



Insulin Access and Affordability Working Group: Conclusions and Recommendations

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There are more than 30 million Americans with diabetes, a disease that costs the U.S. more than \$327 billion per year (1,2). Achieving glycemic control and controlling cardiovascular risk factors have been conclusively shown to reduce diabetes complications, comorbidities, and mortality. To achieve these desired outcomes, the medical community now has available many classes of medications and many formulations of insulin to effectively manage the metabolic abnormalities for people with diabetes. However, the affordability of medications in general, and for insulin specifically, is currently of great concern to people with diabetes, their families, health care providers, insurers, and employers. For millions of people living with diabetes, including all individuals with type 1 diabetes, access to insulin is literally a matter of life and death. The average list price of insulin has skyrocketed in recent years, nearly tripling between 2002 and 2013 (3). The reasons for this increase are not entirely clear but are due in part to the complexity of drug pricing in general and of insulin pricing in particular.

As the price of insulin continues to rise, individuals with diabetes are often forced to choose between purchasing their medications or paying for other necessities, exposing them to serious short- and long-term health consequences (4–9). To find solutions to the issue of insulin affordability, there must be a better understanding of the transactions throughout the insulin supply chain, the impact each stakeholder has on what people with diabetes pay for insulin, and the relative efficacy of therapeutic options. Thus, as the nation's leading voluntary health organization whose mission is "to prevent and cure diabetes and to improve the lives of all people affected by diabetes," the American Diabetes Association (ADA) is committed to finding ways to provide relief for individuals and families who lack affordable access to insulin.

In the spring of 2017, the ADA Board of Directors convened an Insulin Access and Affordability Working Group (Working Group) to ascertain the full scope of the insulin affordability problem, to advise the ADA on the execution of strategies, and to provide high-level direction to the ADA related to this issue. The composition of the Working Group is provided in Supplementary Table 1. The Working Group identified increased transparency throughout the insulin supply chain and a number of other interventions as important steps toward developing viable, long-term solutions to improve insulin access and affordability.

Throughout 2017, the Working Group assembled existing public information about insulin prices and patient cost-sharing, and convened a series of meetings with stakeholders throughout the insulin supply chain to learn how each entity affects the cost of insulin for the consumer. The Working Group also had ongoing conversations with researchers focused on insulin pricing at both the global and national levels. The Working Group talked with more than 20 stakeholders who were representatives of pharmaceutical manufacturers, wholesalers, pharmacy benefit managers (PBMs), pharmacies, pharmacists, distributors, health plans, employers, and people with diabetes and caregivers (Supplementary Table 2). Despite the attempt to interview as many stakeholders as possible, it is important to note that due to time constraints and schedules, the Working Group may have inadvertently overlooked inviting some relevant stakeholders, and there were a small number of individual stakeholders who declined to meet with the Working Group. To guide the discussion with each stakeholder interviewed, the Working Group developed a set of standard questions focused on determining the role each entity plays in the supply chain, the issues the entity faces, and recommendations for change (Supplementary Table 3).

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*A complete list of the members of the Insulin Access and Affordability Working Group can be found in the Supplementary Data online.

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See accompanying article, p. 1125.

BACKGROUND: SCOPE OF THE PROBLEM

Approximately 7.4 million Americans with diabetes use one or more formulations of insulin (10,11). People with diabetes using insulin come from varied economic, racial, and ethnic backgrounds. Almost 20% of African Americans with diabetes use insulin, either alone or with oral medications, as do 14% of Caucasians and 17% of Hispanics with diabetes (10). Of adults with diabetes earning below the poverty level, approximately 24% use insulin, either alone or with oral medications (11).

Currently, there are only three insulin manufacturers serving the U.S. market: Eli Lilly, Novo Nordisk, and Sanofi. Almost 100 years ago, the discovery of insulin, derived from animal sources, literally began to save human lives. The advent of genetic engineering brought human insulin formulations to patients with diabetes in the 1980s. Rapid-acting and long-acting human insulin analogs were introduced in the 1990s. The patents for many of the human insulin and human insulin analog formulations in current clinical use have expired.

Working Group members from the USC Schaeffer Center for Health Policy & Economics have significant experience in studying medication pricing (12,13). Using Centers for Medicare & Medicaid Services data on National Average Drug Acquisition Cost (NADAC), they identified 30 insulin products with NADAC data available between October 2012 and December 2016 and categorized them by product type: short-acting insulin vials, rapid-acting insulin vials, rapid-acting insulin pens, and long-acting insulin pens/vials (Table 1). For each product, they collected monthly Wholesale Acquisition Cost (WAC) from First Databank and calculated average monthly WAC and NADAC for each category by averaging across products in each category. They used Medicare Part D claims from 2006 to 2013 to calculate the average insulin expenditure and out-of-pocket spending per insulin user and the Medicare spending by utilization (i.e., the total spending divided by the number of insulin users times mean annual day supply).

The average U.S. list price (WAC) of the four insulin categories increased by 15% to 17% per year from 2012 to 2016 (Fig. 1). Over the same period, the price pharmacies paid to purchase insulins (NADAC) increased at similar rates. Spending on

insulins by Medicare Part D has also shown an increasing and accelerating trend. For example, Medicare spending by utilization on rapid-acting insulin in vials had a compound annual growth rate (CAGR) of 10% per year between 2006 and 2013 but a CAGR of 13% between 2011 and 2013. As spending on insulins has increased, so too have patient out-of-pocket costs. Between 2006 and 2013, average out-of-pocket costs per insulin user among Medicare Part D enrollees increased by 10% per year for all insulin types (Fig. 2). Comparatively, overall inflation during this time was 2.2%, medical care service costs increased by 3.8%, and spending for all prescription drugs increased by an average of 2.8%.

Insulin affordability and accessibility issues, however, are not restricted to the U.S. Data from the global ACCISS (Addressing the Challenges and Constraints of Insulin Sources and Supply) study found several overarching trends. First, even for the same insulin product, there is a wide range of prices across the world. Second, there is a large price differential between the lower prices of human insulin formulations and the higher prices of human insulin analog formulations on a global level. Third, there has been increasing use of human insulin analogs compared with normal human insulin over the recent past, which is greater in more developed parts of the world (14). This study also reported that the global insulin market is dominated by the same three large multinational corporations that manufacture and sell insulin in the U.S. Those companies represent 99% of the total insulin by value, 96% by total market volume, and 88% of global product registrations.

COMPLEXITY OF THE INSULIN SUPPLY CHAIN AND PRICING MECHANISMS

Pricing of drugs in general, and for insulin specifically, is very complex. Numerous stakeholders (i.e., manufacturers, wholesalers, PBMs, pharmacies, health plans, and employers) are involved in the insulin supply chain, and the distribution and payment systems involve multiple transactions among these stakeholders (Fig. 3). With this system, there is no one agreed-upon price for any insulin formulation. The price ultimately paid by the person with diabetes at the point of sale results from the prices, rebates, and fees negotiated among the stakeholders. Stakeholders in the insulin supply chain have varying

degrees of negotiating power, which adds to the complexity. The following narrative represents the Working Group's understanding of the U.S. insulin delivery system as obtained by research and in specific interviews with the stakeholders.

Overview of Insulin Supply Chain Dynamics

The complexity of the insulin supply chain is outlined schematically in Fig. 3. The insulin supply chain mirrors that of many other prescription drugs. As outlined, manufacturers set the list price for each insulin product. Manufacturers typically sell their medications to wholesalers, who handle distribution to individual pharmacies. But sometimes a pharmacy chain will deal directly with the manufacturer. Wholesalers typically purchase the medications for close to the list price, often receiving a handling fee from the manufacturer that is calculated as a fixed percentage of the list price. Wholesalers then sell the medications to pharmacies, with little to no markup. They may, however, charge the higher list price. Pharmacies dispense the medication to individual patients and collect cost-sharing required by the patient's health plan (if any). Pharmacies then submit a bill to the individual's health insurance plan (if any) to be reimbursed for the cost of the medication dispensed to the patient, less any cost-sharing collected, plus a dispensing fee. If a patient does not have or use health insurance for the medication, the pharmacy typically charges the patient a price relatively close to its purchase price, with a markup.

While the medication itself takes a rather direct path from manufacturer to wholesaler to pharmacy to patient, the flow of money is far less direct and transparent. Furthermore, PBMs often manage the pharmacy benefit portion of a health plan on behalf of their clients. Their clients are the payers for health care, such as large employers, health insurers providing pharmacy benefits to Medicare enrollees, health insurers covering state Medicaid program enrollees, or health insurance plans sold directly to individuals. It is important to note, therefore, that PBMs' primary customers are health plans and employers, not patients.

The Increasing List Prices of Insulin Formulations

Much of the public discussion regarding insulin affordability and accessibility has focused on the rapidly increasing average

Table 1—Categories of insulin

Category label on Figs. 1, 2, and 5	Description	Delivery	Products—brand names ^a	Products—generic names
Short-acting insulin (vials)	Short-acting, intermediate-acting, or mixed intermediate/short-acting vials	Vial	Humulin R, 10-mL vial Humulin R, 3-mL vial Novolin R Novolin R (Relion) Humulin N, 10-mL vial Humulin N, 3-mL vial Novolin N Novolin N (Relion) Humulin 70/30 Novolin 70/30 Novolin 70/30 (Relion)	Insulin regular, human Insulin regular, human Insulin regular, human Insulin regular, human Insulin NPH, human isophane Insulin NPH, human isophane Insulin NPH, human isophane Insulin NPH, human isophane Insulin NPH, human/regular insulin HM Insulin NPH, human/regular insulin HM Insulin NPH, human/regular insulin HM
Rapid-acting insulin (vials)	Rapid-acting or mixed intermediate/rapid-acting vials	Vial	Humalog, 10-mL vial Humalog, 3-mL vial Apidra NovoLog Humalog Mix 75/25 Humalog Mix 50/50 NovoLog Mix 70/30	Insulin lispro Insulin lispro Insulin glulisine Insulin aspart Insulin lispro protamine/lispro Insulin lispro protamine/lispro Insulin aspart protamine & aspart
Rapid-acting insulin (pens)	Rapid-acting or mixed intermediate/rapid-acting pens	Pen or cartridge	Humalog cartridge Humalog KwikPen U-100 Apidra SoloSTAR NovoLog cartridge NovoLog FlexPen Humalog Mix 75/25 KwikPen Humalog Mix 50/50 KwikPen NovoLog Mix 70/30 FlexPen	Insulin lispro Insulin lispro Insulin glulisine Insulin aspart Insulin aspart Insulin lispro protamine/lispro Insulin lispro protamine/lispro Insulin aspart protamine & aspart
Long-acting insulin (vials/pens)	Long-acting vials and pens	Vial or pen	Lantus Levemir Lantus SoloSTAR Levemir FlexPen	Insulin glargine Insulin detemir Insulin glargine Insulin detemir

Categories of insulin products evaluated by the USC Schaeffer Center for Health Policy & Economics investigators as part of the Insulin Access and Affordability Working Group. ^aIn the case of the Novo Nordisk products (Novolin R, Novolin N, Novolin 70/30), one is the Novo Nordisk–branded product, while the other corresponds to the same drug sold under the Relion brand. Each has a different national drug code and sells for a different price. In the case of the Eli Lilly products (Humulin R, Humulin N, Humalog), different vial sizes are referenced (3 mL vs. 10 mL).

list prices of insulin over the past two decades, which nearly tripled between 2002 and 2013 (3). The list price is defined as the price manufacturers set for their medication (Table 2). Along with yearly increases, the published data also suggest that when one insulin manufacturer increases the price for a given insulin formulation, the other insulin manufacturers often increase their prices by a similar amount shortly thereafter (15,16) (Fig. 4).

The Increasing Use of Higher-Priced Insulins

Another important trend affecting overall costs for insulin in the last decade is the shift in insulin utilization from the less expensive human insulins to more expensive human insulin analogs (14,17–19) (Fig. 5). While the prices of both types of insulin have increased, the difference in pricing between them has substantially added

to insulin costs—both to the health care system and to many patients (17,18) (human insulins are available at the pharmacy for \$25 to \$100 per vial compared with human insulin analogs at \$174 to \$300 per vial [19]). This is further discussed below in **FORMULARY DECISIONS AND PATIENT FINANCIAL BURDEN**.

The Growing Gap Between the List Price and Net Price

While the list price is defined as the price manufacturers set for their medication, the list price is not ultimately what is paid for the medication (with some exceptions), nor is it what manufacturers receive for their products. The net price manufacturers receive for their medications is the list price less any fees paid to wholesalers, and/or discounts paid to pharmacies, and any rebates paid to PBMs or health plans.

The Working Group found a number of examples from public sources showing that the net price to the insulin manufacturers has grown at a slower rate, or has gone down, compared to list prices. For example, the net price of the insulin formulation Lantus (glargine) increased more or less in parallel with the list price from 2007 to 2013 (20). However, the net price has decreased in recent years (2014–2016) (Fig. 6) (20). As a result, the net price increased by 57% between 2007 and 2016, increasing 23% as fast as the list price reported as a 252% increase over the same period (Fig. 6).

Reports on other insulin products also illustrate the difference between the rapid increase in list price as compared with the slower increase in net price to manufacturer, a trend that may have started earlier for some insulin formulations (17,21). Bloomberg News reported an estimate by

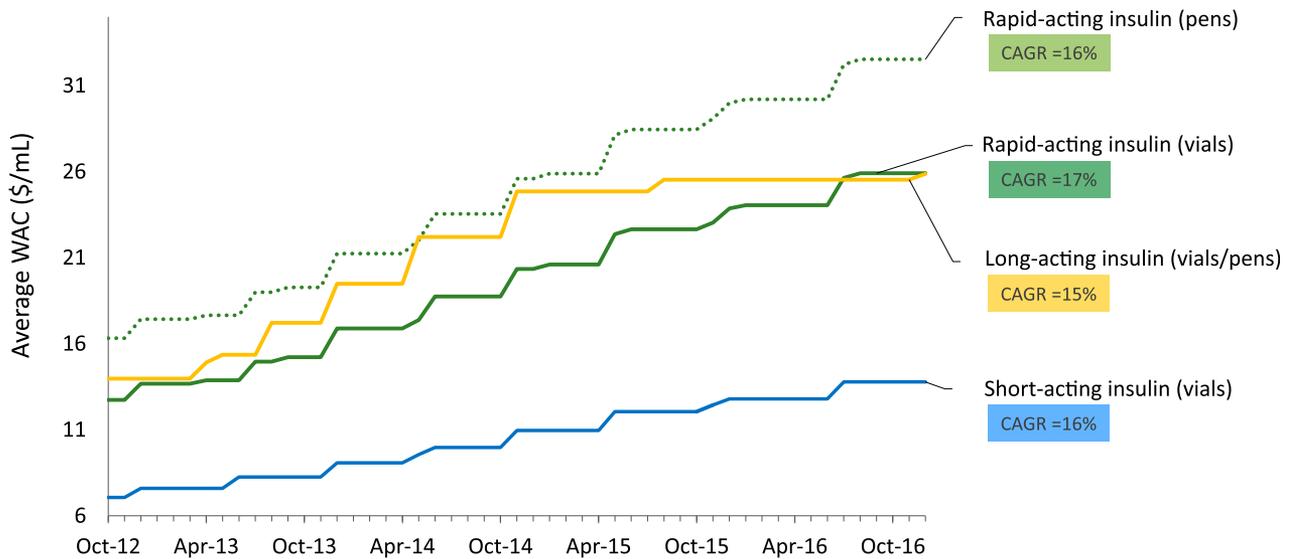


Figure 1—Average WAC for insulins, by product category, 2012–2016. Source: USC Schaeffer Center analysis of First Databank data.

an independent market research firm that the list price of Eli Lilly’s human insulin analog, Humalog, increased by 138% between 2009 and 2015, while the net price to the manufacturer increased by 6% (21).

Novo Nordisk also published data for two of their insulin products, NovoLog and NovoLog FlexPen. Since the early 2000s, the CAGRs for the list prices for NovoLog and NovoLog FlexPen (Fig. 7) have been in the range of 9.8–9.9% (22). This translated into large total increases

in the list prices: 353% (2001–2016) for a NovoLog vial and 270% (2003–2016) for a FlexPen. In contrast, net prices received by the manufacturer increased at a more modest rate (3–36%) with CAGRs of 0.2–2.1%. Novo Nordisk, Eli Lilly, and Sanofi have reported that rebates have grown rapidly in recent years—representing more than 40% of U.S. gross sales in some cases (21,23). The Working Group found the transparency in list versus net pricing for these two insulin formulations helpful, but similar

data on all the other insulin products will be necessary for clarity on this aspect of pricing in the insulin supply chain.

This finding of greater increases in list prices than net prices raises the following questions. Who else has benefited or lost from the substantial increase in insulin list prices over the last decade? And why has the financial burden for people with diabetes who use insulin continued to increase—especially for those without insurance who may have to pay the full list price?

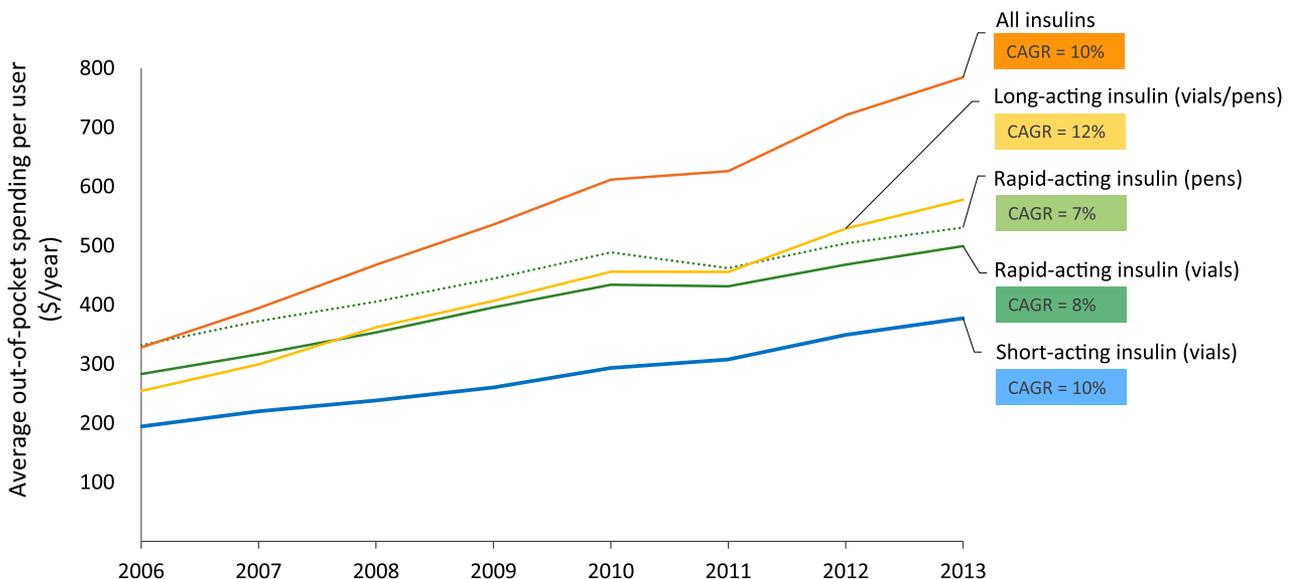


Figure 2—Average Medicare out-of-pocket spending for insulin, per user, by product category, 2006–2013. Source: USC Schaeffer Center analysis of Medicare Part D claims data.

Insulin Supply Chain: A Complex System

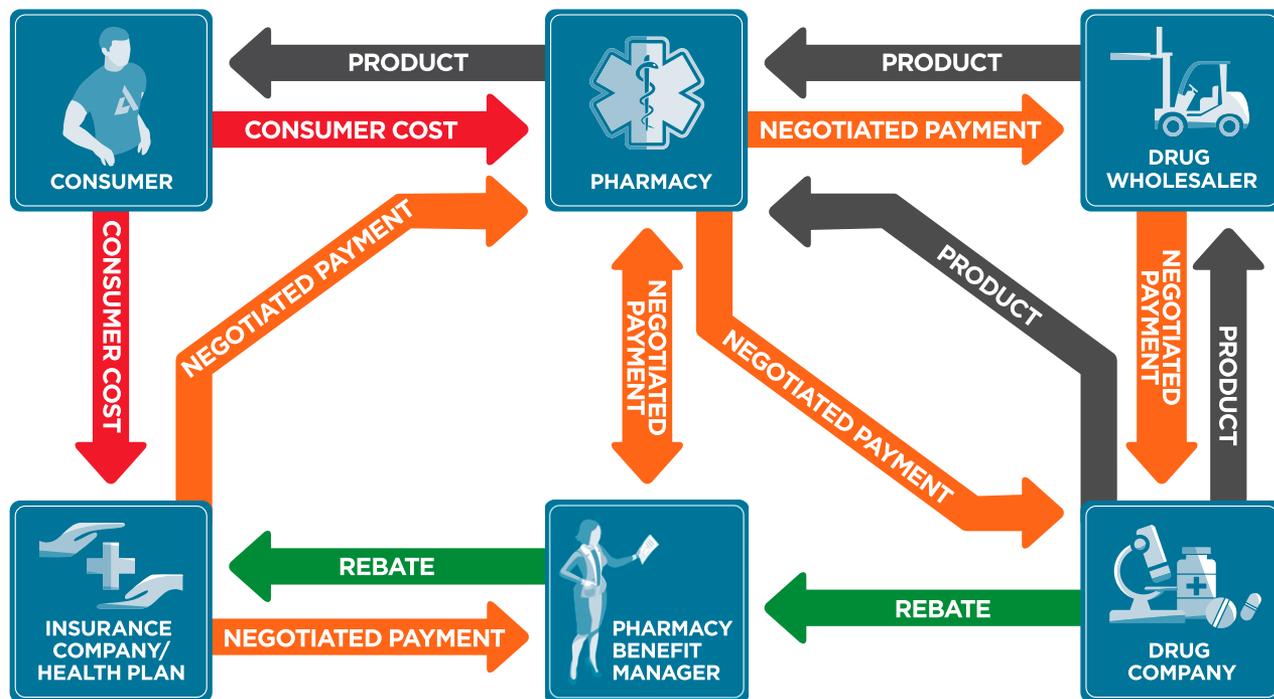


Figure 3—Schematic of insulin supply chain.

Role of Rebates and Discounts in the Pricing of Insulin

The widening gap between the net and list price of insulin in recent years appears to be the result of increasing rebates and discounts negotiated between stakeholders. Manufacturers negotiate with a PBM for discounts from the list price to have their medications placed on a lower cost-sharing tier and/or to avoid constraints on utilization on the PBM’s client formulary. In this process, manufacturers agree to fees and price concessions, typically paid to the PBM after health plan enrollees receive the manufacturer’s medication. These retroactive discounts or rebates are in addition to the fees paid to PBMs by the payers to provide the pharmacy benefit management services. The rate of increase in these rebates has accelerated to approach approximately half of the list price of insulin (21,23). PBMs also negotiate with pharmacies to determine how much participating pharmacies will be paid for medications dispensed to enrollees in the PBM client’s health plan.

Because PBMs design the formulary for their clients, some stakeholders believe PBMs have significant input into which

medications are on the formulary and at which tier, setting the parameters for patient access to and cost-sharing for insulins. Nationally, PBMs administer the prescription medication benefit for more than 266 million Americans, and the three major PBMs (CVS Caremark, Express Scripts, and OptumRx) manage about 70% of all prescription claims (13,24). Arguably, this gives PBMs considerable leverage in any rebate/discount negotiation with stakeholders.

Transparency and Flow of Dollars

A consistent observation made to the Working Group was the lack of transparency throughout the insulin supply chain. Many interviewed stakeholders recommended increased transparency from entities across the insulin supply chain. Manufacturers reported that without knowledge of the negotiations that take place between PBMs and health plans, they are at a disadvantage in determining pricing for their insulin products. Manufacturers state that the need to provide a higher rebate to achieve preferred formulary positioning impacts the list price of insulin. However, manufacturers do not know

where the dollars from increased rebates flow.

Health plans, pharmacists, and people with diabetes also called for increased transparency, including shedding a light on how the list price is set by the manufacturer. Health plans stated that while there is no requirement to report factors that determine increasing list prices, private and public payers are paying for the majority of the costs as list prices continue to rise. Payers would like more transparency in pharmacy acquisition prices and want more information on the therapeutic benefits of more expensive analog insulins. Pharmacists, patients, and providers also would like formulary decisions to be more transparent.

After research and stakeholder discussions, it is still unclear to the Working Group precisely how the dollars flow and how much each intermediary profits. In the vast majority of cases, discounts and rebates negotiated between PBMs and manufacturers and between PBMs and pharmacies, which affect the cost of insulin for people with diabetes, are confidential. Even PBM clients are not privy to many of these negotiations, nor do they know the net price obtained by the PBM for insulins.

Table 2—Glossary of drug pricing and health insurance terms

Term	Definition
Formulary	List of drugs covered under the health insurance plan. Often has tiers with increasing cost-sharing. Also includes utilization management requirements such as prior authorization, step therapy, or quantity limits.
List price	The price manufacturers set for their medications. Also called wholesale acquisition cost or launch price. This price is often the basis for rebates, discounts, and fees throughout the insulin supply chain.
Rebate	A discount paid after the patient has received the medication. Typically, manufacturers pay rebates to PBMs for prescriptions filled by the PBM's clients. Rebates negotiated between manufacturers and PBMs are often contingent on placement of the drug on the PBM's formulary.
Benefits	Health care items or services covered under a health insurance plan.
Coinsurance	Cost-sharing for covered benefits based on the percentage of the plan's cost (for example, 20%). For example, if the cost-sharing for a doctor's office visit is 20% coinsurance, the enrollee will pay 20% of the plan's cost for the visit.
Co-payment	Cost-sharing for covered benefits that is a flat dollar amount (\$20, for example).
Cost-sharing	The portion of the cost of benefits covered by insurance that the plan enrollee pays out of his/her pocket. This term generally includes deductibles, coinsurance, and co-payments, or similar charges, but it does not include premiums.
Deductible	The amount health plan enrollees pay for covered health care services before the insurance plan starts to pay. With a \$2,000 deductible, for example, the plan enrollee must pay the first \$2,000 of covered benefits before the insurance plan will pay for care.
Premium	The amount paid each month for a health insurance policy. Often health plan enrollees are responsible for paying a portion of the cost of the care they receive in addition to the monthly premium amount (see cost-sharing definition).
Prior authorization	Requires prescribers to obtain preapproval from the health plan before a medication will be covered. Often requires clinical information about the medical necessity of the medication.
Step therapy	Requires patients to try and fail on certain medications before the requested medication will be covered by the plan. Often requires clinical information about the patient's history with medications preferred by the health plan.

How rebates and discounts are distributed is also unclear. To lower patient costs for insulin, the rebates would need to be passed through to individuals with diabetes at the point of sale. Health plan representatives who met with the Working Group pointed out that this would minimize the incentive for PBMs to select for their formulary medications with higher rebates. On the other hand, representatives of the PBMs told the Working Group that when they offer part of the rebates to their customers, it is more common for their customers to use the rebates to lower overall premiums for

the plan than to use them to reduce patients' cost-sharing for insulin at the point of sale. The Working Group could not confirm these claims.

An additional argument presented to the Working Group was that the current system appears to transfer profits from one stakeholder to another. So, it is not clear who really benefits from the rebates and discounts provided to the various stakeholders.

Formulary Decisions and Incentives

Based on the Working Group's review of the insulin supply chain, it is clear that the

insulin manufacturers still control the list price of insulin, but a meaningful share of the negotiating power has shifted from manufacturers to the PBMs. PBMs attempt to keep medication costs down by moving market share between competing products, and their market power is directly related to their ability to provide exclusive formulary coverage for particular brands of medications.

The PBMs told the Working Group that formulary determinations are first and foremost based on clinical considerations. However, when the PBM's clinical experts determine that one type of medication is necessary on a given formulary tier but there is no clinical preference for one brand or formulation over another, the PBM will approach manufacturers to seek rebates in exchange for preferential formulary tiering. These types of negotiations help to determine whether a particular insulin will be available at all to insured individuals with diabetes under a given health plan, and on which cost-sharing tier an insulin formulation will be placed. Sometimes a PBM will exclude a medication from its national formulary if the PBM's net cost for the medication is higher than a competitive or similar product. In addition to formulary placement, PBMs determine which and how many medications on the formulary are subject to utilization management, such as prior authorization, step therapy, or quantity limits to steer prescribers and patients to medications with better safety or efficacy profiles and/or lower net costs. PBMs may also develop a list of preventive or essential medications, recommending the health plan cover medications on the list without patient cost-sharing. Some types or brands of insulins may be included on these lists, but it varies from PBM to PBM and health plan to health plan.

The Working Group was informed that the PBMs generally pass a portion of the rebates received from manufacturers back to the employer or health plan and that in some cases, less than 10% of the rebate is retained by the PBM. These statements were not confirmed by the Working Group. In addition to negotiating rebates with manufacturers, PBMs charge employers, plans, and pharmacies administrative fees for a variety of services. Specifically, health plans and employers pay PBMs a fee for utilization management, such as prior authorization requests for plan enrollees. To ensure the

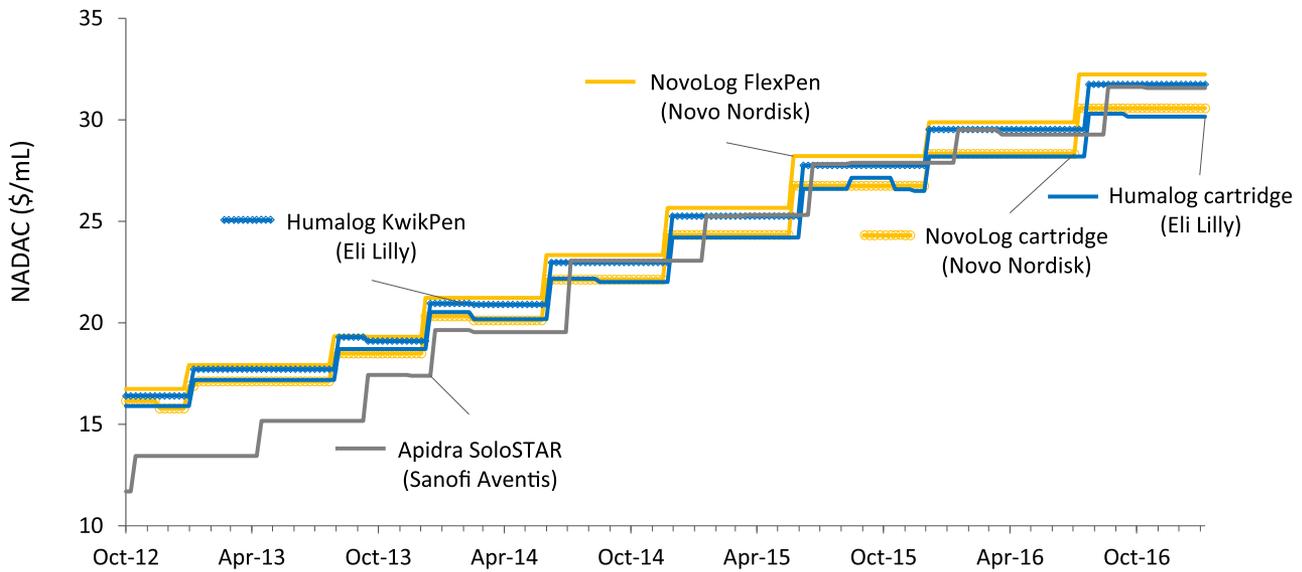


Figure 4—NADAC for five rapid-acting insulin pen or cartridge products, 2012–2016. Source: USC Schaeffer Center analysis of Centers for Medicare & Medicaid Services NADAC data.

PBM does not have a financial incentive tied to the number of medications requiring utilization management, some employers or plans outsource the processing of utilization management requests and approvals to another company.

The insulin manufacturers told the Working Group that they are not privy to the negotiations that take place between PBMs and health plans. Further, employers and health plans that work with PBMs noted that they are not privy to the net prices the PBM negotiates with manufacturers on their behalf. Instead, the PBM guarantees at the beginning

of the plan year the total dollar amount of rebates it will pay to the employer or health plan.

The health plans the Working Group interviewed reported that plans and PBMs have an incentive to select medications for their formularies that offer a higher rebate. It was also suggested to the Working Group that the need to offer higher rebates in order to achieve preferential formulary positioning from PBMs creates an incentive for manufacturers to raise the list price. In addition, wholesalers are paid for their distribution services as a percentage of the list price of the

medications they handle, even though their handling costs may not differ from one product to another. Thus, there are incentives throughout the insulin supply chain for high list prices.

In contrast, stakeholders have noted that the current structure of the Medicaid best price requirements limit the amount of discounts or rebates manufacturers provide in the commercial market. If a manufacturer agrees to provide specific rebates to the Medicaid program, all of its medications will be covered (with some exceptions) (25). The basic Medicaid rebate calculation defined in federal law is

Market Share of Insulin Categories

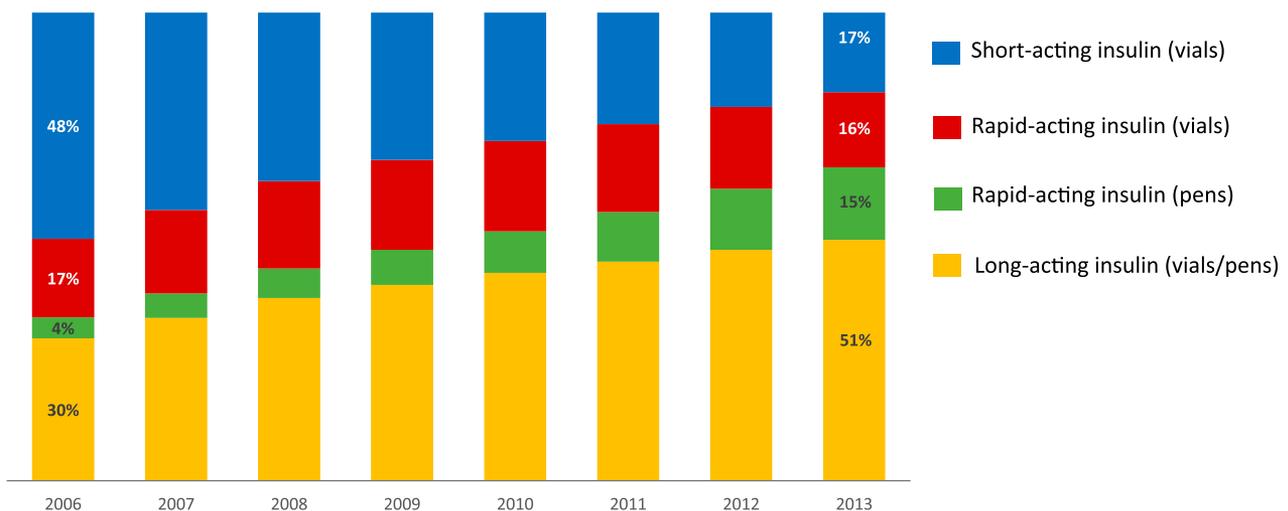


Figure 5—Medicare market share of four insulin product categories, 2006–2013. Source: USC Schaeffer Center analysis of Medicare Part D claims data.

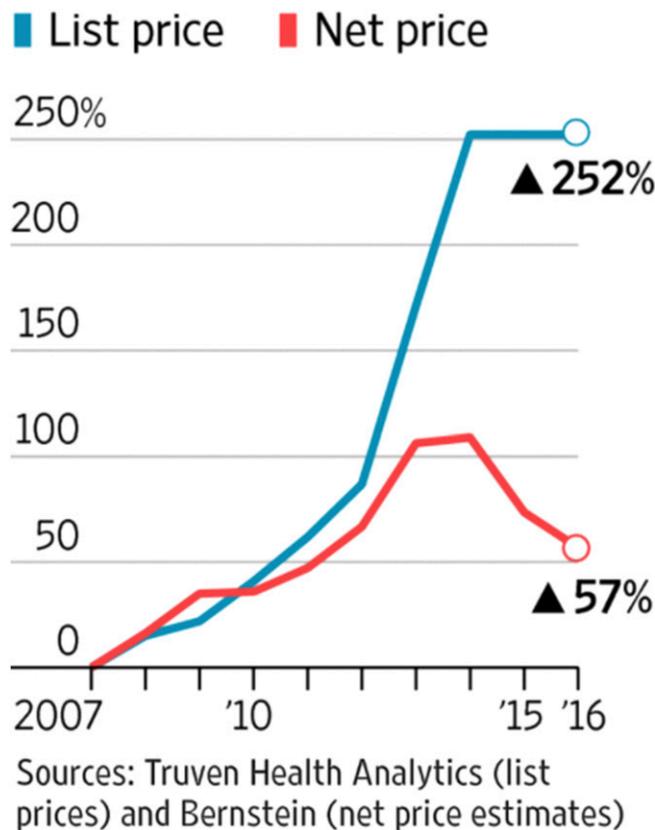


Figure 6—Report of changes in list and net prices for Lantus. Reprinted by permission of the *Wall Street Journal*, Copyright © 2016, Dow Jones & Company, Inc. All Rights Reserved Worldwide. License number 4321941207734 (20).

the larger of a standard percentage of the medication's average net price, or the average net price minus the "best price" the manufacturer provided to another payer. In addition, if a medication's average net price increased by more than inflation, the manufacturer must pay an additional rebate to Medicaid. If a manufacturer's rebate agreement with a non-Medicaid PBM or health plan results in a net price lower than the net price Medicaid would receive using the standard percentage rebate calculation, the manufacturer must use that rebate agreement amount to calculate the medication's rebate for all Medicaid enrollees. Stakeholders shared that the Medicaid best price requirement essentially sets a floor for negotiations with PBMs and health plans since manufacturers are hesitant to provide a very large rebate to non-Medicaid plans that will also have to be paid to Medicaid.

Formulary Decisions and Patient Health

It is clear that decisions made from negotiations between stakeholders that

affect formulary choice may not be in the best financial or medical interest of the patient. People with diabetes informed the Working Group that they have little choice in medication coverage, particularly for those enrolled in employer-sponsored plans. PBMs often exclude from formularies the insulins made by the manufacturer who offers the lowest rebate. As a result of these negotiations, rules for coverage differ from plan to plan and year to year, or even within the same plan year. When insulins are excluded from the formulary, moved to a different cost-sharing tier, or removed during the plan year (sometimes called "non-medical switching"), providers and people with diabetes can be inconvenienced and patients' health may be adversely affected. For example, patients with high cost-sharing may be less adherent to recommended medication dosing and administration, resulting in harm to their health (9,26–30). In addition, formulary exclusions and frequent formulary changes cause uncertainty, increase financial costs for patients, increase work required by

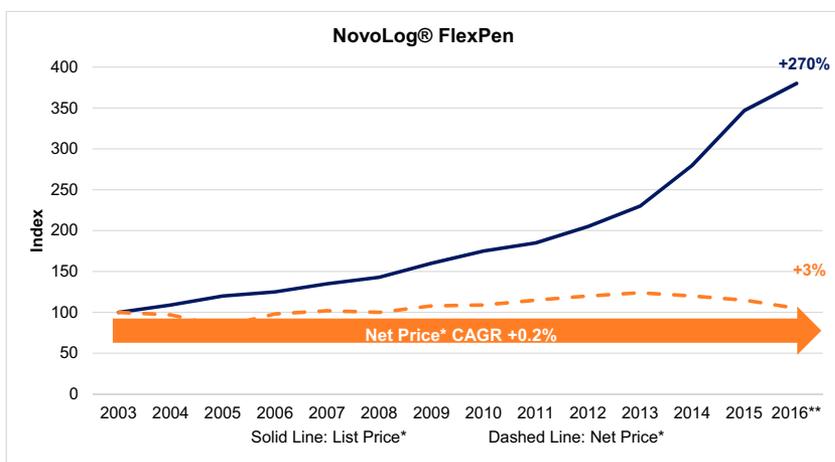
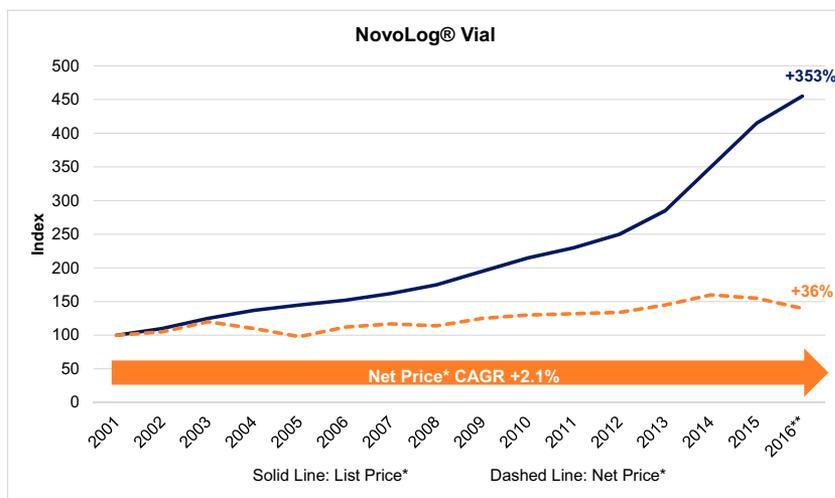
providers, and could be undermining patient health (31,32).

The Working Group noted concern about the increased burden on people with diabetes and reduced adherence to effective management strategies. The ADA was provided with numerous stories and complaints from constituents regarding this concern. One such example comes from Kathy Segó, who signed the ADA's Make Insulin Affordable petition and whose son, Hunter, has type 1 diabetes. Hunter requires approximately four vials of insulin per month to properly manage his diabetes, at a monthly out-of-pocket cost of \$1,948 until the family meets the health plan deductible. Knowing the impact of this cost on his family, Hunter, a college student in 2016, began skipping insulin doses, which can lead to serious and even deadly complications (33). Hunter Segó is one example of the many individuals who struggle to obtain the insulin they need to survive. When people are unable to afford their cost-sharing, many resort to rationing or skipping doses in order to make their insulin supply last longer, risking their health and their lives.

Formulary Decisions and Patient Financial Burden

Formulary exclusions and frequent formulary changes increase financial costs for patients. In addition, patients are bearing more of the cost of medications because of high-deductible plans, increased use of coinsurance, growing number of formulary tiers, and fewer medications covered per tier (34–36). Since negotiated discounts or rebates are usually not passed directly to people with diabetes, their financial obligations for purchasing insulin are often based on the list price. Clearly, this varies depending on the type of insurance the person has and the type of insulin purchased (see below) but specifically impacts those with a high deductible, those who have to pay coinsurance, or those who are in the Medicare Part D coverage gap. People without insurance are often required to pay list price for insulins.

Health plans noted that out-of-pocket insulin costs could be lower for some people with diabetes if health savings account-eligible high-deductible health plans could exempt insulin from the deductible. Manufacturers agree that exempting insulin from the plan's deductible is a critical step in lowering



* Adjusted for inflation
 ** 2016 reflects September YTD

Figure 7—Reported changes in NovoLog list and net prices. Adapted from Hobbs (22). YTD, year to date.

out-of-pocket insulin costs. Until there is a systematic plan that addresses a change in benefit design to lower out-of-pocket insulin costs for people with diabetes, human insulin may be a valid alternative to more expensive analog insulins for some patients (19,37). In this regard, there would need to be significant education of people with diabetes and health care providers on the appropriate use of human and analog insulins, and careful selection of people who may benefit from analog insulin.

While data on average patient out-of-pocket spending for insulin are not widely available, one study found that patient out-of-pocket expenses for insulin doubled over a 10-year period. Using a private insurance administrative claims database for all insulin prescriptions filled at least once, the median out-of-pocket cost to patients went from \$19 per vial of insulin

in 2000 to \$36 per vial of insulin in 2010 (38). In addition, Working Group members with the USC Schaeffer Center found that average Medicare Part D beneficiary out-of-pocket costs for all insulin types doubled between 2006 and 2013, from \$27 per month to \$65 per month. However, it should be noted that these results are average costs and do not capture fluctuations in cost-sharing that patients experience throughout the year (such as during the deductible phase), and they do not capture patient costs when their insulin is not on their health plan’s formulary. In addition, these studies do not include people who are uninsured. More information is needed to better quantify insulin costs for people with diabetes.

Biosimilar Insulins

Another issue raised by stakeholders was the lack of competition in the insulin

manufacturing sector and whether introduction of biosimilar insulins will lead to lower prices. The Working Group spoke with manufacturers who want to introduce a biosimilar insulin into the U.S. market who said the increased regulatory burden associated with the development, as well as U.S. Food and Drug Administration (FDA) approval, of biosimilars is deterring manufacturers from producing biosimilar insulins.

Insulin is a biologic medication made from living cells and far more complex to manufacture than small-molecule medications, which are made by combining different chemical ingredients (37). Before 2010, a regulatory path was not in place to allow for the development of biosimilar medications, as there has been for decades for small-molecule drugs. If a biologic medication no longer had patent protection, another company could manufacture its own version. In order to obtain FDA approval, the company would not be able to rely exclusively on safety and efficacy data from the original manufacturer’s research, as is the case with small-molecule generic drugs. To address this problem, Congress enacted the Biologics Price Competition and Innovation Act (BPCIA) as part of the Affordable Care Act in 2010. Under the BPCIA, companies developing alternatives to biologic medications (called “biosimilar” medications) must prove that their medication is “highly similar” to the original biologic and that there are no “clinically meaningful” differences from the original biologic (39). According to the FDA, “[t]his generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients” (39). The manufacturer of a biosimilar medication can submit additional data to the FDA to be deemed “interchangeable” with the original biologic medication. These data must show that the biosimilar is “expected to produce the same clinical result” as the original biologic medication and that “switching between the proposed interchangeable product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching” (39). Depending on state laws, if a biosimilar is deemed interchangeable by the FDA, a pharmacist

may fill a prescription written for the original version with the biosimilar version, much like they currently do for other types of medications with so-called generic medications. Prior to passage of BPCIA, alternative versions of original biologic medications were referred to as “follow-on biologics.” As of this writing, there are no biosimilar insulins on the market, but to date, three follow-on biologic human insulin analogs have been approved by the FDA (40–42). Discussion with stakeholders revealed differing opinions on how much biosimilars would lower the price of insulin. Currently, the only follow-on biologic insulin on the market was introduced with a list price approximately 15% less than the original version (43,44).

Patient Assistance Programs

The Working Group also reviewed information regarding the value of pharmaceutical patient assistance programs as a solution to help people with diabetes afford their insulin. However, it is beyond the scope of this current report to provide details, benefits, and value of all the available programs. People with diabetes will need to discuss this option with their physician and health plan (if applicable) to determine what, if any, benefit these patient assistance programs could provide to them individually. Although the Working Group did not address this option in detail, it was not deemed to be a long-term or comprehensive answer to the rising cost of insulin for the vast majority of people with diabetes.

Continued Innovation for Diabetes Therapies

One issue of importance to people with diabetes is the need for continued innovation in diabetes management and prevention. New technologies, pharmacotherapies, and strategies continue to be needed to prevent the disease, to diminish adverse side effects like hypoglycemia and weight gain, to promote adherence, and to prevent complications. Such innovation would generate substantial value to people with diabetes both now and in the future (45). One of the best ways to encourage innovation is to better link reimbursement to value (46). With value-based insurance design, the amount of cost-sharing for a medical treatment or service is set according to its value rather than its cost. Value-based insurance design provides coverage for evidence-based

treatments that improve health by lowering or eliminating patient cost-sharing. Efforts to encourage value-based insurance design, wherein cost-sharing is linked to population health outcomes, may improve adherence and lower patient financial burden (47).

PATIENT COST-SHARING: INSURANCE TYPE MATTERS

There are many factors that impact how much people with diabetes pay for insulin, including the amount and type of insulin and delivery system they use. Another major factor is whether the person has insurance and, if so, what type. Whether the person's health insurance plan or its PBM has negotiated rebates with insulin manufacturers also impacts the cost to people with diabetes. In the U.S., there are many different types of health insurance.

Almost half of Americans have health insurance provided through their employer or a family member's employer (48). Employer coverage is generally regulated by federal law, but employers have leeway in determining which benefits to cover and how much to charge enrollees. Medicaid, a health insurance program for low-income individuals, covers more than 68 million Americans (20% of the population) (49). Each state manages and administers the Medicaid programs for their residents; however, they are required to follow federal guidelines, which include limits to the out-of-pocket costs to beneficiaries. Medicare, the federal health care program for Americans over age 65 years, people with disabilities under age 65 years, and people with end-stage renal disease, covers about 14% of Americans (48). Federal rules dictate the benefits covered under Medicare and how much enrollees pay, including Medicare Part D, the program's prescription drug benefit. Approximately 7% of Americans purchase insurance on their own directly from an insurer or through state health insurance exchanges (called individual market insurance) (48). Federal and state laws dictate which benefits are covered in individual market insurance plans as well as enrollees' annual spending on care. Roughly 2% of Americans are covered under other government programs like military or Veterans Administration coverage, and 9% have no health insurance coverage (48).

To further understand how having insurance and insurance type impact

an individual's insulin costs, the Working Group provides several case scenarios, using an insulin with a list price of \$480 per vial as an example. (See Table 2 for a glossary of health insurance terms.)

The Uninsured Person

An uninsured person with diabetes will pay the full \$480 for the insulin, regardless of any rebates offered by the manufacturer. He or she could directly receive payment assistance from the manufacturer or a pharmaceutical patient assistance program, but eligibility for those programs varies based on the individual's income, state, and medication.

The Person With Commercial Insurance

A person with diabetes who has commercial insurance may pay less than the \$480 list price, but the amount paid depends upon the person's insurance contract. If the person is required to pay an annual deductible that has not yet been reached (for example, if this is the patient's first expenditure in the new year), the person with diabetes will pay the full \$480 list price for the insulin until the person spends enough to meet the deductible. Once the deductible is met, if the person's insurance contract specifies a fixed co-payment, he or she will pay a flat amount, for example, \$50 per prescription, even if the person with diabetes uses multiple vials of the same insulin product per month. However, if the insurance plan requires coinsurance, the person with diabetes will pay a percentage, for example, 20% of the cost of each vial of insulin. Importantly, the coinsurance is based on the list price of the insulin, not the net cost after any rebates or discounts negotiated by the PBM. In this case, the out-of-pocket cost by the person with diabetes for the insulin is \$96 per vial (20% of the \$480 list price).

The Person With Medicare

A Medicare beneficiary with Part D prescription drug coverage could face an array of different benefit designs and out-of-pocket expenditures, depending on the type of plan in which the person with diabetes enrolls, where the prescription is filled, and the phase of coverage. For example, in 2018 under the standard benefit (see Fig. 8 for overview of Medicare standard benefit structure) (50), beneficiaries face a deductible of \$405 and a coinsurance rate of 25%. Thus,

on the first fill, the first \$405 is paid out-of-pocket, plus 25% of the remaining cost of the drug (25% of \$75) for a total of \$423.75. The 25% coinsurance rate applies to additional fills until the person reaches the plan’s initial coverage limit (\$3,750 in most plans in 2018) and enters the coverage gap, commonly known as the “donut hole.” Historically, beneficiaries paid 100% of the Part D plan’s brand-name drug costs in the donut hole, but the Affordable Care Act has reduced some of that burden. In 2018, beneficiaries pay 35% of the Part D plan’s brand-name drug costs (or \$168 per prescription in this example) in the coverage gap until their annual out-of-pocket expense reaches \$5,000. After that, beneficiaries pay 5% of a drug’s list price (\$24) for the remainder of the calendar year. Beginning in 2019, beneficiaries in the standard plan will pay 25% (or \$120 per vial in this example) of the cost of their brand-name prescription drugs once they meet their deductible until they reach the out-of-pocket maximum.

The Person With Medicaid

For a person with diabetes with Medicaid drug coverage, co-payments are generally limited to a nominal amount (\$1–\$5) for drugs on the preferred drug list. Medicaid drug coverage varies from state to state, however, all states include some insulins on their preferred drug lists. If a Medicaid enrollee needs a medication not on the state’s preferred drug list, the prescriber can

submit a request on his or her behalf stating the medical need for the drug.

CONCLUSIONS AND RECOMMENDATIONS

After discussions with more than 20 stakeholders in the insulin supply chain, the Working Group remains concerned by the complexity of the system. As outlined, there are numerous stakeholders involved in the delivery of insulin, with multiple opaque transactions between and among these stakeholders (Fig. 3). It was also the consensus of the Working Group that incentives throughout the insulin supply chain facilitate and may even promote high list prices. The following sections provide the conclusions and recommendations of the Working Group.

Conclusions

- List prices of insulin have risen precipitously in recent years. Between 2002 and 2013, the average price of insulin nearly tripled.
- The current pricing and rebate system encourages high list prices.
 - As list prices increase, the profits of the intermediaries in the insulin supply chain (wholesalers, PBMs, pharmacies) increase since each may receive a rebate, discount, or fee calculated as a percentage of the list price.
- There is a lack of transparency throughout the insulin supply chain. It is unclear precisely how the dollars flow and how much each intermediary profits.

- Manufacturers are rarely paid the list price for insulin. The so-called net price—which reflects what the manufacturers receive—is much lower; however, in most cases, the data are not available.
- In the vast majority of cases, discounts and rebates negotiated between PBMs and manufacturers and between PBMs and pharmacies, which affect the cost of insulin for the person with diabetes, are confidential.
 - PBM clients (often large employers in most cases) are not privy to these negotiations, nor do they know the net price obtained by the PBM for insulins.
- Formulary considerations and decisions are not transparent.
- PBMs have substantial market power.
 - PBMs’ primary customers are health plans and employers, not patients.
 - PBMs negotiate rebates from manufacturers using formulary placement as leverage.
 - PBMs often exclude from formularies the insulins made by the manufacturer who offers the lowest rebate.
 - As a result of negotiation, rules for coverage differ from plan to plan and year to year, or even within the same plan year.
 - When insulins are excluded from the formulary, moved to a different cost-sharing tier, or removed during the plan year, it places a burden on people with diabetes and providers and may have a negative health impact.
 - PBMs receive administrative fees from their clients (health insurance plans) for utilization management services (prior authorization, etc.). Often it is the PBM that determines which and how many drugs on the formulary are subject to utilization management.
- People with diabetes are financially harmed by high list prices and high out-of-pocket costs.
 - Regardless of the negotiated net price, the cost of insulin for people with diabetes is greatly influenced by the list price for insulins.
 - Out-of-pocket costs vary depending upon the type of health insurance each individual has and the type of insulin prescribed. The costs can be

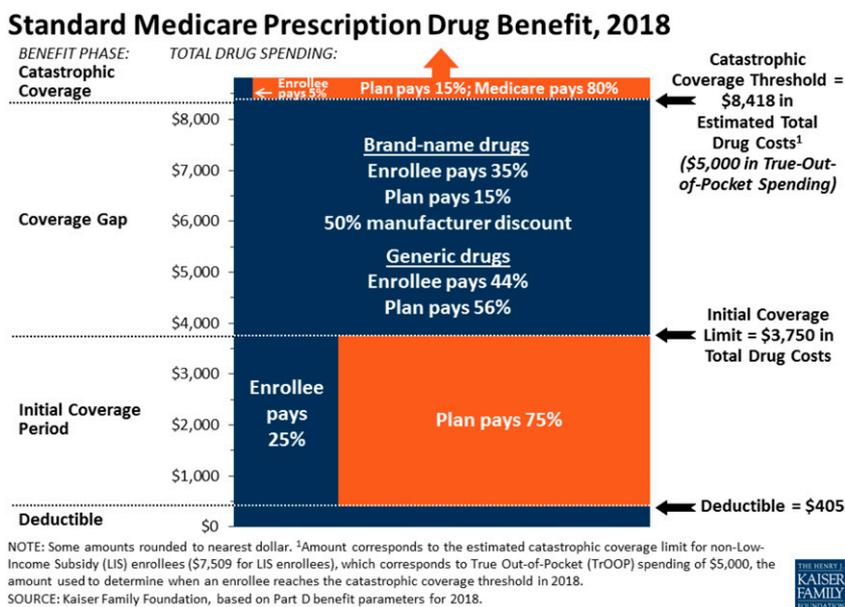


Figure 8—Standard Medicare prescription drug benefit, 2018 (50).

significantly higher for people who are uninsured, who have an insurance plan with a high deductible, or who are in the Medicare Part D donut hole.

- Manufacturer rebates often are not directly passed on to people with diabetes.
- Patients' medical care can be adversely affected by formulary decisions.
 - People with high cost-sharing are less adherent to recommended dosing, which results in short- and long-term harm to their health.
 - Formulary exclusions and frequent formulary changes cause uncertainty, increase financial costs for people with diabetes, and could have serious negative consequences on the health of people with diabetes.
- The regulatory framework for development and approval of biosimilar insulins is burdensome for manufacturers.
 - There are not enough biosimilar insulins on the market.
 - Prices for biosimilar insulins are not likely to be lower unless there are multiple biosimilars that can be substituted for the brand-name analog insulin, rather than only one.
- Prescribing patterns have favored newer, more expensive insulins.
 - Newer insulins, including analogs, are more expensive than older insulins including human insulins.
 - Human insulin may be an appropriate alternative to more expensive analog insulins for some people with diabetes.

Recommendations

- Providers, pharmacies, and health plans should discuss the cost of insulin preparations with people with diabetes to help understand the advantages, disadvantages, and financial implications of potential insulin preparations.
- Providers should prescribe the lowest-priced insulin required to effectively and safely achieve treatment goals.
 - This may include using human insulin in appropriately selected patients.
 - Providers should be aware of the rising cost of insulin preparations and how this negatively impacts adherence to the clinical treatment by people with diabetes.
 - Providers should be trained to appropriately prescribe all forms of insulin preparations based on evidence-based medicine.

- Cost-sharing for insured people with diabetes should be based on the lowest price available.
- Uninsured people with diabetes should have access to high-quality, low-cost insulins.
- Researchers should study the comparative effectiveness and cost-effectiveness of the various insulins.
- List price for insulins should more closely reflect net price, and rebates based on list price should be minimized. The current payment system should rely less on rebates, discounts, and fees based on list price.
- Health plans should ensure that people with diabetes can access their insulin without undue administrative burden or excessive cost.
 - Payers, insurers, manufacturers, and PBMs should design pharmacy formularies that include a full range of insulin preparations, including human insulin and insulin analogs, in the lowest cost-sharing tier.
- PBMs and payers should use rebates to lower costs for insulin at the point of sale for people with diabetes.
- There needs to be more transparency throughout the insulin supply chain.
- Payers, insurers, manufacturers, PBMs, and people with diabetes should encourage innovation in the development of more effective insulin preparations.
- The FDA should continue to streamline the process to bring biosimilar insulins to market.
- Organizations such as the ADA should do the following:
 - Advocate for access to affordable and evidence-based insulin preparations for all people with diabetes.
 - Ensure that health providers receive ongoing medical education on how to prescribe all insulin preparations, including human insulins, based on scientific and medical evidence.
 - Develop and regularly update clinical guidelines or standards of care based on scientific evidence for prescribing all forms of insulins and make these guidelines easily available to health care providers.
 - Make information about the advantages, disadvantages, and financial implications of all insulin preparations easily available to people with diabetes.

pricing. D.G. is also a consultant to Precision Health Economics and owns equity in its parent company, Precision Medicine Group. W.H.H. serves as Chair, Data Safety Monitoring Board, Merck Sharp & Dohme, and as a consultant for Janssen Scientific Affairs, LLC. K.V.N. received research support from the ADA to examine trends in insulin pricing and has consulted for Precision Health Economics. A.C.P. has served on the Board of Directors for the ADA. S.I.T. has served as a consultant for Ionis Pharmaceuticals; has received research support provided to University of Maryland School of Medicine by Regeneron Pharmaceuticals; and owns stock in Celgene, Amgen, and Abbott Laboratories. A.L.Y. served on the Board of Directors for the ADA and owns stock in Amgen and Bristol-Myers Squibb through a broker-managed account. No other potential conflicts of interest relevant to this article were reported.

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