, which increases patient incentives to use these drugs.⁶³

Reference pricing is effective only when there is at least one therapeutic alternative available on the market. Furthermore, when there are only a small number of alternatives, including other on-patent drugs that are clinically comparable, firms have strong incentives to keep prices high—incentives that would not necessarily be overcome by a reference pricing policy.

Value-based benchmarking

In value-based benchmarking, a payer decides whether a drug is cost-effective at a manufacturer's proposed price. Payers can judge a product to be cost-effective if the cost associated with its use is not expected to exceed an explicit or implicit cost-effectiveness threshold.

In practice, rarely is a cost-effectiveness threshold defined formally or publicly. In fact, the threshold used by a payer may vary for different categories of drugs.⁶⁴ For example, the thresholds for drugs used to treat rare conditions may be higher, meaning that a payer would be willing to pay a higher price for these medications.⁶⁵ However, an implicit threshold can often be inferred from previous coverage and reimbursement decisions.

A number of payers undertake (or require drug companies to submit) an assessment of a drug's cost-effectiveness to inform the reimbursement decision-making process. Among those that do so are Australia, England, Italy, the Netherlands, New Zealand, Scotland, and most Canadian provinces. Systems vary greatly in how these assessments are used in decision-making.⁶⁶

Value-based benchmarking is used by the U.K.'s National Institute for Health and Care Excellence to develop coverage recommendations to the country's health care systems. The institute recommends against coverage of a drug if the incremental benefits expected from its use are not considered sufficient to justify the additional cost compared with the current standard of care.⁶⁷ It can also recommend that a product be covered only for certain patients for whom the drug is most cost-effective.⁶⁸

Other health systems (for example, those in France and Germany) do not routinely consider cost-effectiveness analyses to develop all pharmaceutical policies. In France, such analyses have been used to guide price negotiations for new products that, according to manufacturers, provide an advantage over existing therapies.⁶⁹ However, this information is not used to make coverage decisions, which are made by a different government entity not involved in price negotiations.⁷⁰

Because some drugs have multiple uses, or indications, countries have adopted various approaches to assess the cost-effectiveness of such drugs in order to inform their coverage and reimbursement decisions. A study of select OECD countries found that payers commonly ensure that a drug can be used cost-effectively for its first approved indication at the price offered.⁷¹ Then payers either reject additional indications that are not cost-effective at the original price or negotiate with the drug developer to set an alternative price that takes into account additional uses.

Value-based pricing raises numerous measurement and methodological challenges, among them the question of how to properly capture the overall value of a drug. For example, some drugs may provide nonhealth benefits, such as improved workplace productivity. Norway and Sweden, in their value assessments, are unusual in adopting a societal perspective that considers expected savings in areas such as unemployment benefits.⁷² In principle, this approach will take into account downstream savings beyond those relevant to the health care payer. Such a method can be more challenging to implement in health systems like those in the U.S., in which a significant share of health care is privately financed and individuals tend to switch insurers and insurance programs over time.

Impact of value-based benchmarking. No systematic review has been undertaken on the impact of value-based benchmarking on drug prices. But some evidence suggests that payers can obtain lower prices by incorporating information from cost-effectiveness analysis (CEA) into their reimbursement decision-making processes. For instance, one study of ACE inhibitors (drugs used to treat hypertension and congestive heart failure) in six European markets from 1991 through 2006 found that the use of CEA led drug companies to offer lower list prices in order for their products to be reimbursed.⁷³ At the same time, adoption of value-based

benchmarking would not necessarily have a cost-reducing effect for all drugs, since the price of some highly effective products could actually be increased based on the results of a CEA.

Evidence also suggests that value-based benchmarking may affect patient access. A 2012 study of reimbursement policies for cancer drugs in 13 countries found that four of the five payers that did not use CEA in reimbursement decisions (Finland, France, Germany, and U.S. Medicare Parts B and D) had the broadest levels of drug access for patients.⁷⁴ The study authors also concluded that the use of CEA affected reimbursement decisions in five of the eight countries or provinces (Australia, England, New Zealand, Ontario, and Scotland) where payers took into consideration the recommendations of an advisory committee that assessed the cost-effectiveness of pharmaceuticals. The advisory committee in each of these countries recommended against coverage between 52 and 74 percent of the time, with recommendations against coverage due in part to a lack of cost-effectiveness occurring between 32 and 69 percent of the time. Nevertheless, many of these recommendations were subsequently altered, resulting in a final approval rate between 46 and 74 percent for all indications reviewed.⁷⁵ It was beyond the scope of the study to determine whether value-based benchmarking policies affect patient health outcomes.

Applicability to the United States. While some U.S. payers use information on cost-effectiveness in making coverage and reimbursement decisions, no payers are known to have adopted a formal system in which payment amounts are set or capped according to an assessment of a product's value.

Value-based benchmarking is of particular interest when it comes to specialty drugs, since the question of whether their high prices are justified is central to the ongoing policy debate. In fact, research suggests that some specialty pharmaceuticals in the United States offer value that is comparable to that found in lower-priced products.⁷⁶ Nevertheless, because pharmaceutical firms are rarely required to conduct a formal CEA to demonstrate the value of their products to U.S. payers, it is likely that the prices paid for some drugs are too high for the benefits that they provide. For example, in 2013, imatinib, which is used to treat chronic myeloid leukemia,⁷⁷ cost payers approximately \$6,200 a month in the United States, compared with just \$2,700 in the United Kingdom.⁷⁸

An example of a U.S. payer's rejecting use of a drug because of cost-effectiveness considerations comes from Memorial Sloan Kettering Cancer Center (MSKCC) in New York. In 2012, MSKCC oncologists publicly announced that they would not use the cancer drug Zaltrap (afibercept) because of its high price and the lack of evidence of additional benefit over Avastin (bevacizumab). MSKCC's actions ultimately prompted the manufacturer to offer discounts to lower the effective price of Zaltrap by 50 percent.⁷⁹

Restricting off-label use

Prescribing medicine for an off-label use—such as for a disease or condition or at a dosage that has not been approved by regulators—is not always supported by clinical evidence, so the practice raises concerns about patient safety and health outcomes as well as cost. It occurs at least occasionally in most high-income countries, with health systems differing in the extent to which the practice is supported by payers, and is common in the United States,⁸⁰ where payers are notable for having a greater acceptance of the practice.

A 2012 study of coverage policies for 10 cancer drugs in 13 health systems found that six payers provided reimbursement for at least one off-label use.⁸¹ Along with the health systems of Finland and Sweden, the U.S. Medicare program had the most comprehensive benefits, covering all 48 uses assessed by the study's authors, including 40 indications approved by the U.S. Food and Drug Administration and eight off-label uses. In contrast, seven payers reimbursed only the on-label indications for all or some of the drugs approved by their respective regulatory authorities.⁸²

In health systems that have policies to deny coverage of at least some medicines prescribed off-label (among them Australia, Canada, Germany,⁸³ and Japan⁸⁴), a physician is generally required to specify the indication for which the drug is prescribed.⁸⁵ In Australia, off-label uses are not eligible for reimbursement.⁸⁶ (Moreover, with coverage in Australia limited to those indications deemed cost-effective, a medicine might not even be reimbursable for all of its approved indications.) For example, the cost of erythropoiesis-stimulating agents (ESAs) is reimbursed for patients with anemia due to renal disease, but not for patients with cancer who have anemia as a side effect of chemotherapy, an indication that does not have regulatory approval.⁸⁷ To enforce this policy, physicians must seek prior authorization to prescribe an ESA and must provide information on the patient's diagnosis as well.

In most cases, health systems provide for exceptions. Japan, for instance, has special reimbursement rules in place for the off-label, pediatric use of some drugs that are only approved for use in adult populations.

Other health systems act to deter off-label use without explicitly denying reimbursement. Some (for example, Sweden)⁸⁸ ban or greatly restrict pharmaceutical industry marketing to physicians—a practice known as detailing—in which sales representatives make in-person visits to physicians to provide information about a product and its uses; evidence shows that limits on detailing can have a substantial impact on reducing off-label use.⁸⁹ Other countries have similar policies. In Australia, detailing is supposed to be limited to discussions of indications that are both on-label and reimbursed in the health system.

Impact of off-label use restriction. While questions about cost and patient safety have been raised in research literature, there is limited information about the impact on health care costs of reducing the off-label use of drugs. In theory, such a reduction could lower health care costs. However, other factors must be considered: the availability and cost of substitute therapies, and any changes in health outcomes, such as adverse events, that can affect total health care costs.

When it comes to patient safety, research indicates that a significant portion of off-label prescribing—for example, 79 percent in Canada—is unsupported by evidence and that patients who are prescribed medicines for such off-label uses are 54 percent more likely to experience an adverse event than patients prescribed drugs for approved uses.⁹⁰ In addition to harming patients, these adverse events can also add to health care costs by increasing emergency room visits and hospitalizations.⁹¹

Nevertheless, some off-label uses have been shown to be effective.⁹² And, while providers often justify off-label prescribing for medical reasons, the case of Avastin (bevacizumab) and Lucentis (ranibizumab) provides an illustration of how off-label use can also reduce costs. Both drugs are used to treat patients with wet age-related macular degeneration, though Lucentis is approved for this use in the U.S. while Avastin is not. But in some European countries (for example, France and Italy), Avastin is covered for this off-label use and can even be covered instead of Lucentis,⁹³ since the two drugs are clinically comparable⁹⁴ and Lucentis is much more

expensive.⁹⁵ The practice continues despite a judgment by the European Union's highest court prohibiting off-label use as a cost-containment measure in cases where approved alternatives exist.⁹⁶ It has also raised safety concerns, since Avastin must be compounded into smaller doses, a practice that requires sterile preparation.⁹⁷

Applicability to the United States. Payers in the United States, including Medicare, generally reimburse medications used off-label;⁹⁸ in fact, approximately 20 percent of prescribing in the U.S. is for off-label uses,⁹⁹ and in 2009, 75 percent of U.S. payers reimbursed some off-label uses of prescription drugs.¹⁰⁰ Medicare Part B is required to cover anti-cancer drugs used off-label when published compendia—privately owned pharmaceutical reference guides—support their use.¹⁰¹ Furthermore, restrictions on how drugmakers can distribute information about off-label use have been eased significantly in recent years.¹⁰²

In some medical specialties, such as oncology, off-label use is common, even when evidentiary support for it is lacking. A 2013 study of U.S. cancer drug prescriptions found that one-third of the use of chemotherapy drugs under patent was off-label.¹⁰³ The study's authors estimated that \$4.5 billion of the \$12 billion spent on chemotherapy in 2010 could be attributed to off-label uses, including \$2.5 billion spent on uses unsupported by clinical guidelines.

Widespread reimbursement for off-label use in the United States has also allowed some high-priced drugs approved for use in narrow patient populations to attain a larger-than-anticipated volume of U.S. sales. The Orphan Drug Act of 1983 was put in place to encourage development of treatments for rare diseases. Today, more than a third of all new drugs are designated as orphan drugs.¹⁰⁴ These are drugs developed to treat a disease that affects fewer than 200,000 people in the U.S., or a disease that affects more than 200,000 people but for which manufacturers are not expected to recover the costs of developing and marketing the drug.¹⁰⁵ Such a designation exempts the drugs' developers from some user fees levied by the U.S. Food and Drug Administration and makes these developers eligible for tax credits for clinical trial costs, extended market exclusivity, and expedited review.¹⁰⁶ Once approved by FDA for a limited indication, some orphan drugs are commonly prescribed off-label in much larger populations.¹⁰⁷

Orphan drugs enter the market with high prices that are ostensibly justified by the need to recoup R&D costs for a medication that will be used to treat a relative few patients. However, several orphan drugs such as Epogen (epoetin alfa) and Genotropin (recombinant human growth hormone) have achieved blockbuster-level sales (i.e., sales value exceeding \$1 billion annually) due to extensive off-label use.¹⁰⁸

Some analysts have called for U.S. payers to limit payment for off-label uses in order to maintain patient safety and the efficient use of health care resources.¹⁰⁹ For example, experts have urged payers to reject reimbursement for the off-label use of psychotropic drugs, pointing to safety concerns and the availability of FDA-approved alternatives.¹¹⁰ They have also cited the potential for savings from reductions in drug spending as well as from reductions in the number of adverse events requiring medical attention, if the use of drugs for off-label indications is curtailed.

Medicare has sought to reduce off-label use of some drugs in the past, though the purpose was to improve patient health outcomes and not to reduce costs. And Medicare currently has an initiative in place to reduce off-label uses of antipsychotics in nursing homes, since these drugs are not approved by FDA to treat patients with dementia.¹¹¹ Such efforts, however, are not common.

A policy to further restrict or eliminate off-label use—either across all drugs, or just for cases in which evidence is lacking—would require physicians to report the indication when prescribing a drug. Payers would also need to develop more sophisticated payment policies, such as limiting either the conditions under which off-label use is reimbursed or the payment level for such uses.¹¹² Drug utilization and costs would be likely to decrease in the short run (though these decreases would be offset somewhat by patients switching to on-label treatments when available). Initially, changes in reimbursement would also be likely to face substantial resistance from doctors and patients who are accustomed to off-label uses (particularly in oncology and pediatrics).

However, the longer-term impact of restricting off-label prescribing is less clear. Pharmaceutical firms could respond by expanding the number of indications for which they seek FDA approval, which could increase R&D costs because of the number of clinical trials that would be required. Additional financial incentives might be needed for manufacturers to fund additional research, including for products whose patents have expired.

Payer-seller agreements

Many payers enter into product-specific agreements—so-called payer-seller agreements (PSAs)—with pharmaceutical companies in order to manage expenditures, ensure that prices paid for drugs are consistent with their value, and/or reduce the financial risk associated with adding a costly new drug to a formulary. Although information about the use of PSAs is limited due to their confidential nature (the very existence of an agreement is often not publicly disclosed), the practice is known to be increasingly common internationally for high-priced, on-patent drugs. In a 2012 study of 13 payers and their reimbursement policies for cancer drugs, nine had implemented PSAs for at least one of 10 pharmaceuticals studied.¹¹³ One health system, New Zealand, had negotiated a PSA for all 12 cancer drug indications it approved for reimbursement.¹¹⁴

PSAs fall into three categories. The first consists of agreements that *reduce the effective price paid* for a drug, by providing either rebates and/or discounts to payers or free drugs to patients. Another type *limits the payer's risk of incurring higher-than-anticipated costs* by adjusting the effective price of a drug through the payment of rebates that are linked to volume of use. These agreements cap total spending on a drug at an agreed-upon level, or cap the volume of product for which the payer will pay—generally an effort used to control expansion of sales through off-label use. A third category consists of *performance-based risk-sharing agreements*, in which the cost of a drug is retroactively adjusted based on patient outcomes.

Reducing the effective price paid. These PSAs are now in use by some payers in high-income countries. A survey of payers in 31 European countries, conducted in 2011-12, found that payers in 11 of them¹¹⁵ had engaged in negotiations to obtain effective price reductions through discounts, rebates, or the provision of free product.¹¹⁶ A 2012 survey of nine OECD countries also found that payers in seven—Australia, Canada, Germany, Italy, New Zealand, the U.K., and the U.S.—reported using confidential reimbursement contracts to establish effective payment levels below publicly available list prices.¹¹⁷ (Austria and the Netherlands did not use such agreements.) The U.S. and New Zealand were early adopters of confidential reimbursement contracts, with other payers taking up the practice in the past five to 10 years.

The practice of negotiating effective prices has become more common as pharmaceutical sellers have become more willing to grant rebates or discounts for their products in order to obtain market access or to increase market share. In recent years, as a response to external price benchmarking and the threat of parallel trade (in which payers in countries with high prices purchase pharmaceuticals from countries with lower prices),¹¹⁸

the pharmaceutical industry has attempted to keep list prices within a more narrow range, particularly in the European Union, and to keep negotiations confidential. Some analysts have identified potential negative implications arising from the confidentiality of PSAs and drug prices, especially for smaller countries with less leverage and sophistication to negotiate with drugmakers.¹¹⁹ In part to address these concerns, Germany began a practice in 2012 of publicly disclosing the effective prices achieved through its negotiations with drug companies,¹²⁰ a move with the potential to greatly influence prices in other countries. Because of the substantial size of the German market, the pharmaceutical industry felt obliged to accept the new policy.

Limiting the risk of higher-than-anticipated expenditure. These PSAs limit the payer's risk of incurring unforeseen costs associated with a high-priced drug. In some cases, such as with orphan drugs, the risk of prescribing for off-label indications or expansion of the prospective patient population can be controlled through the terms of a PSA. For example, manufacturers can agree to refund a portion of sales if a certain usage threshold or expenditure cap is exceeded. This approach can help payers offset industry efforts to expand utilization of its products.

A 2011-12 survey of 31 European countries found that about a third (11 countries)¹²¹ had negotiated agreements through which the payer would be refunded 1 to 8 percent of sales value, depending on the volume of products sold.¹²² While some countries that reported using this practice also reported having negotiated price discounts, this was not always the case. Belgium, Spain, and the United Kingdom reported negotiating only deals related to sales volume; Norway and Slovakia reported negotiating only price discounts.

In Australia, Canada, and the United Kingdom, a type of volume-based agreement has been recommended by the agencies in each country responsible for assessing the cost-effectiveness of drugs. For example, these agencies have urged payers to enter into agreements that would establish a maximum expenditure per patient in order to manage the risk associated with the potential excessive use of ranibizumab (Lucentis) for age-related macular degeneration.¹²³

Performance-based agreements. These agreements, also known as outcome guarantees or outcomes-based risk-sharing agreements, are voluntary payer-manufacturer contracts in which the payment level for a drug is based on the health outcomes achieved. Typically, the amount paid for a drug is retroactively adjusted through rebates (paid by drugmakers to payers) or bonus payments (from the payer to a manufacturer). These agreements are relatively new compared with price and volume-based agreements, and have been used relatively seldom to date, due in part to the technical challenges of assessing patient outcomes.

The U.K. entered into one of the first known such agreements with the manufacturer of Velcade (bortezomib), a drug used to treat multiple myeloma, in 2007. Instead of reducing the drug price to a level at which the National Institute for Health and Care Excellence would assess it as cost-effective, the drug manufacturer offered to reimburse treatment costs for patients who did not respond favorably to the medicine.¹²⁴ Also in the U.K., four firms selling beta-interferons to treat patients with multiple sclerosis agreed to discount their products on the condition that prices could later be adjusted higher if future studies showed that the drugs were more effective than expected.¹²⁵

In Italy, the health system negotiated a so-called success fee for pirfenidone (Esbriet), a new high-cost therapy approved for idiopathic pulmonary fibrosis.¹²⁶ The fee constitutes an additional payment to the manufacturer for patients who are documented to have benefited from treatment.

Impact of payer-seller agreements. Limited evidence suggests that price-related PSAs can have a significant impact on the price paid for a drug. A study from 2012 noted that countries engaging in such negotiations reported having received effective discounts of up to 50 percent off the drug's list price.¹²⁷ Of course, the size of the discount depends on the list price; it is likely that drug companies inflate their list prices in anticipation of negotiations with payers.

The magnitude of discounts that payers can obtain through negotiations with manufacturers depends on several factors, among them the payer's relative market power, including its share of the global pharmaceutical market; its ability to direct sales volume to the seller's product and away from that of competitors; and its ability to limit (through guaranteed confidentiality or otherwise) the impact of the bargaining on negotiations with other payers.

For drug companies, market power depends on demand for their product, which is affected by the availability of therapeutic alternatives. Under certain circumstances, a seller might also be concerned that the payer could use alternative means to obtain an on-patent drug. For example, nations could allow compulsory licensing of on-patent drugs (a policy in which the government permits domestic manufacturing of an on-patent drug without the consent of the patent owner) or the importation of lower-cost products from outside the country.

It is unclear whether health systems in countries such as France and Germany, which are large markets with sophisticated payers and high income, negotiate lower drug prices than payers in the smaller, less wealthy countries (e.g., Croatia, Portugal, Slovakia, and Slovenia) or those in the U.S. (public and private). It can be in the manufacturer's interest to accept a lower price rather than withstand the lower sales volume if a drug is either not launched or not covered in a market. If the manufacturer agrees to a lower price, however, the company will probably seek to avoid spillover effects into other markets—which could occur, for example, as a result of parallel trade agreements or if price negotiations with one payer are influenced by information about price concessions in other markets. For this reason, confidential agreements are likely to remain popular unless changes in the global market make confidentiality less beneficial to sellers.

Owing to the confidential nature of many risk-sharing and performance-based agreements as well as their relatively recent emergence, little evidence exists on their impact. A recently published review of the Italian experience with risk-sharing agreements concluded that savings achieved since 2006 have been minimal,¹²⁸ with the agreements generating savings of €121 million out of a total of €3.7 billion paid (approximately 3 percent).

Barriers to implementing risk-sharing and performance-based agreements have proved significant. Based on five case studies, two of which were U.S.-based and three U.K.-based, a report issued in 2011 identified barriers that include high implementation costs, measurement challenges (such as for health outcomes), and the need for improved health care information systems.¹²⁹

While drug companies have sought to keep negotiated agreements and their details confidential to avoid influencing effective prices paid elsewhere, evidence from Germany suggests that transparent price negotiations can also yield discounts, at least in cases where the payer has sufficient global market share. In the first two transparent price negotiations that followed Germany's move away from seller-defined pricing in 2012, AstraZeneca agreed to a 17 percent price concession for ticagrelor (Brilique) and InterMune agreed to an 11 percent discount for pirfenidone (Esbriet).¹³⁰ These discounts were in addition to Germany's legally mandated 16 percent rebate from the list price.

Applicability to the United States. In the United States, pharmacy benefit managers typically negotiate PSAs on behalf of health plans, public and private insurers, and plan members,¹³¹ often in exchange for preferential formulary placement that gives products an edge in attaining market share. The discounts and rebates they negotiate are generally passed on—in whole or in part—to consumers. While there are examples of cost- and performance-based agreements in the U.S., year-to-year turnover in the insured population—a result of consumers switching from one insurer to another, which can happen when they change employers—presents additional challenges to the implementation of such contracts in this country, as compared with countries that offer universal coverage through a national health service or single-payer model.

In comparison with their international peers, U.S. payers face a number of obstacles that reduce their negotiating power. First, each U.S. payer (or intermediary negotiating on the payer's behalf) represents only a share of the national market. Second, because of legal constraints and market preferences, U.S. payers have minimal authority to reject coverage on the grounds of cost-effectiveness or total cost impact, a situation that has the effect of inflating demand or willingness to pay for a given drug.

Some experts have also identified potential barriers for performance-based agreements in the U.S., where the anti-kickback statute,¹³² which prohibits the exchange of anything of value, or an offer of such an exchange, with the intent to influence the use of a product or service paid for in federal programs, may limit the design of these agreements, as may FDA regulations that limit the ability of manufacturers to communicate to payers information not included on a drug's label. Current pricing laws for federal programs, including for Medicare Part B, Medicaid, and the Veterans Health Administration, set the price of drugs based on a statutorily defined benchmark price. Technical challenges include how prices paid in an outcomes-based contract—in which there may be two prices for a drug depending on whether it works—would be incorporated into pricing for these federal programs.¹³³

In Medicare, participating prescription drug plans can negotiate individually with drug companies. However, Medicare itself is legally prohibited from negotiating collective PSAs on behalf of its beneficiaries.¹³⁴ Analysts have taken different positions on the likely consequences of giving Medicare the ability to negotiate drug prices. And even if the legal barriers were to be lifted, a number of technical considerations would need to be addressed in implementation, including the drugs for which the Medicare program would negotiate; whether negotiated terms would apply to prices and/or formulary design; and how such negotiations would work in a system based upon competing private plans.

Declining coverage of medicines deemed unaffordable

While many health systems reject or restrict coverage of products determined not to be cost-effective at the price offered by drug companies, some also deny payment for a product that they simply consider unaffordable (i.e., the projected cost of coverage exceeds the financial means of the payer). England's National Health Service (NHS) is statutorily obliged to cover any drug determined to be cost-effective and recommended for use by the National Institute for Health and Care Excellence (NICE), which advises the NHS with research on the cost-effectiveness of drugs.¹³⁵ In contrast, payers in a few developed countries (among them Australia, Canada, and New Zealand) occasionally decline to cover certain drugs due to their anticipated budget impact.

Such a decision can be implicit or explicit. Often, a decision that a medicine is unaffordable effectively means delaying access, rather than rejecting coverage permanently. In New Zealand, for example,¹³⁶ funds to pay for increased spending on new drugs sometimes must come from savings generated elsewhere in the health

care system, such as when patent-protected drugs lose their market exclusivity and face generic competition. Alternatively, New Zealand policymakers can choose to increase the health care budget to pay for new, high-cost medications. Otherwise, New Zealand's pharmaceutical reimbursement agency, the Pharmaceutical Management Agency of New Zealand, chooses which new drugs to fund within its available budget. It also has the option of reconsidering coverage of unfunded products in future years when money becomes available.

In Australia, any drug expected to cost more than AU\$20 million during any of the first four years of listing on the national formulary—the Pharmaceutical Benefits Scheme—is subject to a special requirement: The Australian Cabinet must endorse the health minister's decision to list the drug.¹³⁷ The Pharmaceutical Benefits Advisory Committee (PBAC), an independent expert body appointed by the Australian government, makes recommendations to the health minister on whether to include products on the formulary. The PBAC can recommend against a drug on affordability grounds, such as when a drug's potential utilization is likely to be excessive or when its use cannot be limited to the population for which it is considered cost-effective.¹³⁸ Drugs excluded from coverage on the basis of budget impact include those that have widespread application in the population as well as those with a specialized use. For example, Australia's health minister declined to list Viagra on the national formulary in 2002, despite a positive recommendation from the PBAC, due to concerns that the potential cost to the program could exceed AU\$100 million a year.¹³⁹

A drug can be cost-effective and still be considered unaffordable. For instance, the new hepatitis C drugs, such as Gilead's Sovaldi and Harvoni,¹⁴⁰ have been determined to be cost-effective in some analyses, yet these therapies present budget challenges to health systems due to the number of patients potentially eligible for treatment. New Zealand did not add any of the new hepatitis C drugs to its national formulary until July 2016.¹⁴¹

Cancer Drug Coverage Among Cost-Sensitive Payers

The case of cancer drug coverage illustrates differences among high-income countries in how they manage spending on high-cost medicines. Payers in some countries make coverage decisions informed by the recommendations of an advisory committee that considers the impact of a drug on overall costs.

A 2012 study of coverage policies for 10 cancer drugs (used for 48 indications) found that Australia's expert advisory committee recommended that the program not cover 9 percent of indications due to "excess cost." Similarly, advisory panels in Ontario (Canada) and New Zealand recommended that payers not cover 13 percent and 52 percent of indications, respectively. These three countries or provinces had some of the least comprehensive coverage among those included in the study. In comparison, Medicare covered all 48 indications in the United States.

Continued on next page

Although many factors contribute to differences in cancer outcomes across countries, there is limited evidence on whether access to drugs plays a role. A 2007 study funded by the pharmaceutical industry linked access to new drugs to improved survival and larger reductions in cancer mortality rates.[†] However, the study has been criticized for methodological limitations.[‡] At the same time, a 2004 literature review found that chemotherapy to treat 22 different cancers made a relatively small impact on overall cancer survival in Australia and the U.S.;[§] the effect of chemotherapy was similar in Australia and the U.S., and was estimated to account for 2.3 percent and 2.1 percent of five-year survival, respectively. This suggests that differences in cancer drug access between the two countries had a very modest effect on differences in health outcomes.

If countries including the U.S. were to follow the lead of Australia, Ontario, and New Zealand in taking costs into account in making coverage decisions, the impact on drug spending could be considerable. Worldwide spending on cancer drugs reached \$100 billion in 2014, representing 10.8 percent of total drug spending, and it is projected that cancer drug spending will rise to \$117 billion to \$147 billion in 2018.^{||} The United States accounted for about 42 percent of total cancer drug spending.

* P.K. Cheema et al., "International Variability in the Reimbursement of Cancer Drugs by Publicly Funded Drug Programs," *Current Oncology* 19, no. 3 (2012): e165-76, doi:10.3747/co.19.946.

† B. Jonsson and N. Wilking, "A Global Comparison Regarding Patient Access to Cancer Drugs," *Annals of Oncology* 18, Suppl. 3 (2007): iii1-iii77, doi:10.1093/annonc/mdm095.

‡ Marina Karanikolos et al., "Health Systems Performance and Cancer Outcomes," *Journal of the National Cancer Institute Monographs* 2013, no. 46 (2013): 7-12, doi:10.1093/jncimonographs/igt003; M.P. Coleman, "Not Credible: A Subversion of Science by the Pharmaceutical Industry. Commentary on 'A Global Comparison Regarding Patient Access to Cancer Drugs,'" *Annals of Oncology* 18, no. 9 (2007): 1433-35, doi:10.1093/annonc/mdm363.

§ G. Morgan, R. Ward, and M. Barton, "The Contribution of Cytotoxic Chemotherapy to 5-Year Survival in Adult Malignancies," *Clinical Oncology* 16, no. 8 (2004): 549-60, doi:10.1016/j.clon.2004.06.007.

|| Bill Berkrot, "Global Cancer Drug Spending Hits \$100 Billion in 2014: IMS Health," *Reuters*, May 5, 2015, <http://www.reuters.com/article/us-health-ims-oncology-idUSKBN0NQGD20150505>.

Impact of declining coverage of high-cost medicines. Declining coverage of an effective or cost-effective medicine because of its overall cost impact affects patient access to the drug. However, such a policy may or may not affect health outcomes, depending on whether clinically comparable alternatives are available.

Drug companies may decline to launch products in a market where patient use is expected to be very low due to noncoverage. However, patients can choose to pay out of pocket for drugs that are not covered. In some countries, private supplemental health insurance coverage may be available to subsidize medicines not covered by the publicly financed health system; in other systems, such coverage is not available or is prohibited.

For payers, the potential cost impact of choosing not to cover products considered unaffordable depends on the time horizon over which costs are counted. The cost of drug therapies for hepatitis C, for example, can potentially offset future medical costs (the cost of liver transplants for a small percentage of hepatitis C patients). For health systems that are funded with annual budgets, however, the immediate cost impact of drugs can be as big a factor in influencing policy decisions as the potential cost savings that can be realized years in the future.

Increasing negotiating leverage for payers could yield additional cost savings to them. If manufacturers recognize that payers are willing to reject coverage of their products, they may offer increased discounts and other rebates.

Applicability to the United States. There has been little pressure from U.S. consumers to deny coverage for new FDA-approved drugs as a way to reduce drug costs and, in fact, a great deal of pressure, including from patient advocacy groups,¹⁴² for more inclusive coverage policies. Many private payers are contractually or legally obligated to cover medically necessary care, and health plans are able to pass on to consumers higher-than-expected costs as premium and/or cost-sharing increases.

Among public payers, Medicare Part D plans are required to cover “all or substantially all drugs” in six protected classes as well as at least two drugs in every drug class.¹⁴³ While payers, including Medicare Part D plans, can consider a drug’s cost as one factor among many in reimbursement decisions when therapeutic alternatives exist, there is generally no mechanism for denying payment for an effective medicine on the basis of cost alone. Insurers may restrict coverage to subgroups of patients, though these policies are justified clinically rather than for reasons of cost.

More overt limiting of access to drugs has been politically feasible in the Medicaid program. For example, beginning in 1990, the state of Oregon determined coverage and noncoverage of services, including pharmaceuticals, by prioritizing them according to cost-effectiveness as well as other criteria. As a result, certain very high-cost services, such as organ transplants, were not covered.¹⁴⁴ Increased costs in Medicaid, unlike in other programs, cannot be passed on to program beneficiaries and, because Medicaid constitutes a significant share of state budgets, policymakers have been willing to test new policy approaches in order to lower costs.

Conclusion

This report examined six policies used in various nations to manage pharmaceutical costs. The analysis, summarized in Table 1, suggests that the use of similar tools may have the potential to reduce drug spending in the United States, where per capita prescription drug costs are significantly higher than in many other countries. While some of these policies have reduced access to some medicines—such as when a drug is not covered due to high cost or because it is not determined to be cost-effective—other payment policies have served to expand access by improving the affordability of available medicines. Little research exists regarding the impact of these payment policies on patient health outcomes, which likely are affected by many other factors, such as the availability of effective substitutes. Furthermore, some policies, such as those that restrict off-label use, may improve health outcomes by reducing the number of adverse events associated with inappropriate use.

Table 1

Summary of International Experience and Considerations for Use in the United States

	International experience	Considerations for use in the U.S.
External benchmarking	<p>Suggests a price-lowering effect, although this is highly dependent on benchmark selection and the formula used to set a reference price.</p> <p>Assessing the cost impact is challenging, since drug companies have adapted pricing strategies to reflect widespread use of external benchmarking, such as increasing list prices. Higher list prices may reduce access to medicines in health systems where payers lack the leverage or authority to negotiate larger rebates and discounts.</p> <p>There is no evidence about the impact on patient health outcomes.</p>	<p>Adoption by Medicare for select specialty drugs could have a significant short-term impact on expenditures.</p> <p>Long-term effects might include increased list prices internationally, with manufacturers granting larger confidential discounts and rebates.</p>
Internal benchmarking	<p>Strong demonstrated impact on expenditures and prices of drugs included in reference groups (i.e., drugs for which there are one or more acceptable alternative therapies).</p> <p>The small number of studies found no evidence that internal benchmarking has had a negative impact on patient health outcomes.</p>	<p>Adoption by Medicare for drugs with comparable therapeutic alternatives, including the availability of multiple drugs in the same therapeutic class, could lower expenditures significantly.</p> <p>Drugs for which there are no comparable alternatives are ineligible for reference pricing.</p>
Value-based benchmarking	<p>Some payers use health technology assessments, including cost-effectiveness analysis (CEA), to guide coverage and reimbursement decisions. Some evidence suggests that payers can obtain lower prices by incorporating information from CEA into their reimbursement decision-making process and that drug manufacturers may offer products at lower prices in health systems in which CEA is used. Although use of CEA would suggest a lower price for some drugs, it is also possible that prices might increase for undervalued drugs.</p> <p>There is no evidence regarding the impact on patient health outcomes.</p>	<p>A move to value-based benchmarking in coverage and payment could help to reduce use of drugs that offer minimal incremental effectiveness at relatively high cost. Savings would be possible from reduced payment for drugs that offer few or no new benefits.</p>
Restriction of off-label use	<p>A few health systems (e.g., Australia, Germany, and Japan) refuse reimbursement for off-label use.</p> <p>Cost savings may accrue from reductions in the use of medicines that are not supported by evidence and from reductions in costly adverse events. Restricting inappropriate off-label use could also improve patient health outcomes.</p>	<p>If Medicare or private payers were to restrict reimbursement for off-label indications, drug expenditures would most likely decrease in the short run, but the longer-term impact on health outcomes and total health expenditure is unknown. For drugs with lower-cost, FDA-approved alternatives, however, such a policy could reduce long-term costs.</p>

Continued on next page

	International experience	Considerations for use in the U.S.
Payer-seller agreements (PSAs)	<p>PSAs have resulted in effective price discounts of up to 50 percent and may also offset the cost impact of off-label prescribing.</p> <p>Because of the confidential nature of these agreements, evidence regarding cost and health impact is limited.</p>	<p>Private health plans and pharmacy benefits managers in the U.S. currently negotiate PSAs, though the use of performance-based agreements is rare. U.S. payers face a number of obstacles that reduce their negotiating power, including fragmentation of payers and limited ability to deny coverage. Removing these obstacles could allow U.S. payers to be more effective in negotiating favorable PSAs.</p>
Declining coverage for medicines deemed unaffordable	<p>Savings accrue from the averted cost of drugs rejected for coverage, and the added leverage that payers would have to negotiate discounts or rebates on expensive drugs that have limited competition in the market.</p> <p>There is little evidence on health outcomes. The impact on patients would depend in part on the availability of clinically comparable therapies.</p>	<p>Both public and private insurers face significant sociocultural and legal barriers to rejecting drugs for coverage based on cost.</p> <p>While a drug’s cost can sometimes be considered in reimbursement decisions when therapeutic alternatives exist, including by Medicare Part D plans, there is generally no mechanism for denying payment for an effective medicine on the basis of cost alone.</p>

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In practice, the effects of the different policies in various countries also depend on the context in which they are used, including the regulatory framework and the relative market power of payers and drug manufacturers. Furthermore, no single policy operates in isolation; the effect of any one tool can be difficult to disentangle from that of others. Sometimes, policies can work against one another, reflecting political trade-offs between different policy objectives, such as increasing patient access and reducing drug spending.

Most high-income countries also rely on other regulatory tools, in addition to payment and coverage policies, to manage spending on drugs. These include prohibiting direct-to-consumer advertising (allowed only in the United States and New Zealand), easing of restrictions on the importation of patented medicines, and limiting practices that extend the length of time for which a drug enjoys market exclusivity. These tools may also be used in the U.S. to better manage spending on pharmaceuticals.

The fact that the U.S. health care system has failed to adopt many policies in common use elsewhere indicates that U.S. payers, including public programs such as Medicare, are technically, legally, and/or politically constrained in their ability to implement them.

To the extent that barriers are legal or social in nature, advancing new policies to address the rising cost of drugs will require public consensus on the objectives and priorities of U.S. pharmaceutical policy. Therefore, additional expert, stakeholder, and public engagement is needed to make the case that decisions on drug coverage and payment should explicitly incorporate economic considerations such as cost-effectiveness and affordability.

Glossary

Active ingredient. An ingredient in a drug that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. Some medications contain more than one active ingredient.

Biologic. A drug made up of proteins or other materials derived from living cells through a complex manufacturing process. Biologics are used to treat a wide range of health conditions, including cancer, rheumatoid arthritis, and multiple sclerosis.

Biosimilar. A “follow-on” drug that is highly similar to an FDA-approved biologic. Like generic versions of conventional drugs, biosimilars are intended to reduce prices by creating competition in the marketplace.

Clinically comparable. Term for two drugs for which there are no clinically meaningful differences in terms of safety and effectiveness.

Cost-effectiveness analysis. A form of economic analysis that compares the relative costs and outcomes of different treatments.

Drug class. A set of medications grouped together based on a common active ingredient (or ingredients) or by pharmacologic or therapeutic class (see definitions below).

Effective price. The actual per-unit cost of a drug, after accounting for rebates, discounts, and other price concessions negotiated between drug companies and payers such as insurance companies or health plan sponsors.

Formulary. A list of brand-name and generic drugs that payers cover, typically organized in tiers. Patients are required to pay different out-of-pocket costs for drugs in different tiers.

Indication. A particular use for a diagnostic, treatment, or drug. For example, insulin is indicated—or prescribed—to treat diabetes. FDA approves each drug for one or more indications.

Mechanism of action. The specific process through which a drug produces its pharmacological effect.

Medically necessary. Health care services or supplies needed to prevent, diagnose, or treat an illness, injury, condition, disease, or its symptoms—and that meet accepted standards of medicine.

Off-label use. The use of a drug for indications that have not been approved by the relevant regulatory authority, such as FDA.

Payers. Entities other than patients responsible for paying for health care costs. In the United States, payers generally include insurance companies, health plan sponsors—such as employers or unions—and pharmacy benefit managers. The nation’s largest payer is Medicare.

Pharmacologic class. A group of active moieties (i.e., parts of molecules) that share scientifically documented properties and are defined on the basis of any combination of three attributes: 1) mechanism of action, 2) physiologic effect, and 3) chemical structure.

Pharmacy benefit manager (PBM). A third-party administrator of prescription drug programs for insurance companies. PBMs often process pharmacy benefit claims, develop and maintain formularies, and negotiate prescription drug prices with drug manufacturers. In the United States, PBMs manage prescription drug programs for commercial health plans, self-insured employer plans, Medicare Part D plans, the Federal Employees Health Benefits Program, and state government employee plans.

Therapeutic alternative (also referred to as a **therapeutic equivalent**). A drug that is not chemically identical to another drug but has similar effects when given in therapeutically equivalent doses.

Therapeutic class. A group of drugs used to treat the same disease or condition.

Utilization. A measure of the amount of use of health care items and services, including drugs.

Endnotes

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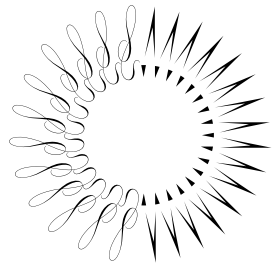
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