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20TH ANNIVERSARY 1995-2015

ADA 2015 COVERAGE INCLUDED

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Evidence-Based Diabetes Management

TECHNOLOGY SPECIAL ISSUE

Policy Commentary

Medicare's Failure to Cover CGM at Odds With Other Health, Research Agencies

SENATOR SUSAN M. COLLINS

As the founder and co-chair of the Senate Diabetes Caucus, I have learned a lot about this disease and the difficulties and heartbreak it causes for so many American families as they await a cure. Diabetes is a lifelong condition that affects people of every age, race, and nationality. It is the leading cause of kidney failure, blindness in adults, and amputations not related to injury.

The human and economic toll of diabetes is devastating. Nearly 30 million Americans have diabetes and 86 million more have prediabetes.[1] If present trends continue, 1 in 3 adults—1 in 2 among minority populations—will have diabetes in 2050.[2] The annual cost of diagnosed and undiagnosed diabetes, gestational diabetes, and prediabetes skyrocketed to $322 billion in 2012.[3] This is unacceptable and unsustainable.

The lives of people living with, and at risk for, diabetes are better because of National Institutes of Health (NIH) research and CDC prevention activities. Due to the Special Diabetes Program, which was renewed as part of the Medicare Access and CHIP Reauthorization Act of 2015, and increased investments in diabetes research, we have seen some encouraging breakthroughs and are on the threshold of a number of important new discoveries. We've made progress, but much more must be done.

This is particularly true for the estimated 1.2 million Americans living

(continued on page SP378)

mHealth Research

Can mHealth Revolutionize Evidence-Based Practice in Diabetes Care?

BETSY J. LAHUE, MPH; KATHLEEN E. HUGHES, MBA; BETHANY J. HILLS, JD, MPH; SOPHIA S. LI, MPH; AND JO CAROL HIATT, MD, MBA, FACS

ABSTRACT

Mobile health (mHealth) is a branch of the digital health market that specifically uses mobile technologies. Data from mHealth can inform, assess, anticipate, and aid in interventions while monitoring and coordinating patient health status and care. The vast majority of American adults own cell phones, and innovators in mHealth have been developing platform-agnostic, validated instruments for patient-centric real-time mobile data capture. With high technology access in place and mHealth tools emerging, the potential exists to revolutionize the way health services are delivered and experienced. To date, mHealth applications and devices have been used within the areas of epidemiology, general public health, and clinical trials. As mHealth can collect and analyze multifaceted data in near real time, these technologies may dramatically alter the speed with which evidence-based practice can be customized toward achieving the triple aim of high-quality care, improved outcomes, and lower costs. Challenges to achieving this revolution are seen in the complexities of integrating new technologies into the existing health service record systems, the needs of multiple and diverse healthcare stakeholders, and the research burden of

(continued on page SP379)

Artificial Pancreas

Multiple Teams Move to Testing Phase of the Artificial Pancreas

ANDREW SMITH

Devices that substantially automate the treatment of type 1 diabetes mellitus (T1DM) are still years away from the market, but Aaron Kowalski, PhD, says that several academic and commercial projects have reached a key inflection point—a shift from device development to the sort of large-scale testing that must precede commercialization.

"When we started supporting this idea, there were a few insulin pumps on the market, some experimental glucose monitors, and a small number of secretive efforts to combine the 2 technologies with intelligent software," said Kowalski, chief mission officer and vice president for research at JDRF.

"We now have nearly a dozen major academic research teams, half a dozen device makers, and many more smaller organizations doing serious research and development. A large number of small trials have validated various approaches, and a handful of organizations are ready to launch pivotal trials. Patients won't be able to buy an artificial pancreas this year, but they may well be able to buy the first artificial pancreas system that begins to dose insulin in 2017."

What constitutes an artificial pancreas? The goal is a system that maintains blood glucose levels and insulin delivery without the need for the user to make adjustments for meals or exercise, according to summary from the JDRF. From the start of JDRF's funding for the project, it was anticipated that progress would come in steps, with the "closed loop" system coming after 5

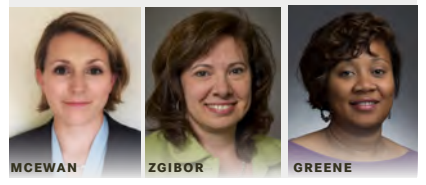
(continued on page SP382)

SPIROMETRY REQUIRED SP366

Sanofi, which is marketing the new inhaled insulin, Afrezza (shown above), is taking steps to educate physicians about FDA spirometry requirements before the drug is prescribed.

Also in this issue...

ADA 2015



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SP372

A vintage travel kit, used by patients to check their blood sugar levels, was part of the anniversary display at the 75th Scientific Sessions of the American Diabetes Association, held in Boston June 5-9, 2015. As products and studies from the meeting showed, technology in diabetes care has come a long way. See coverage, SP372-SP377.

Photo courtesy of American Diabetes Association

EDITOR IN CHIEF

Joslin Diabetes Center

ROBERT A. GABBAY, MD, PhD

Editor in chief **Robert A. Gabbay, MD, PhD,** took part in a key symposium on new payment models in diabetes care during the 75th Scientific Sessions of the American Diabetes Association in Boston. See our coverage, **SP372**.

Tech Advances in Diabetes Care Show Entrepreneurial Spirit


MIKE HENNESSY, SR

Almost a decade ago, continuous glucose monitoring (CGM) technology offered a leap forward for patients with type 1 diabetes mellitus (T1DM) and some with type 2 disease (T2DM). The ability to watch patterns in one's blood glucose levels over the course of a day, instead of just at intervals accompanied by painful finger sticks, meant not only improved glycemic control but also more freedom to take part in sports or travel without fear of costly hypoglycemic episodes. Today, as we learn in our cover story, those with T1DM can look forward to the long-awaited arrival of the "artificial pancreas" before the end of the decade. With support from JDRF, academic researchers, major medical device companies, and small entrepreneurs are racing to be the first to bring this technology to patients. Trends in diabetes mean that more with T2DM will need this technology. It appears patients will have choices, which should help tailor products to individual needs and keep prices in check. Better still, device companies are teaming up with consumer electronics manufacturers to create products that are discreet, highly portable, and synchronized with Cloud-based systems to securely store patient data. These market-driven solutions promise better health and quality of life for diabetes patients, and they may also cut healthcare costs by preventing trips to the emergency department. Yet with these advances on the horizon, Medicare patients with T1DM still await coverage for CGM technology, which is now covered by most commercial insurers. A commentary from the US Senate's leading voice for diabetes care, Senator Susan Collins, R-Maine, asks why CMS' reimbursement policy for CGM is outdated and out of step with the research and health agendas at FDA and the National Institutes of Health. This issue also features updates from the Scientific Sessions of the American Diabetes Association (ADA), which always showcase the latest advances in both the tech and therapeutic areas. Additional coverage from ADA is featured in our special recap issue. You will want to read both to learn all that is happening to treat this devastating disease.

As always, we appreciate your readership. Please look for updates on our live meetings and our conference coverage at www.ajmc.com.

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in diabetes management.

Evidence-Based Diabetes Management

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THE PAN CHALLENGE:
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In collaboration with
The American Journal of Managed Care

- How does federal policy regarding healthcare cost-sharing (eg, deductibles, co-pays, coinsurance, and out-of-pocket limits) affect the ability of individuals with chronic and rare diseases to have affordable access to critical therapies?

- What policy solutions are likely to improve access to critical therapies for individuals with chronic or rare diseases?

Eligibility

The PAN Challenge is open to individuals and teams of up to 4 individuals who are 18 years of age or older at the time of entry. **Entrants must be residents of the United States and sponsored by (a) a university or college or (b) a health system**. Entrants may submit 1 paper that addresses the questions above for 1 of the following patient populations:

a) Medicare population, including individuals covered by original Medicare and by Medicare Advantage.

b) Insured population, including individuals with employer-sponsored insurance (ESI) or coverage by a Qualified Health Plan (QHP) offered on an Exchange or Marketplace.

How to Enter

- **Entrants are required to read the rules and judging criteria upon registering for the Challenge.**
- Entrants can **register** and submit abstracts from June 1 to September 15, 2015.
- Selected semifinalists will be asked to submit papers (2500 to 5000 words) between October 1 and December 15, 2015.
- Two winning entries (1 entrant per population category) and 2 runners-up (1 entrant per population category) will be chosen from the semifinalists on January 15, 2016.

Prizes

- Winners' sponsor organizations (1 from the Medicare population category and 1 from the insured population category) will each receive $10,000. Second-place winners' sponsor organizations (1 from the Medicare population category and 1 from the insured population category) will each receive $5000.
- First-place winners will be given an opportunity to attend and present (1 member per winning entrant; expenses paid) at the Cost-Sharing Roundtable to be held in Washington, DC, in mid-February 2016 (date to be determined).
- Papers of first-place winners will be published in a future print and online supplemental edition of *The American Journal of Managed Care*.

For more information, contact Arny Niles at **challenge@panfoundation.org** or **(202) 661-8073** or visit **http://www.panfoundation.org/challenge**.

A Digital Solution to Your Regulatory Problem

How Digital Therapeutics Can Help Payers Comply With Upcoming Government Guidance—and Deliver Outcomes

Sean Duffy

SEAN DUFFY

Mr Duffy is the CEO of Omada Health.

Across the healthcare system and aided by provisions of the Affordable Care Act, programs incentivizing preventive treatment options are becoming increasingly widespread, and in some cases popular.

The last 5 years have seen monumental—and rapid—shifts in the approach to healthcare delivery. A system that for decades measured success by the number of tests, procedures, and general activity is now shifting its focus to value, prevention, and above all, *outcomes*.

This shift couldn't come at a more critical moment for Americans' health. In 2009, the CDC called chronic diseases like obesity, diabetes, and heart disease "the public health challenge of the 21st century." The agency reported that the corrosive effects of sedentary lifestyles and poor diets will cause 75% of Americans to develop preventable chronic conditions that lead to shorter, less healthy lives. Currently, 29 million Americans have type 2 diabetes mellitus (T2DM), and the CDC estimates that, if current trends continue, 40% of all Americans will be diagnosed with the disease in their lifetimes. Even more alarming, 87 million Americans already have prediabetes—the clinical precursor to T2DM. Between 1990 and 2013, the prevalence of diabetes in the United States rose by 71%.[1]

But diabetes is just one of several obesity-related chronic conditions poised to wreak havoc on the American healthcare system in the coming years. While the percentage of overweight and obese Americans (those with a body mass index over 30 kg/m^2) is no longer rising at a truly drastic rate (from 1998 to 2006 the number increased by 37%), 60% of all Americans are now considered overweight or obese—with the percentage of those considered "obese" continuing to rise (**FIGURE 1**).

Obesity-related conditions have become some of the most pervasive and deadly diseases in the country. In addition to the clinical impact and toll in individual suffering, addressing the obesity epidemic has become an economic imperative. Direct medical costs for obese Americans are nearly $2000 higher than those for persons with normal weight—and that's not including the indirect costs of other medical conditions caused by obesity.

For individuals with chronic conditions like diabetes, the numbers are even more staggering. A recent study by the Health Cost Institute estimated that a patient with diabetes costs their health plan and employer, on average, about $10,000 more per year.[2] As the cost burden continues to shift toward payers and patients, organizations are wrestling with how to deal with this growing problem.

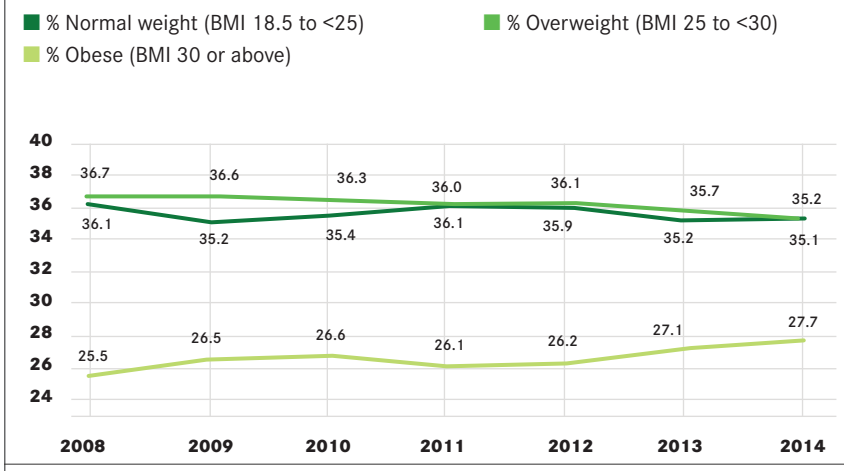
FROM PILLS TO PREVENTION

Policy makers, payers, and providers all agree something has to change. There is a growing consensus that preventive behavioral and lifestyle changes—not pills or procedures—are the most effective solutions. However, these behavioral interventions—our first line of defense against the progression of chronic disease—have to date been offered only in person. Unfortunately, such face-to-face programs have had difficulty with geographic coverage—making it difficult for potential patients to access providers to administer the program—and with scaling quickly enough to meet the needs of the large populations who require behavioral interventions.

Across the healthcare system and aided by provisions of the Affordable Care Act, programs incentivizing preventive treatment options are becoming increasingly widespread, and in some cases popular. But 2 recent government actions in particular offer both a challenge, and hope, for US health plans and employers.

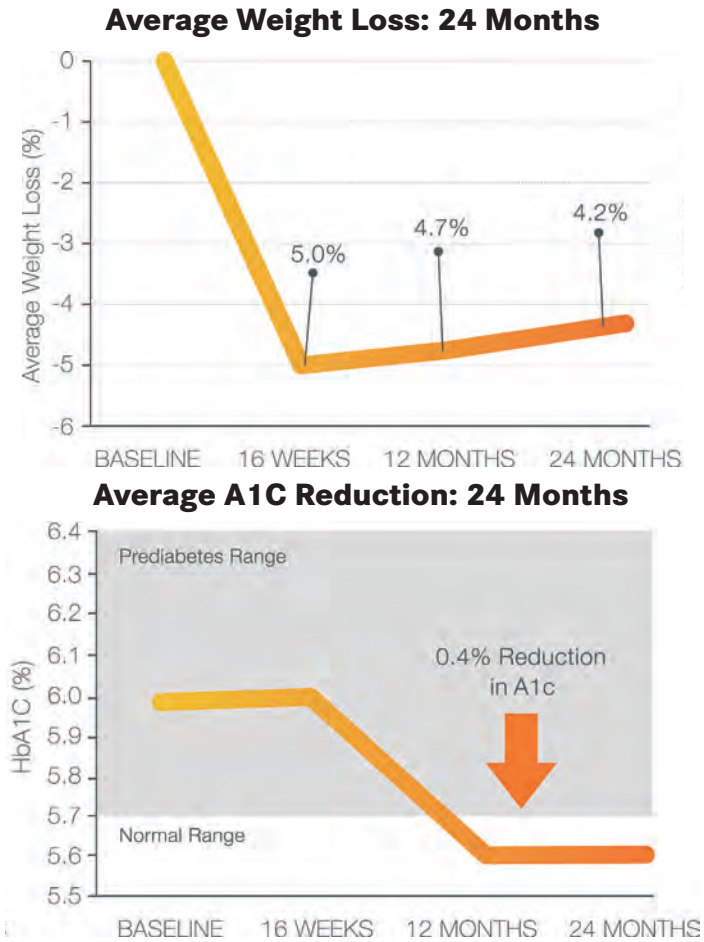
Last August, the US Preventive Services Task Force (USPSTF), an indepen-

FIGURE 1. American Adults, by Weight Category



BMI indicates body mass index. Weight category as determined by BMI.
SOURCE: Levy J. U.S. Obesity Rate Inches Up to 27.7% in 2014. Gallup website. http://www.gallup.com/poll/181271/obesity-rate-inches-2014.aspx. Published January 26, 2015. Accessed February 2015.

FIGURE 2. Digital Therapeutics: Reviewing the Evidence



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dent body of primary care physicians, scientists, and medical professionals, provided guidance for commercial health plans. The USPSTF Task Force issued a final recommendation that doctors should provide or refer obese individuals, or overweight individuals with at least 1 cardiovascular risk factor, to intense behavioral counseling programs aimed at promoting a healthy diet and increasing physical activity. To underscore its importance, the USPSTF gave this recommendation a "B" rating—meaning that for any commercial health plan starting August 2015 or later, behavioral counseling must be covered as a preventive health benefit. Plans starting January 1, 2016, or later must begin complying with this recommendation within the following year.

In making this recommendation, the USPSTF relied heavily on a landmark clinical trial published almost 2 decades ago. The study analyzed the Diabetes Prevention Program (DPP), which tested how diet and activity changes could delay the onset of diabetes for those at high risk for the disease. It found that lifestyle interventions—not medication or a placebo—were the most effective treatment for prediabetes, lowering the incidence of the disease by 58%. In follow-up analyses of DPP data, participants in the lifestyle intervention group saw an improvement in high blood pressure, triglycerides, HDL cholesterol, and other risk factors for heart disease. In its August recommendation, the USPSTF specifically cited the DPP as a potential solution for those individuals needing intensive behavioral counseling.

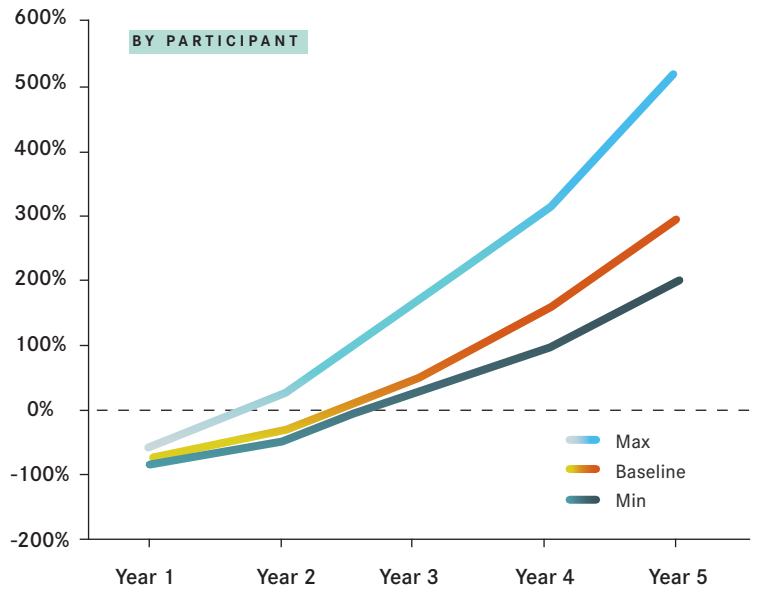
Based on the results of this study, in 2010 Congress authorized the CDC to create the Diabetes Prevention Recognition Program (DPRP) and to give programs that met the DPRP's evidence-based standards official recognition. But, until recently, DPRP programs were only offered in face-to-face settings—making them expensive to set up, and less accessible to large population segments.

DIGITAL MEETS DEMANDS

This past March, the door was opened to a more cost-effective, and scalable, solution. For the first time, the CDC recognized a class of digital programs as meeting the evidence-based standards of the DPRP. The Prevent program offered by Omada Health was among the inaugural group of digital programs that received the DPRP's recognition. Recognized programs must meet or exceed the outcomes achieved by the original in-person DPP.

By embracing online programs, the CDC has recognized the power of the digital health industry to address a pressing health crisis, and the fact that a new branch of medicine, dubbed digital therapeutics, may hold the key to delivering lifesaving interventions to those who most need them. For the first time, health plans and self-insured employers have a tool that can (1) fulfill their regulatory obligations for this type of preventive benefit; (2) demonstrate successful outcomes and cost-effectiveness; and (3) be quickly scaled and delivered to the populations with the greatest need for intervention.

FIGURE 3. Projected Cumulative Percentage Return on Investment of the Prevent Program



SOURCE: Omada Health Prevent Program Monograph. December 2014.

By embracing online programs, the CDC has recognized the power of the digital health industry to address a pressing health crisis, and the fact that a new branch of medicine, dubbed digital therapeutics, may hold the key to delivering lifesaving interventions to those who most need them.

Digital therapeutics are not simply health or health coaching applications, or even wellness programs. They are evidence-based translations of behavioral interventions that engage participants, maintain clinical fidelity, and deliver lasting, verifiable outcomes (**FIGURE 2**). At Omada Health, we expanded our Prevent curriculum at the beginning of the year to include hypertension, heart disease, and conditions beyond diabetes—the same set of conditions included in the USPSTF guidance. Other companies such as Propeller Health and Recovery Road are developing therapeutics for chronic conditions beyond diabetes.

Digital therapeutics offers a cost-effective alternative for health plans and employers. Instead of creating behavioral intervention programs from scratch, without knowing whether they'll be effective in preventing diabetes and keeping down enterprise costs, these organizations now have the option to implement turnkey yet customizable programs, backed by CDC recognition, with proven efficacy and cost-effectiveness. Initial economic projections for digital therapeutic pilots such as Prevent demonstrated a break-even point at the end of year 2 and a projected savings of $1300 to $3500 per participant over 5 years (**FIGURE 3**).

In addition to cost-effectiveness and scalability, digital therapeutics potentially offers another advantage over traditional in-person behavioral interventions. By collecting data in the form of weigh-ins, time between log-ins, lesson completion, and more, as well as measuring which patient populations respond more readily to certain incentives or challenges, these programs can reach participants in the right way at the right time, leading to increased engagement and better outcomes. Finally, social networking features, and, in the case of Prevent, personalized coaching by full-time health professionals, add a level of support and accountability that enables lasting change.

As part of our company's commitment to accountability, we conduct ongoing clinical trials. Earlier this year, we became the first digital health company to publish 2-year results for participants in our diabetes prevention program. In summary, those results demonstrated that individuals who complete our digital translation of the DPP achieve clinically meaningful reductions in body weight and blood sugar, and maintain those reductions 2 years after completion. While there are still more data to analyze and more studies to publish, early results indicate that digital behavioral interventions can be as effective, or even more so, than in-person versions.

Benefits managers, health plan actuaries, and healthcare systems across the country will now be required to incorporate a new preventive benefit for their employees or beneficiaries. They will have to do so in a way that generates positive health outcomes while maintaining the financial interests of the organization. Many payers are already carefully evaluating which preventive programs should be implemented and looking for demonstrable benefits for their organizations. It's quite possible that digital therapeutics presents the ideal solution to their regulatory problems.

Disclosures: The Prevent program offered by Omada Health is among the digital programs recognized by the CDC to meet the regulatory requirements discussed in this article. **EBDM**

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Sanofi Addresses Need for Spirometry Before Physicians Can Prescribe Afrezza

Mary K. Caffrey

Rarely does a new therapy generate as much divided opinion—and passion—as Afrezza, the inhaled insulin developed by MannKind Corporation and now marketed by Sanofi.

The fast-acting human insulin, administered through an inhaler that fits in a palm, has won loyal fans among users with type 1 diabetes mellitus (T1DM). Those who praise the product cite its ability to provide better glycemic control as well as a winning design, which offers convenience that those with T1DM have long sought.

Social media plays an important role in the T1DM community, and Afrezza has been a hot topic on Twitter since its launch. It's common to see an Afrezza user post "Best A1C results ever"; some users have even uploaded copies of test results to show the drug's effectiveness. Others share tales of taking insulin in public places or aboard planes without being noticed. Although Afrezza complements, but does not replace, long-acting insulin, users describe the product in life-changing terms:

"I can finally eat and enjoy family gatherings, barbecues, and holidays without worrying if my (blood sugar) will spike into the 200s for hours," one wrote.

And then, there are the skeptics: throughout the spring, analysts who follow MannKind reported slower than expected sales and reluctance from some physicians to prescribe the product, often because of a requirement imposed by the FDA at approval:[1] Because the insulin powder is inhaled, underlying lung problems must be ruled out before a patient can gain access to the therapy. (Afrezza is not indicated for patients with chronic obstructive pulmonary disorder or other chronic lung diseases, such as asthma. Safety and efficacy in patients who smoke have not been established.[2])

Ruling out lung problems requires spirometry, a test that until now may have been uncommon among endocrinologists, although it better known among primary care physicians.

The test involves the use of specialized medical equipment called a spirometer (**FIGURE 1**). According to educational information from Sanofi, a clip is placed over the nose, which forces the patient to breath by mouth through an attached tube. The patient is asked to breathe at different rates to measure lung capacity and volume. Results are expressed as a percentage, which is a measure of the patient's actual performance compared with anticipated results based on age, height, gender, and ethnicity. A result is considered abnormal if it is less than 80% of what is predicted.

Besides testing before the first use of Afrezza, spirometry must be repeated after 6 months of therapy and then annually, even if the patient shows no sign of pulmonary symptoms.[2]

Analysts watching early drug sales saw these requirements as a barrier. This May 11, 2015, quote from Seeking Alpha is typical: "JP Morgan's Cory Kasimov downgrades MannKind…due to lower-than-expected prospects for Afrezza. He attributes the inhalable insulin's slow ramp to significant impediments to adoption that may be difficult to overcome." The first "impediment" mentioned is the need for spiromentry.[3]

Sanofi is taking steps to turn the tide. At the annual Scientific Sessions of the American Diabetes Association (ADA) held June 5-9, 2015, in Boston, the education session on Afrezza was packed with physicians seeking information. The Afrezza floor display included efforts to deal with the spirometry issue head on, such as a document, "Guide to spirometry," which described who can give the test and how, what the parameters mean, and—most important of all—which codes to use for reimbursement, both current procedural terminology and *ICD-9* diagnosis codes.[3]

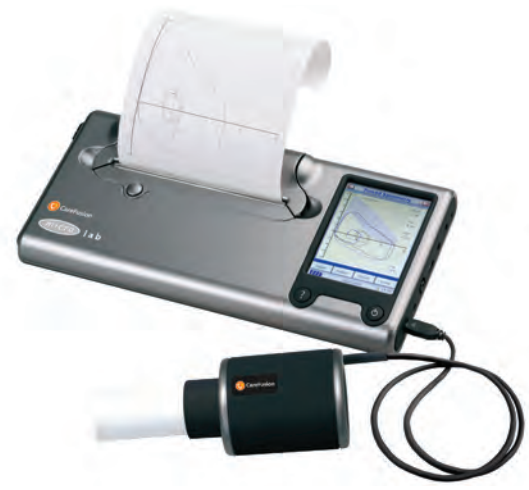
Officially, Sanofi does not see spirometry as a challenge to broader use of the drug. "While spirometry testing is required in order for a patient to be prescribed Afrezza, we do not see this as a barrier since many healthcare professionals are familiar with and have spirometry equipment in their offices," said Susan Brooks, spokeswoman for Sanofi Diabetes, in an email to *Evidence-Based Diabetes Management*. "We have and will continue to make sure to get feedback and input from healthcare professionals and patients to help make Afrezza available to appropriate patients."

Wall Street reports following the ADA meeting have been mixed. Adam Feuerstein of TheStreet.com, a consistent skeptic of Afrezza, reported on June 30, 2015, that sales thus far did not match those of Exubera,[4] an earlier generation of inhaled insulin made by Pfizer. Exubera's failure was widely attributed to its oversized inhaler, which patients said looked like a "bong" and required cleaning. The small Afrezza inhaler (**FIGURE 2**) has been praised by users as a dramatic improvement.[5]

An analyst whose firm attended ADA reported positive feedback. "At the ADA meeting we spoke to 20 US physicians who were familiar with Afrezza and found that while only 6 had prescribed the drug to date, only 1 physician was fundamentally concerned about prescribing it. The 1 physician who expressed caution about prescribing Afrezza said that he remained worried about delivery of insulin, a hormone, into the lung," said Shaunak Deepak of Jeffries.[6]

Physicians and insurers may start getting more requests for Afrezza soon. Sanofi is expected to launch a direct-to-consumer marketing campaign in the third quarter of 2015, focused on publications that reach patients with T1DM. **EBDM**

FIGURE 1. Spirometer



CareFusion's MicroLab model is capable of recording spirometry results as required by the FDA.
SOURCE: CareFusion

FIGURE 2. Afrezza Inhaler

The Afrezza inhaler is much smaller than the inhaler for Exubera, a failed inhaled insulin from Pfizer.
SOURCE: MannKind

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On Lessons Learned: Express Scripts' Steve Miller, MD, Discusses HCV Experience, PCSK9 Inhibitors, and More

Andrew Smith

The pharmacy benefits manager (PBM) Express Scripts has made news in recent months with its novel strategies for containing drug costs. Steve Miller, MD—the company's senior vice president and chief medical officer—explains to Andrew Smith why costs have risen so fast, which new drugs could break the bank, and how payers might be able to keep prices reasonable without stifling innovation.

What factors really determine drug prices?

In recent years, pharmaceutical makers have been shifting the rationale they give for the high price of drugs. In years past, they said that (drug development) failures and R&D (research and development) and manufacturing costs justified the price of drugs. More recently, however, they have begun saying they deserve all the value created by their drugs—that is, if the medications prevent liver transplants, if they prevent hospitalization, the drug makers are saying that they should get all that value. Thank goodness this line of thinking wasn't used with the polio vaccine in the 1950s and 60s, or nobody would have been able to afford it.

In real life, a lot of it just seems to be that drugs are priced at what the market will bear. Drug companies and Wall Street analysts clearly believe that if you have a unique therapy and if you have the patent, then you have almost unlimited pricing power. In the past, that was held in check by a social contract that drugs would be introduced at prices reasonable enough that patients would be able to access them. That contract has broken down recently, leading to extraordinarily high drug prices that are entirely dissociated with the investment needed to develop the drug.

What does Express Scripts do to slow cost growth?

When we look at our formularies, every drug falls into 1 of 3 categories. There are certain drugs out there that are unique in the market and beneficial to patients, and we will always include them on our formulary—that's the first category. We pretty much have to accept the company price for those drugs. The second category contains older drugs that still have their FDA approvals, but there is no longer any good reason to use them. We don't include these in any formulary because there is no good reason to have them. And finally, the third and largest category contains 85% of drugs that are clinically useful but not clinically unique. For example, there are 10 penicillins out there that are essentially interchangeable, which gives us an opportunity to go and ask the drug makers, "Which of you will give us the best price to get access to our patients?" On most drugs, we pit drug maker against drug maker to get the best price, and that's how we help payers and patients.

How are you trying to change that without discouraging innovation?

PBMs reward innovation. If you have a "me too" drug, we punish you on the price of that drug, but when something is truly unique, that drug maker can command superior prices. That said, you can only command top prices until something similar arrives, even if it's not a generic. Our specific tactics for encouraging price competition have been evolving. A decade ago, we checked Lipitor off our formulary, and that gave us the first big opportunity to show that we could move market share. That one move saved members and clients about a billion dollars because it was such a big drug. This last year with hepatitis C virus (HCV), we were able to align our clients behind the idea of excluding one of the products, and in turn negotiate a substantially better deal on an equally good drug. By having that pre-commitment from our membership, we were able to negotiate at a level that's never been achieved before, and that's why we had such great success. (Editor's Note: Express Scripts negotiated a steep discount on AbbVie's new HCV treatment, Viekira-Pak, by agreeing to steer virtually all its patients toward that therapy rather than competitors from Gilead Sciences.)

This last week (May 27, 2015), we announced something to take it to the next level. Historically, we all have negotiated prices at the drug level. What we are going to try going forward, and we will start with cancer, is adjudicate down to the indication level. We will be reimbursing for drugs differently based upon their efficacy for particular conditions. Historically, this has been tried, without success, but we think we have figured out how to do it properly. This could potentially be a very powerful next-generation tool for getting value for our patients.

How willing have pharma companies been to do this?

Just as with hepatitis C, we got our clients to pre-commit to this. We got them to accept, in advance, the notion that a drug might technically be on the formulary but generally unavailable for a particular indication, if the company that makes the drug is unwilling to reduce its price for that indication to reflect the fact that a drug performs differently in different situations.

The differences here are dramatic. Tarceva extends the life of lung cancer patients by about 5 months, and that is the indication that brought it to the marketplace and justified its pricing. Tarceva was then approved to treat pancreatic cancer. Unfortunately, according to the guidance on the Tarceva web page, the drug only extends life for patients with pancreatic cancer by about 12 days. Nevertheless, we currently pay the same premium for Tarceva regardless of whether it's used in patients with lung cancer or patients with pancreatic cancer, and we think it's only fair to change that.

This idea has generated an unbelievably good response from plan sponsors, which is how we got them to commit to it. As for pharmaceutical companies, we have just now started preliminary discussions, but many of them have been quite interested. They have been asking for years for prices that reflect value.

Isn't there already a discount with less effective cancer medications because the patient dies sooner?

You do pay less overall, but you pay the same amount per pill, and many of these medications do much more for certain types of patients on a per pill basis than they do for others. The price the pill costs should realistically reflect what you expect it to accomplish for any given patient.

Do you begin negotiating prices before drugs are approved?

We have always talked to pharmaceutical manufacturers all through the development process, but we definitely increased the emphasis on early discussions during the development of the new hepatitis C drugs. We saw that drug companies heard much less from payers during the development process than they heard from investors, advisory boards, doctors, and patients, and we decided that providing a stronger voice for payers, as early as possible, was necessary for a sustainable process.

There has been a sharp increase in potentially important new drugs and drug classes nearing approval. The old social contract, as I said before, has broken down, which is why we've recently seen pharmaceutical makers charging orphan drug prices for mass market drugs. We clearly couldn't afford to have things continue on that path, so we reached out more aggressively than before and said we wanted to discuss a way that we could reward innovation without costs spiraling beyond what payers can endure. We have been gratified to find that the drug companies have responded. We are having more conversations than ever, at higher levels than ever. We are talking to CEOs and boards of directors at pharmaceutical manufacturers about value-oriented prices. Some of the most important of those discussions have revolved around PCSK9 inhibitors, which have the potential to have a major impact on how we treat high cholesterol. (**See stories** on advisory committee approvals, **SP368-SP369).**

STEVE MILLER, MD

Dr Miller is the chief medical officer of Express Scripts.

> *"Drug companies and Wall Street analysts clearly believe that if you have a unique therapy and if you have the patent, you have almost unlimited pricing power. In the past, that was held in check by a social contract... That contract has broken down."*
>
> —STEVE MILLER, MD

How big an impact do you expect that class of drugs to have on pharmaceutical expenditures?
A significant impact. You have what appears to be a great group of drugs. They're the first new type of cholesterol medication in 20 years. There are 71 million Americans with high cholesterol. Now, we know that not all of those people are going to need these new drugs, but if you look just at those patients who face high risk of strokes and heart attack and don't meet targets with existing medications, you could have 10 million people on this class of medication. There are 3 big variables that we're working on with the pharmaceutical companies and our payers. Number 1 is the price. That's an enormously important point. Number 2 is the indication. A lot of that will be determined by the FDA labels. How broad or narrow those are will help determine use. Number 3 is the use management program that makes sure that the right patients use these drugs and that patients who should not be on these drugs do not use them. These variables let our payers calculate how big the impact is likely to be and take steps to prepare themselves.

Overall, this single drug class has enormous ramifications. A competitor of ours forecasted the price to society to be $150 billion a year. We don't think that our clients are going to be spending anywhere close to that level, but even if you say it's just going to be $15 billion per year, that would have a major impact in overall drug spending, all by itself.

Is there any chance PCSK9s will create net savings on healthcare expenditures?
Whenever new technologies come into healthcare, the common refrain is that they're going to save us money. I've been in healthcare for 30 years, and I know the savings rarely materialize. CT scanners came in and the doctors said, "I'm going to be able to look into your body and do more precise diagnoses and prevent unnecessary surgeries and the cost of healthcare will come down from this technology alone." That promise was never fulfilled. You hear the same argument about a lot of drugs. They are going to improve patient lives and reduce complications and there will be tremendous cost offsets and these drugs will pay for themselves. A CMS administrator told me that if all the cost offsets promised by new technology materialized, Medicare would not cost the nation anything. It would actually make us money.

The reality is that very few technologies have had a cost-saving effect. Patients are complex. If you take patients who are at highest risk of heart disease, high cholesterol is generally just 1 of the comorbidities that put them at risk. Even if you remove that risk factor completely, a patient's hypertension doesn't go away, a patient's diabetes doesn't go away, a patient's lack of exercise doesn't go away, a patient's smoking doesn't go away, and a patient's poor diet doesn't go away. I don't think we want to overstate the benefit and lull ourselves into false expectations until we prove that there is a savings.

Looking forward, what other drug classes are likely to have a major impact on expenditures?
There are many, but I'll give you 3 disease categories, starting with NASH (nonalcoholic steatohepatitis), which is not on anyone's radar screen. It's a liver disease that is more common than hepatitis C, and data from trials indicate that new drugs could make a big difference. The next category, and a more important category, is cancer. There are 7000 drugs in the pipeline, and over a quarter of them are for cancer. The new pricing model has cancer drugs at very high costs, and there are a number of immunomodulating drugs that look like they could extend lives by many years. Trouble is, it's unclear how long the patient has to stay on many of these drugs, so you could have patients on combinations of these drugs for long, long periods of time, and the costs could become extraordinarily high. The final category that people have to be on the lookout for is Alzheimer's drugs. Biogen, about 6 months ago, published an incredibly exciting study. They have a product that not only caused a regression of the plaque in the brain but also produced stabilization of cognitive decline. Obviously, they would have unlimited pricing power for a drug like that. If you consider the 4.5 million people who have Alzheimer's and all of the people who are over 65 who would like to prevent Alzheimer's, the potential costs are incredible.

That gives you a flavor of how great some of the innovation in the pipeline is, but also how threatening it is to drug expenditures. **EBDM**

Caution in PCSK9 Inhibitor Votes Reflects Sentiment of Earlier Reviews

Mary K. Caffrey

MARC SABATINE, MD, MPH

Dr Sabatine is a senior physician, Division of Cardiovascular Medicine, Brigham and Women's Hospital.

In separate votes in June, an FDA advisory panel recommended approval for the first 2 PCSK9 inhibitors, a powerful new class of drugs that has been shown to lower cholesterol by as much as 60% in clinical trials.

However, the 13-3 vote to recommend alirocumab, which came on June 9, 2015, followed by the 11-4 vote to recommend evolocumab on June 10, 2015, showed a cautious approach on the part of the FDA's Endocrinologic and Metabolic Drug Advisory Committee (which had slightly different makeup over the 2 days).

As the panel discussed alirocumab, a drug from Sanofi-Regeneron that will be marketed as Praluent, advisory committee members expressed concern that patients might abandon statins, which are cheap and have a proven safety record, for these lesser-known newcomers. Fewer than half the panel members taking part in the alirocumab vote were on board with approving the drug for patients who cannot tolerate statins—which had to unsettle drug makers, since statin-intolerant patients have been viewed as an important market for this drug class.[1]

In fact, when Amgen made its presentation the next day on evolocumab, to be marketed as Repatha, the company brought in Marc Sabatine, MD, MPH, to make the case for why patients who cannot tolerate statins should have access to the therapy. But when the vote came, only 4 panel members were satisfied that evolocumab should be approved for patients who were statin-intolerant; a slim majority voted for its use in patients who have high cholesterol and high cardiovascular (CV) risk.[2]

The caveats concerning both votes have the potential to take significant markets for the drugs off the table. But for anyone who's been following editorials in leading journals, the ambivalence shouldn't have come as a surprise.

The PCSK9 inhibitors nearing FDA approval are monoclonal antibodies that have been touted as a revolutionary way to lower cholesterol. They target a protein in the liver, the proprotein convertase subtilisin kexin 9, inactivating it to dramatically lower low-density lipoprotein (LDL), or "bad," cholesterol. Their development is based on the discovery of a genetic mutation among groups of patients with very low levels of cholesterol.[3]

FDA advisory committee members agreed that both drugs are worthwhile and much-needed solutions for patients who suffer from a genetic disorder, familial hypercholesterolemia. Voting on alirocumab also seemed likely to extend access to younger patients who have extremely high cholesterol levels, who have been unable to control cholesterol with other therapy, or who have uncontrolled cholesterol coupled with a high risk of heart attack or stroke.

Beyond that, the split votes over the 2 days make it hard to say who else will gain access, and what restrictions the FDA will include on the label.

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In discussing both drugs, panel members addressed the same concerns that were raised during a press conference

at the March meeting of the American College of Cardiology (ACC) and in editorials in the *New England Journal of Medicine* and *Annals of Internal Medicine*.[4-6] FDA panel members made it clear that PCSK9 inhibitors should not be viewed as a routine substitute for statins, the standbys on which most patients rely. Their sentiments echoed the editorial that appeared in *Annals* on April 28, 2015, which said while the drugs hold promise, long-term data on CV risks will not be available until at least 2017.[6]

"Confirmation of these findings in long-term, ongoing, pivotal trials with pre-specified CVD [cardiovascular disease] end points and monitoring of a range of adverse events will help establish the role of these novel agents in CVD risk management," the writers said at the time.

In March, when the CV benefits of rival drug evolocumab were presented at ACC and published in *NEJM*, the reaction was "not so fast," in contrast to the intense marketing present at that conference. "The evidence-driven cholesterol guidelines did not endorse the concept that lower LDL cholesterol levels are better at all costs," the writers said, adding that "how you get there" matters, and risks to patients must be assessed.[5]

The FDA's concern about long-term CV effects is rooted in the experience of the last decade, when the diabetes drug rosiglitazone became a blockbuster, only to be linked in an *NEJM* meta-analysis to increased heart attack risk. The FDA now requires CV outcomes trials for all new diabetes drugs. While there have been some promising CV results for PCSK9 inhibitors, it has been noted that the evidence has come from small trials with short-term follow-up.[3]

If an FDA approval reflects the advisory committee sentiments, it will be welcome to pharmacy benefit managers and health plans who have been bracing themselves for the "next Sovaldi," as prices for the PCSK9 inhibitors have been estimated at about $10,000 a year. While that is not as expensive as the high-priced cure for hepatitis C virus, the prospect of waves of patients switching from low-cost statins to a costly branded drug had many nervous.[7] **EBDM**

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Review of Amgen Cholesterol Drug Favored by FDA Panel

Michael R. Page, PharmD, RPh

An FDA regulatory panel has recommended approval of Amgen's proposed cholesterol-lowering medication, evolocumab, to be marketed as Repatha. The panel's 11 to 4 vote on June 10 suggests that the drug is likely to be approved in the near future.[1]

Proposed indications for evolocumab include:

- Use in adults with primary hyperlipidemia—including heterozygous familial and nonfamilial hyperlipidemia, as well as mixed dyslipidemia—as an adjunct to dietary interventions for reducing low-density lipoprotein (LDL) cholesterol levels, total cholesterol levels, apolipoprotein B, and other unfavorable lipid parameters, as well as for increasing levels of the salutary biomarker high-density lipoprotein (HDL) cholesterol.
- Use in combination with statins and non-statin lipid-lowering therapies, such as ezetimibe.
- Use in statin-intolerant patients.

Current FDA-approved treatments for primary or mixed dyslipidemias include atorvastatin, simvastatin, pitavastatin, lovastatin, fluvastatin, pravastatin, extended-release niacin, fenofibrate, rosuvastatin, atorvastatin/ezetimibe, and simvastatin/ezetimibe. For patients with homozygous familial hypercholesterolemia (HoFH), oral lomitapide and injectable mipomersen are also available for reduction of non-HDL cholesterol levels.

MECHANISM OF ACTION

The circulating protein proprotein convertase subtilisin/kexin type 9 (PCSK9) was initially considered a drug target due to literature reports of mutant individuals with low PCSK9 activity having unusually robust cardiovascular health. For instance, African Americans with a nonsense allele encoding PCSK9 had, on average, 29% lower LDL cholesterol levels, and an aggregate 88% lower risk of developing coronary heart disease.

One woman in her early 20s who had a complete loss-of-function mutation for PCSK9 had an LDL cholesterol level of 15.5 mg/dL and an HDL cholesterol level of 54 mg/dL. Another woman in her early 30s had a heterozygous loss-of-function mutation for PCSK9, an LDL cholesterol level of 14 mg/dL, and an HDL cholesterol level of 65 mg/dL.

Mechanistically, the human monoclonal immunoglobulin G2 (IgG2) antibody evolocumab binds to the circulating PCSK9 protein, inhibiting it from binding to LDL receptors (LDLRs) on the surface of hepatocytes. These LDLRs serve to clear LDL cholesterol from the blood. By inhibiting PCSK9 activity, medications such as evolocumab increase LDLR levels on the surface of liver cells, increasing the intensity of LDLR-mediated LDL cholesterol clearance.

DOSING

Proposed dosing for evolocumab is 140 mg administered subcutaneously every 2 weeks, or 420 mg administered subcutaneously every month. Potential concerns with the monthly dosing option include a more limited opportunity for dosage titration in patients achieving very low LDL cholesterol levels.

PHARMACOLOGY AND PHARMACOKINETICS

The FDA's briefing document suggests that no dosage adjustments will be necessary in geriatric patients or those with mild-to-moderate renal or hepatic impairment.[2]

Important pharmacokinetic considerations include a 20% increase in evolocumab clearance rates when it is coadministered with statins, an estimated half-life of 11 to 17 days, and 2- to 3-fold accumulation with repeat dosing. The medication has limited tissue distribution, and a volume of distribution averaging 3.3 L. Maximum levels are achieved within 3 to 4 days, and bioavailability has been estimated at 72% following a single dose of evolocumab.

In efficacy studies, evolocumab-binding antibodies have developed in <1% of patients using the drug, but there have been no cases of neutralizing antibodies to evolocumab.

CLINICAL STUDIES

Clinical data are based on 5 short-term phase 2 trials, 1 long-term phase 2 trial, 4 short-term phase 3 trials, and 2 long-term phase 3 trials.

General efficacy statements noted in the FDA's briefing document concerning the drug include:

- LDL cholesterol reduction of 55% to 75% within 1 week of starting therapy in patients with primary hyperlipidemia, and a maximal response within 2 weeks of therapy.
- LDL cholesterol reduction of 31% within 12 weeks in patients with HoFH not receiving lipid apheresis.
- A lower rate of treatment response in HoFH patients receiving lipid apheresis versus patients not receiving lipid apheresis over 24 weeks of evolocumab therapy (response rates of 20% with apheresis vs 25% without apheresis, respectively).
- A 6% greater reduction in LDL cholesterol among HoFH patients receiving an intensified dosing regimen of 420 mg every 2 weeks versus the usual dosage of 420 mg monthly.

WARNINGS AND PRECAUTIONS

In evolocumab trials, nonfatal serious adverse events (AEs) occurred in 3% of patients receiving active treatment versus 2.4% of patients receiving placebo alone. These events included myocardial infarction, angina pectoris, and pneumonia, each of which occurred in 0.1% of patients receiving evolocumab.

Pancreatitis, appendicitis, pneumonia, and back pain were also reported. Cardiac disorders, increases in creatinine phosphokinase levels, and nausea were the most common serious AEs leading to treatment discontinuation.

In evolocumab monotherapy trials, the most common AEs of any severity were nasopharyngitis (5.9%), upper re-

spiratory tract infection (3.2%), back pain (3.0%), and nausea (2.1%), each of which occurred in patients taking evolocumab at a modestly higher rate than in those taking placebo.

When taken with standard-of-care treatments, evolocumab was associated with slightly higher rates of arthralgia (3.4%), back pain (3.1%), myalgia (2.5%), and extremity pain (2.5%) versus patients receiving only standard-of-care medications. Monthly evolocumab dosing increased the risk of nasopharyngitis, headache, and fatigue more than every-2-week dosing.

In early trials, neurocognitive AEs occurred in 11 patients, including 6 in control groups. In trials lasting up to 1 year, a total of 22 neurocognitive AEs were recorded, unrelated to the degree of LDL cholesterol reduction achieved.

In phase 3 trials, 0.1% of patients taking evolocumab developed renal disease or proteinuria, while no such cases were identified in control groups. These renal events may be more likely to occur in statin-intolerant patients and diabetics. In addition, a possible safety signal related to pancreatitis risk was detected.

Injection site reactions were reported at rates of 3.3% to 5.7%, varying by trial duration and design. A total of 5 cases of angioedema have been reported, all of which occurred in patients using evolocumab.

DRUG-DRUG INTERACTIONS

Studies of drug-drug or drug-food interactions have not been conducted with evolocumab. Due to the drug's properties, no such interactions are expected. However, a 20% increase in the clearance of statins is a notable finding from pharmacokinetic studies.

GENOTOXICITY AND TERATOGENICITY

Genotoxicity assays were not performed, as a DNA interaction with evolocumab was not expected, based on the drug's mechanism of action. To assuage lingering carcinogenicity concerns, the manufacturer conducted a 2-year study in hamsters. No drug-related tumors were identified.

Animal studies in hamsters and monkeys showed no relationship between evolocumab exposure and fetal variations or malformations, even at supratherapeutic doses. A total of 7 women became pregnant in all evolocumab research programs, and a total of 9 men fathered children. Among these 16 pregnancies, 1 of the 7 in the maternal exposure group and 3 of the 9 in the paternal exposure group resulted in a full-term birth without complications.

CONCLUSIONS

Given the favorable FDA panel opinion of evolocumab, Amgen is optimistic about the drug's future.

"If approved, Repatha would provide patients and physicians with an important new treatment option for managing high cholesterol," stated Sean E. Harper, MD, executive vice president of research and development for Amgen.[3]

The FDA is expected to act on Repatha's biologics license application on August 27, 2015. **EBDM**

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PHARMA FEATURE

NEJM Study: Aflibercept Offers Benefits Over Rivals for DME if Vision Loss Is Worse at Outset

In Analysis, Firm Gives Drug Nod on Cost, Safety Record

Mary K. Caffrey

About 750,000 people in the United States are affected by diabetic macular edema (DME).[1] This results from diabetic retinopathy (DR), in which damage to the blood vessels in the retina progresses to the point where fluid leaks from the macula, the central area of the retina. Vision is clouded and it becomes impossible to focus.[2]

Until recently, laser treatments were the only available standard of care, and they are still part of the care regimen. Starting in 2012, however, the FDA approved injections of vascular endothelial growth factor (VEGF) inhibitors,[3] which were first approved in 2006 for age-related macular degeneration.[4] This new class of therapy proved more effective than laser treatments, and by 2013 a survey of US retina specialists found that 90% were using anti-VEGF agents for the initial treatment of vision loss from DME.[5]

Within weeks of the first approval of a VEGF inhibitor for treatment of DME, the Diabetic Retinopathy Clinical Research Network began a randomized clinical trial, sponsored by the National Institutes of Health, to compare 3 commonly used intravitreous VEGF inhibitors: aflibercept, marketed as Eylea; ranibizumab, marketed as Lucentis; and bevacizumab, marketed as Avastin. Only aflibercept and ranibizumab have FDA approval for treatment of DME. The trial ran from August 22, 2012, to August 28, 2013, and results were published online March 26, 2015, in the *New England Journal of Medicine*.[1]

Researchers, studying 660 adult patients at 89 sites, found that all 3 VEGF inhibitors improved vision in eyes with center-involved DME, but the relative effect depended on visual acuity at baseline. When vision loss was mild at the outset, there were no apparent differences among the 3 drugs. However, for those patients with more impaired vision at the start of the study, aflibercept was more effective at improving vision, the study found.

STUDY PARTICIPANTS AND METHODS

Study participants had either type 1 or type 2 diabetes mellitus (T2DM), with 90% having T2DM. The mean duration of their diabetes was 17 years ±11 years. The mean age of the participants was 61 years ±10 years, 47% were women, and 65% were white. Each had at least 1 eye affected by DME, with the mean baseline visual acuity letter score of 64.8 ±11.3 at baseline on a scale of 0 to 100, with higher scores indicating better acuity. This would translate to an equivalent of 20/50. Baseline characteristics were similar in the 3 groups.

SOURCE: Regeneron

Patients were randomly assigned to 1 of the 3 groups: 224 received aflibercept at a dose of 2.0 mg, 218 received a dose of bevacizumab at 1.25 mg, and 218 received a dose of ranibizumab at 0.3 mg. Doses were administered according to individual protocols, as often as every 4 weeks. A subset of patients required laser photocoagulation at 24 or 48 weeks, based on measurements of visual acuity and central subfield thickness. The primary end point was measurement of the mean visual acuity letter score at 1 year. With deaths excluded, the overall completion rate to the 1-year visit was 96%.

RESULTS

During the year, laser treatments were necessary at least once between 24 and 48 weeks for 76 of the 208 aflibercept-treated eyes (37%), 115 of the 206 bevacizumab-treated eyes (56%), and 95 of the 206 ranibizumab-treated eyes (46%).

When initial visual acuity was 20/32 to 20/40, the median number of injections was 9 in each group, with 36% in the aflibercept-treated eyes, 47% in the bevacizumab-treated eyes, and 43% in the ranibizumab-treated eyes receiving photocoagulation therapy. When initial visual acuity was 20/50 or worse, median injections were 10 for those treated with aflibercept, 11 for the bevacizumab group, and 10 for the ranibizumab group. Photocoagulation therapy was

necessary for 37%, 65%, and 50% of the treated eyes, respectively.

Vision improved more after a year for those treated with aflibercept than with the other 2 therapies. Those treated with aflibercept improved their scores by 13.3 on average, compared with 9.7 for bevacizumab and 11.2 for ranibizumab. However, when initial visual acuity scores were higher, equivalent to 20/40 vision or better, the mean improvement scores were within a point for all 3 drugs (8.0, 7.5, and 8.3). When initial visual acuity scores were below 69, or the equivalent of 20/50, the mean improvement scores grew farther apart:

- 18.9 ±11.5 for aflibercept
- 11.8 ±12.0 for bevacizumab
- 14.2 ±10.6 for ranibizumab

Results showed all 3 therapies produced improvement by 4 weeks; for those with the worst initial vision, the benefits of aflibercept became apparent early on. The 1-year visit also showed that all 3 therapies reduced central subfield thickness, with the benefits varying based on initial thickness.

All 3 groups had similar rates of adverse events (AEs). The rate of death from any cause was 1% in the aflibercept group, 2% in the bevacizumab group, and 2% in the ranibizumab group. Vascular event rates were 3%, 4%, and 5%, respectively; an analysis found more participants in the ranibizumab group reported AEs when the Medical Dictionary for Regulatory Activities system of organ classes of cardiac and vascular disorders were combined. Researchers wrote that this may be due to chance.

CONCERNS ABOUT COST

The price of VEGF inhibitors used in the treatment of ocular conditions has raised eyebrows for years. Ranibizumab's full price listed at $1950 when it hit the market in 2006,[6] which is the price researchers list for aflibercept in their study.[1] A recent cost and safety analysis by Adverse Events, Inc, listed the per prescription price of aflibercept at $1471.56 and ranibizumab at $1408.71 for several indications, including diabetic retinopathy.[7] In an interview with *Evidence-Based Diabetes Management*, Robert Kyle, chief product officer for Adverse Events, said the pricing information is based on averages from 2014.

Among patients with greatest initial vision loss, aflibercept produced more improvement than its rivals in the study, published in the New England Journal of Medicine.

Bevacizumab, approved as a cancer drug, is not indicated for any eye condition but has been widely used off-label in repackaged doses, which are a fraction of the size used in cancer care. At $50 per dose, it's also a fraction of the cost of the FDA-approved rivals.[6,8] Because bevacizumab and ranibizumab are both made by Genentech—the *Washington Post* called them "biological cousins"—there has been controversy dating back to 2006 regarding why eye patients are being sold a much more expensive drug, with much of the tab going to Medicare.[6,8]

However, the results of the *NEJM* study indicate that while the off-label formulation produced some vision improvement for DME patients, it was not as effective for patients who began treatment at greater levels of vision loss.

ADVERSE EVENTS ANALYSIS

On April 21, 2015, Adverse Events, Inc, which evaluates safety data of new drugs for payers, issued a report to clients, "Cost Comparison and Safety Analysis of Eylea vs Lucentis for Diabetic Retinopathy."[7] The report actually covered multiple indications, including DR, DME, retinal vein occlusion, and wet macular degeneration. The report concluded, "Eylea (aflibercept) appears to be a safer alternative to [the] existing DR drug Lucentis (ranibizumab)."[7]

Adverse Events based its assessment on a number of factors, including the fact that ranibizumab was associated with a higher downstream cost per prescription of $25.19 versus $8.87 for aflibercept. The report noted that aflibercept was less likely to be associated with AEs, based on the firm's analysis of records to the FDA's Adverse Event Reporting System.[7] In the interview with *EBDM,* Kyle said ranibizumab was more frequently associated with cardiovascular events and hospitalizations.

While aflibercept may have a higher cost per prescription, Kyle explained, its treatment course differs from ranibizumab's. Both drugs require injections every 4 weeks for the first 5 cycles, but then aflibercept requires injections every 8 weeks. Adverse Events' report listed the annual cost of aflibercept at $7,694,584, compared with $26,739,226 for ranibizumab.[7] **EBDM**

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FDA UPDATE

FDA Approves Software Update for Dexcom Pediatric CGM System

Mary K. Caffrey

The FDA has approved updated, more accurate software for the Dexcom G4 Platinum pediatric continuous glucose monitoring (CGM) system. The approval, granted May 22, 2015, reflects software changes to improve accuracy for detecting glucose levels of 70 mg/dL or lower. According to an FDA notice, the approval lets Dexcom remove warnings from the device receiver and labeling.[1]

Dexcom's G4 Platinum system for adults, first approved in 2012, offered improved accuracy and other advances from its earlier CGM technology.[2] The May software update for the pediatric model, while not a major technological advance, represents the ongoing fine-tuning of devices for those with diabetes who use insulin to keep blood glucose levels in check. The pediatric version is designed for children aged 2 to 17 years; almost all potential users have type 1 diabetes mellitus (T1DM).

The Dexcom pediatric device allows patients (and their parents) to monitor blood glucose levels more easily than with finger sticks. While finger stick tests are still part of T1DM care, they offer only a snapshot in time, not a view of how blood glucose levels have changed over the course of a day.

Dexcom is among several competitors at work on an "artificial pancreas," which would combine CGM technology, an insulin pump, and improved sensors to sharply reduce a patient's need to monitor glucose levels throughout the day, including during exercise (see **Cover Story**). Until this technology arrives, pediatric patients in particular require monitoring for hypoglycemia events. **EBDM**

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Session on Population Management Highlights Shift Toward Value-Based Models in Diabetes Care

Mary K. Caffrey

MARSHALL CHIN MD

Dr Chin is the director, Chicago Center for Diabetes Translation Research.

ROBERT A. GABBAY, MD, PHD

Dr Gabbay is the chief medical officer, Joslin Diabetes Center, and editor in chief of *Evidence-Based Diabetes Management*.

JULIE SCHMITTDIEL, PHD

Dr Schmittdiel is a research scientist with Kaiser Permanente.

The shift from delivering healthcare 1 patient at a time to being responsible for a population requires both a new mind-set and new payment structures. In diabetes care, for reasons of health and cost, achieving both will be hard—but essential.

How this can be accomplished was discussed by 4 speakers and moderator Debra J. Wexler, MD, at a June 5, 2015, symposium titled "Population Management: Coordinating High-Value Diabetes Care in Diverse Settings." Held at the 75th Scientific Sessions of the American Diabetes Association in Boston, the symposium moved from explaining why diabetes measures are so central to population health management, to specific strategies deployed at state and even local levels.

Darren A. DeWalt, MD, MPH, director of the Learning and Diffusion Group at the Center for Medicare and Medicaid Innovation (CMMI) of CMS, shared the rationale for a population-based approach. "When I think of population management, it means taking care of patients and having accountability for their outcomes," he said. This structure has been building over 20 years and is now taking hold across the country. It requires:

- The ability the gather analytics about the patients, not only their health data but also "the context in which they live."
- The ability to segment patients to identify those at risk.
- The ability to translate the information and use it in a meaningful way.

Use of contextual information, DeWalt said, "forces us to say that medical care is no longer the 10 to 15 minute visit …it's between-visit care." Care occurs at home, in an e-mail to the patient, and through community partners. Most of all, he said, "Patients need to be active participants in their own care, so they can make evidence-based decisions for themselves."

But physicians find this transformation very hard, especially when it comes to realigning payment systems to match. Among other challenges, physicians don't always see changing their approach as having the potential to yield a good return on their investment. DeWalt discussed 4 tools that CMS has deployed to promote its goals of better alignment of incentives, increased access to actionable data, and better-integrated care for chronic illness and behavioral health:

- Starting this year, primary care practices have a new Medicare billing code for chronic care management; DeWalt said practices can receive about $43 per patient per month, although there is a learning curve for documentation.
- The Comprehensive Primary Care demonstration in 500 primary care practices nationwide having yielded mixed results, CMS will examine why some states are seeing savings and some are not.
- The Pioneer accountable care organizations have been leaders in population segmentation and community partnerships, and unlike the Medicare Shared Savings Program, these groups have a "2-sided" risk; they can lose money by failing to meet population health targets.
- The new Transforming Clinical Practice initiative seeks to support 150,000 clinicians over 4 years with $800 million of investment, "regardless of specialty." DeWalt emphasized that this program is not just for primary care physicians; rather, endocrinologists, cardiologists, and others who see high numbers of patients with chronic conditions could benefit.

Use of contextual information "forces us to say that medical care is no longer the 10 to 15 minute visit… it's between- visit care." Care occurs at home, in an e-mail to the patient, and through community partners. Most of all, "Patients need to be active participants in their own care, so they can make evidence-based decisions for themselves," said Dewalt.

Julie Schmittdiel, PhD, a research scientist at Kaiser Permanente, discussed how the health system's alignment with a research arm has given each a stake in the other's success. The research section—which relies mostly on funding from foundations and the National Institutes of Health—provides evidence that affects healthcare across the country.

Schmittdiel said Kaiser Permanente was among the early adopters of a population management approach to diabetes care: its diabetes registry dates to the 1990s, and for some time it's had a team-based approach, which gets nurse case managers, pharmacists, nutritionists, and others involved in care.

Four principles are essential, she said:

- Population registries: "It seems so fundamental to know who has diabetes, and how do we reach them?"
- Evidence-based practice requires knowing the right risk factors to target, and the right medications to use.
- Health systems must receive relevant feedback on performance of individuals and facilities.
- Leveraging efficiencies is essential.

The goal, Schmittdiel said, is "to reduce micro- and macro-vascular complications by optimizing glucose control and cardiovascular risk factors at the population level."

"We do this by providing team-based care for all diabetes patients," she said. Everyone receives "light touches," and those whose glycemic control is poor get more intensive outreach.

Kaiser Permanente's fully integrated electronic health record is key to clinical practice and research. "It keeps everybody on the same page," she said. But no matter how strong a population health management system is, Schmittdiel said, "There will be people who fall through the cracks. You have to have tailored strategies for those patients." This is especially true when there are language barriers or cultural issues, and health systems must have ways to address this.

Robert A. Gabbay, MD, PhD, chief medical officer of Joslin Diabetes Center and editor in chief of *Evidence-Based Diabetes Management*, previously led the Penn State Institute for Diabetes and Obesity. His talk covered a Patient Centered Medical Home (PCMH) initiative that began during his tenure at Penn State, which is now bearing fruit. An article on the initiative appeared June 1, 2015, in *JAMA Internal Medicine*.[1]

"Diabetes, in many ways, has been at the vanguard of the many changes in healthcare delivery," Gabbay said. The concepts of team-based care, promoting self-care, the early studies of the chronic care model—all started with the need to address diabetes. "It's common, it's increasing, and it's expensive," he said, so early on, it was a disease that healthcare leaders realized needed new approaches.

It has required a "paradigm shift" away from treating patients "when we see them" to the population management approach, which takes responsibility for patients even "when we don't see them." This team-based approach "is well accepted for diabetes, but it is a newer concept elsewhere," Gabbay said.

Enter the PCMH, and the 2009 launch of the Pennsylvania Chronic Care Initiative, which transformed care across 150 practices in phases, taking 1 geographic area at a time. The initiative, which involved 17 different payers, 1000 providers, and 96,000 patients with diabetes, employed a "learning laboratory" approach. As Gab-

bay explained, lessons learned in each region were folded into the launch of the project into the next region. Elements of the initiative included:

- A quarterly learning collaborative, guided by facilitators.
- Practice coaches who worked on individual changes that were discussed.
- Practice-embedded data on care management, the "secret sauce."
- Monthly quality outcome reporting.
- Supplemental payments from participating insurers, which varied by region.

As Gabbay discussed, the Pennsylvania initiative had some successes early on, but the evidence was mixed on whether it was saving any money. By year 3, however, the lessons learned had helped fine-tune the project as it moved into new regions; these regions have seen more rapid improvements. As the evidence accumulates, the PCMH model is making headway on increasing 4 measures of diabetes process care while reducing rates of all-cause hospitalization and emergency department visits,[1] with a recent study also showing cost savings.[2]

What have researchers learned? Practices benefit from:

- Specific performance expectations
- Earlier support for care management, with training
- Strong communication between practices and payers (this is key, because, for example, payers may know right away if a patient is in the emergency department, while the practice may not.
- Understanding the shared savings methodology.

Gabbay said states can provide a "convening function" to promote payment reform on a regional basis, since antitrust laws would prohibit payers from gathering for such a purpose. As Medicaid providers, states are large payers themselves. Finally, he pointed out, federal innovation dollars often flow through states.

Marshall Chin, MD, MPH, serves as director of the Chicago Center for Diabetes Translation Research, part of the University of Chicago School of Medicine. He practices where theory meets reality: his patients have some of the highest rates of diabetes and its complications, but they don't trust institutions. For Chin, the road map to reducing disparities means earning patients' trust before interventions can even begin.

Bringing change requires planning and steps: interventions take commitment to quality, planning, structure, and good design. They must be evaluated and adjusted as needed, and they must be sustained. Chin discussed the importance of understanding the population's belief systems, suggesting that it wasn't enough to just take traditional measurements like weight or blood pressure—the healthcare system must understand what motivates the population if it is to grasp the intrinsic and extrinsic motivators that will bring change.

For providers, financial incentives are changing quickly, as payment models based on population management take hold. This has given Chin more ability to work with community partners, such as Walgreens, which has increased its healthy offerings in "food deserts" and hosts store tours to help clients make better choices. He capitalizes on opportunities like farmers' markets and food pantries, bringing in medical students for blood pressure checks or education sessions. "We turn it from a good event to a health event," he said.

From diabetes-friendly cooking competitions, to putting physicians on local radio programs, Chin passes up no opportunity to connect with his audience. But the key, he said, is listening. "You have to talk to your patients." **EBDM**

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ITCA 650 Results Point to "Transformational" Method to Deal With Poor Adherence in T2DM

Mary K. Caffrey

A drug delivery system that eliminates the problem of poor adherence could be "transformational" in helping patients with type 2 diabetes mellitus (T2DM) achieve lower blood glucose levels, according to the lead investigator of a phase 3 study presented June 8, 2015, at the 75th Scientific Sessions of the American Diabetes Association (ADA).

Julio Rosenstock, MD, director of the Dallas Diabetes and Endocrine Center at Medical City, and clinical professor of medicine at the University of Texas Southwestern Medical Center, Dallas, presented results involving ITCA 650. Using a matchstick-sized mini-pump implanted beneath the skin, ITCA 650 delivers a continuous dose of exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist previously approved by FDA. Rosenstock presented results for FREEDOM-1, a placebo-controlled trial, showing that patients had an average reduction of 1.4% in glycated hemoglobin (A1C) at 39 weeks, with even better results achieved by those not on concomitant sulfonylureas (SUs).[1]

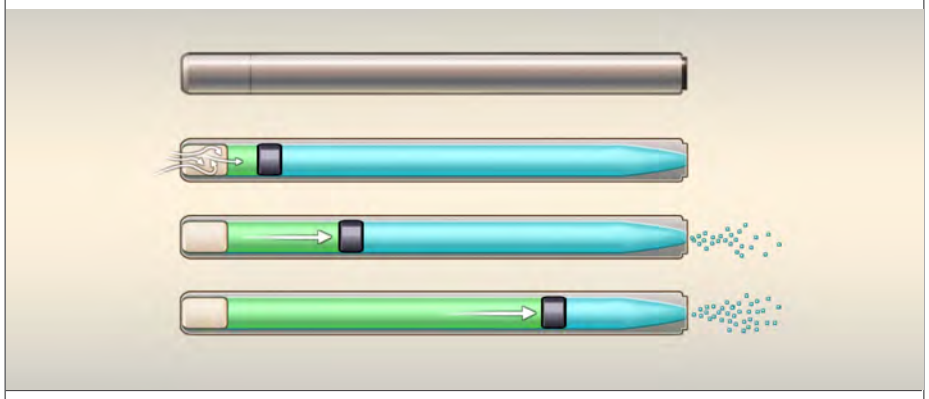
"A large part of the population remains inadequately controlled," Rosenstock told the packed session in Boston. While it is hard to say precisely how much of this is due to poor medication adherence, some health economists rate adherence as "good" when patients take medication even 80% of the time.[2] ITCA 650, made by Intarcia Therapeutics, Inc, ensures 100% adherence and only requires that the mini-pump be replaced with a fresh supply of exenatide, typically every 6 months.[1]

Throughout the weekend at ADA, attendees crowded the Intarcia booth in the exhibition hall to watch demonstrations of how the mini-pump works and how it is placed under the skin. ITCA 650 delivers therapy when a tiny engine fires a piston to continuously suspend the exenatide (see **FIGURE**). While it is thought that the device will be replaced every 6 months, it can work for longer periods. "This can be easily done by a doctor, a physician assistant, or a nurse practitioner," Rosenstock said at his oral abstract session.

The drug was well tolerated, said Rosenstock; the most common adverse event was nausea, and results were consistent with studies of other drugs in the GLP-1 class. In general, patients have gastrointestinal issues when they start therapy, but these resolve over time, he noted.

Intarcia is also completing a study on cardiovascular effects, now required by FDA for new diabetes therapies, and filing is anticipated to occur in 2016.

FIGURE. Stages of ITCA 650



The matchstick-sized device seen above features a tiny engine that continuously fires a piston to suspend daily doses of 20, 40, or 60 mcg of exenatide.
SOURCE: Intarcia Therapeutics

Results for Freedom-1.[1] The placebo-controlled trial involved patients who started the study with A1C between 7.5% and 10%. Patients were randomized to daily exenatide doses of 40 mcg, 60 mcg, or placebo. For both groups receiving the study drug, patients received 20 mcg of exenatide for 13 weeks, then the higher dose for 26 weeks. Baseline characteristics were similar across all 3 groups, which totaled 460 patients: average A1C was 8.5%, body mass index (BMI) was 33.5 kg/m^2, and the average duration of T2DM was 9 years.

At 39 weeks, average A1C reductions, compared with placebo, were 1.1% for patients taking the 40-mcg dose and 1.2% for those on the 60-mcg dose. Patients who were not taking SUs saw an average A1C decline of 1.7%; a majority of these patients were also on metformin. According to the study abstract, patients taking the 60-mcg dose achieved more weight loss.

High-baseline patients.[3] A separate

study without a control group examined how well ITCA 650 would work for patients with A1C levels between 10% and 12%, who were "too high to risk randomizing them to placebo," according to a statement from Intarcia.

In this study, 60 patients with a mean A1C of 10.8% and a mean BMI of 32 kg/m^2 were given the study drug for 39 weeks, starting at the 20-mcg dose for 13 weeks and continuing at the 60-mcg dose for 26 weeks. Any oral antidiabetic drugs patients were taking prior to the study were continued.

These patients achieved an average A1C reduction of 3.4% by week 39, but researchers noted that significant reductions had been observed by the 6-week mark: 22% of the patients saw reductions of 4% or greater, and 25% achieved an A1C of <7%

"I am very pleased with these phase 3 results," said lead author Robert R. Henry, MD, chief of endocrinology and metabolism at the VA in San Diego and professor of medicine in residence, University of California at San Diego. The results show that this delivery method "may provide an uninterrupted, smooth, and continuous dose that delivers powerful reductions in A1C without the need for patient action in terms of managing their medication, which we all know can be very challenging." **EBDM**

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Medtronic Makes News at ADA With 640G Results, Samsung Partnership, Start of Pivotal Trial

Mary K. Caffrey

FRANCINE KAUFMAN, MD

Dr Kaufman is the chief medical officer of Medtronic Diabetes.

The annual Scientific Sessions of the American Diabetes Association (ADA) always serves as the year's most important coming out party for makers of insulin pumps and continuous glucose monitoring (CGM) technology. The sessions offer an opportunity to share clinical trial results and prototypes of what's in the pipeline, and device manufacturer Medtronic did some of each this year.

The ADA sessions offered a backdrop for Medtronic to announce partnerships with Glooko and Samsung,[1] as medical device makers increasingly collaborate with leaders in consumer technology. Advocates in the diabetes community have long called for products that not only provide better glycemic control with less patient interaction, but also are better designed and more discreet,[2] with the ability to share data on platforms such as smartphones or watches.

Medtronic received pushback in September 2013 when it unveiled its MiniMed 530G with Enlite, describing the system, with its "threshold suspend" technology as a "first-generation" artificial pancreas system.[3] While Medtronic received recognition among those with type 1 diabetes mellitus (T1DM) for taking a genuine step forward, the use of the words "artificial pancreas" was viewed by some as an overreach in the case of this product.

By contrast, Medtronic received generally positive feedback from leading reviewers on the news it rolled out at ADA in Boston.[4,5] Besides the deal with Samsung and Glooko, the company announced:

- A user evaluation study for its MiniMed 640G system, the system that will succeed the 530G, which is currently available in Australia and Europe.
- Medtronic is enrolling patients in the first pivotal trial study of a hybrid closed-loop system, which the company said "is designed to automatically control glucose levels 24 hours a day with less input from patients."[6]
- FDA approval of MiniMed Connect, a data-sharing system for its insulin pump and CGM combination. Real-time data from 2 current Medtronic CGM systems can be connected to Medtronic's CareLink software, with data uploaded to a smartphone. Family members—such as parents of children with T1DM—can get a text message in the event of blood sugar highs or lows. The system requires a small uploader device about the size of a thumb drive, which costs $199 and will be available this fall.[7]

Results From the 640G. This advance features a technology called SmartGuard, which has a feature called "suspend before low." The next step after "threshold suspend," it is designed to be forward looking, and stops insulin before the sensors show a glucose level falling below a preset low limit; the technology also restarts the insulin delivery once glucose levels return to normal.

The study evaluated 40 adults and children with T1DM at 3 sites in Europe for 30 days. The mean age of the participants was 31 years, and participants had lived with T1DM an average of 17 years. In that period there were 2402 events in which insulin was suspended, including 2322 "suspend before low" and 80 "suspend on low." In 83.1% of the "suspend before low" events, insulin levels did not reach the preset low limit. Four mild adverse events were reported: 2 skin reactions, a cold, and a urinary tract infection.[6,8]

MiniMed Connect 640G

SOURCE: Medtronic

Francine Kaufman, MD, chief medical officer at Medtronic Diabetes, told *Evidence-Based Diabetes Management* before the ADA sessions that the predictive glucose management system in the 640G is the result of input from T1DM patients. "Rather than wait until you get to the threshold, we'll stop the insulin in anticipation of where we'll be 30 minutes from now," she said in an interview. This "predictive horizon" concept keeps patients from ever approaching a severe hypoglycemic episode, which can cause brain injury and even death.

As Kaufman explained, the 640G also allows patients with T1DM to adjust the insulin-suspension threshold at different times of day, depending on activity levels or food consumption. In terms of quality of life, these advances are a huge step forward, because they reduce the likelihood that patients will have a hypoglycemia episode at night while sleeping, which is a major concern of persons with T1DM.

While approval for 640G is the short-term goal, the pivotal trial is a more concrete step toward a closed-loop system. "We're not going to stop until we get there," Kaufman said.

Working With Glooko, Samsung. Medtronic's announcement that it will partner with Glooko, a Cloud-based diabetes management platform developed in collaboration with Joslin Diabetes Center's Howard Wolpert, MD, will reportedly lead to better integration of data from its insulin pumps and CGM devices with other related food and wellness data. Wolpert described the Glooko technology this spring at Patient-Centered Diabetes Care, a conference jointly presented by *The American Journal of Managed Care* and Joslin. He said caregivers and providers will be able to access the data via smartphones, improving care management and making it possible to find out earli-

THE AMERICAN JOURNAL OF MANAGED CARE 20

MiniMed Connect with uploader

SOURCE: Medtronic

er about imminent hypoglycemia events.

Samsung's involvement (both Medtronic and Samsung have invested in Glooko)[9] is aimed at tapping the company's "deep understanding of consumer mobile technology,"[1] with the goal of creating CGM products that are more user-friendly—and less obviously medical devices. In a joint statement, the companies said that Android technology is used by 80% of smartphone users globally. **EBDM**

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Links Found Among Higher Co-Payments, Lower Adherence, Higher Medical Costs in T2DM Medicare Patients

Mary K. Caffrey

An analysis of Medicare claims data found that when seniors with type 2 diabetes mellitus (T2DM) did a better job of sticking with their medication, the result was less overall healthcare spending. Conversely, higher out-of-pocket costs for drugs reduce adherence and can cost Medicare in the long run.

The associations among higher out-of-pocket costs, lower adherence, and higher total spending, culled from Medicare claims data from 2006 to 2009, were presented July 7, 2015, at the 75th Scientific Sessions of the American Diabetes Association (ADA).

Joanna P. MacEwan, PhD, research economist with Precision Health Economics, told the attendees at the session, "Cost-Effectiveness of Managing Diabetes and Related Complication," that her findings were consistent with earlier literature, but she added some important wrinkles: the data show, for example, that small differences in adherence really add up when it comes to spending. That's important for policy makers to know, she said.

In a follow-up email after ADA, *Evidence-Based Diabetes Management* asked MacEwan what implications her results have in light of the many new, powerful, but very expensive diabetes medications that have come on the market since the period of the claims analyzed. "Medicare may be tempted to increase cost sharing in an attempt to control prescription drug spending on new treatments," she said in an e-mail. "However, in the long run, this strategy could be worse for patients and increase Medicare spending overall by increasing spending in Parts A, B, and C."

The study used a sample of 12,305 person-year observations, all in patients at least 65 years of age. A diagnosis of T2DM was confirmed through *ICD-9* diagnostic codes and at least 1 prescription claim for an antidiabetic drug. Researchers segmented the cost and adherence outcomes into deciles, and used the medication possession ratio to further analyze levels of adherence. Age and gender did not differ across deciles.

Unsurprisingly, the patients who accounted for the highest overall spending had the poorest overall health, MacEwan said. However, these costs were not on the pharmacy side. "Healthcare spending that increases dramatically, and accounts for the bulk of the total spending, is coming from the medical side," she said, which would include items like hospitalizations or visits to the emergency department.

According to the authors' abstract, the most adherent patients, those in the top decile, had higher pharmacy costs compared with those who were least adherent: $4839 versus $3046. However, these highly adherent patients had lower overall expenditures: $12,531 compared with $24,468. Of note, their medical expenses were about one-third of those who were least adherent to medications: $7692 compared with $21,421.[1]

In her presentation in Boston, MacEwan presented data to show that higher out-of-pocket costs were associated with poor medication adherence, and that poor adherence was associated with higher healthcare spending. Her slide showed that while pharmacy spending stayed relatively flat, the more adherence improved, the more medical and total spending fell. This, she said, showed that "Medical and total expenditures could be relatively sensitive to small differences in adherence."

JOANNA P. MACEWAN, PHD

Dr MacEwan is a research economist with Precision Health Economics.

Cost-sharing programs aimed at lowering pharmacy costs could be counterproductive, MacEwan said, because, "Small differences could have a large impact on spending."

In the follow-up e-mail, *EBDM* asked MacEwan if it was possible to tell whether cost was the most important factor

affecting adherence, as opposed to other elements such as the complexity of a therapy regimen. "Our study cannot predict whether price plays the most important role in determining adherence for Medicare beneficiaries with T2DM, but it supports the hypothesis that price is a critical factor," she said in an e-mail. "In some clinical circumstances/diseases, we know that eliminating co-payments will improve adherence by 10 percentage points, up to about 75%, implying that other factors are also at play."

However, she noted that a review of studies on adherence shows that among all the many factors, cost has the greatest effect on adherence.[2]

She recommended additional research to pinpoint connections between levels of co-payment and health outcomes. The study was supported by AstraZeneca.

Controlling the ABCs. Ping Zhang, PhD, presented an analysis on behalf of the CDC that tried to identify the point at which it ceases to be cost-effective to add an additional medication to treat glycated hemoglobin (A1C), blood pressure (BP), or low-density lipoprotein (LDL) cholesterol.[3] Treatment to control the 3 is a fundamental part of T2DM care. While the CDC abstract says that some evidence now questions this approach, providers cannot ignore these measurements, because CMS is increasingly connecting Medicare reimbursement to the ability of physicians and health systems to keep T2DM patients at goal.

The CDC analysis looked at the cost-effectiveness, in quality-adjusted life-years (QALYs), of adding a separate drug to treat A1C, BP, or LDL cholesterol. The analysis, however, did not consider the synergistic effects that some medications would have in combination, or the fact that some T2DM therapies also help patients achieve weight loss. The failure to include these elements caused some alarm during the question-and-answer period.

The analysis found that for a newly diagnosed patient, adding a second and third drug for A1C would yield incremental cost-effectiveness ratios (ICERs) of $17,225 and $106,059 per QALY, respectively (ICERs above $50,000 are considered not cost-effective).[4] For an established T2DM patient, adding a second or third A1C drug would yield ICERs of $20,275 and $112,710 per QALY, respectively. For a newly diagnosed or established T2DM patient taking 2 BP drugs, adding a third would yield an ICER of $31,000 per QALY. For a newly diagnosed or established patient with uncontrolled, untreated cholesterol, a moderate-dose statin would yield ICERs of $15,267 and $15,929 per QALY, respectively.[3] **EBDM**

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Study Funded by ADA Shows CDEs in Primary Care Improve Health of T2DM Patients

Mary K. Caffrey

American Diabetes Association.
A study funded by the American Diabetes Association®

JANICE C. ZGIBOR, PHD, RPH

Dr Zgibor is associate professor of epidemiology, University of Pittsburgh.

The effect of "clinical inertia" on patients with type 2 diabetes mellitus (T2DM) is well known—patients stay on lower doses of therapy longer than they should, and they may not get the most personalized advice about diet, exercise, or self-care.

A study funded by the American Diabetes Association and presented at its 75th Scientific Sessions in Boston on June 7, 2015, examined what would happen if certified diabetes educators (CDEs) were attached to primary care practices in a meaningful way—with access to the electronic health record (EHR), with the ability to recommend prescriptions, and, most important of all, with easier access to patients themselves. Results justified expanding the role of CDEs in primary care—assuming practices can find ways to pay for it.

Presented by Janice C. Zgibor, PhD, RPh, associate professor of epidemiology at the University of Pittsburgh, the study was a randomized controlled trial that used CDEs in 2 different groups across 15 nonacademic practices. The practices would identify and refer patients who met eligibility criteria for a diabetes diagnosis to the CDE, for either diabetes management protocols or usual care. Patients who met the criteria could also self-refer, and there were materials in the offices with instructions on that process.

In this study, patients meeting the criteria for referral had to have glycated hemoglobin (A1C) of at least 7%, low-density lipoprotein (LDL) cholesterol of at least 100 mg/dL, or blood pressure of at least 140/80 mm Hg.

- In the practices randomized for the diabetes management protocols, staff identified and referred 175 patients, who were eligible for intensified therapeutic management based on evidence-based guidelines. Access to the EHR was critical, as the CDEs often left recommended prescriptions for doctors, who could act on them within a day.
- In the usual care practices, staff identified 65 patients who were eligible for a monthly visit from the CDE. Zgibor speculated that the fact that the CDEs were only in these practices once a month may have led to the smaller number of referrals.

The average age of the patients in both groups was 61 years, evenly divided between men and women, and 83% were white. After 3 months, results showed that the patients in practices where CDEs were using diabetes management controls were experiencing more rapid improvement in health outcomes, as follows:

- **A1C:** For the patients receiving care under diabetes management protocols, A1C decreased from 8.8% to 7.8%; for the usual care group, it went up slightly, from 8.2% to 8.3%.
- **LDL cholesterol:** For the diabetes management protocol group, LDL cholesterol decreased from 104.9 mg/dL to 88.2 mg/dL; for usual care, it went down from 100.2 mg/dL to 89.6 mg/dL.
- **Blood pressure** differences were not significant.

Zgibor observed that patients receiving care from the CDEs administering evidence-based protocols were more likely to have medication adjusted quickly, while changes took longer to implement for the usual care group. This is the hallmark of "clinical inertia," and patients can suffer health effects during the time it takes for primary care physicians to realize that medication doses need to increase, she explained.

Members of the audience asked about the challenge of billing for CDEs, and Zgibor said this is her next area of research. **EBDM**

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Family-Focused Intervention Produces Positive Health Outcomes for African Americans With T2DM

Mary K. Caffrey

Natasha Greene, PhD, FNP, BC, created an innovative way to give low-income African Americans lessons in diabetes self-management, but the study participants taught her a few things, too.

Greene, an assistant professor of nursing at North Carolina Central University, is the principal investigator for the Diabetes Family Project, which aims to tackle the high rates of type 2 diabetes mellitus (T2DM) and early deaths by addressing the cultural challenges of behavioral change.

Specifically, Greene and her team realized that getting the person with T2DM to eat properly means educating others in the house who prepare meals or influence what the family eats.

She presented her findings at the session, "Effective Strategies for Overcoming Barriers in Self-Management," which took place June 7, 2015, during the 75th Scientific Sessions of the American Diabetes Association in Boston. Her study, "Effect of Family-Focused DSME on Physiological Outcomes in African Americans with Type 2 Diabetes," found that having an influential family member—typically the spouse—take a diabetes education course alongside the person with T2DM produced measurable, positive health outcomes, compared with a control group of T2DM patients who took the course without a family member.

The research team trained 5 community lay persons and 2 dieticians in curricula that included 3 classes about diabetes, 1 about exercise, and 4 devoted to nutrition. T2DM participants had to be at least 40 years old of age diagnosed at least 1 year ago. The team recruited participants from a rural area of North Carolina to take part in the study, either in the intervention or control group. That's when the surprises began.

Greene said recruitment took place in churches, community centers, and even in local restaurants that served families. "We emphasized that this was something that was for the family and about the family," she said. To get spouses to take part, Greene said they were told, "It's so that you can be healthier, too." When the research team held its first meeting with the participants, 74 families were scheduled to show up. Instead, 80 appeared. Word had spread.

Fifty-two couples began the intervention, with the other T2DM patients taking the education course as individuals. Mean age of the participants was 58.8 years, and the average income was $21,000 per year.

TABLE. Results of a Family-Focused Diabetes Education Intervention

Results	Baseline	3 months post intervention
A1C	8.1% IG; 7.8% CG	92.4 ± 5.4
Blood pressure		
Systolic (mm Hg)	154.2 IG; 146.3 CG	139.5 IG; 140.2 CG
Diastolic (mm Hg)	75 IG; 72.2 CG	69 IG; 73.5 CG
LDL cholesterol (mg /dL)	106 IG; 95 CG	96.3 IG; 99.0 CG

A1C indicates glycated hemoglobin. CG is control group; IG is intervention group.
SOURCE: Greene N, Eaton S, Hoag J. *Diabetes*, 2015;64(suppl1): abstract 204-OR.

Natasha Greene, PhD, FNP, BC, of North Carolina Central University, gives instructions to study participants at the start of the Diabetes Family Project. Photo courtesy of North Carolina Central University.

Each of the 8 weekly classes lasted 90 minutes, and participants completed surveys to evaluate the content and the educator's presentation skills, and to test their knowledge. Focus groups were held 3 weeks after the end of the course. Health measurements were conducted at baseline and 3 months after course completion.

Results. Forty-eight couples completed the intervention, each attending at least 6 of the 8 classes. Participants rated the course 27 out of 28 possible points in an evaluation of its design, content, objectives, and teachers' knowledge. Health measurements (averages) for the intervention group compared with the control group were as follows:

- **Glycated hemoglobin.** The intervention group went from 8.1% at baseline to 7.8% at follow-up; the control group, from 7.8% at baseline to 7.7% at follow-up.
- **Blood pressure (BP).** Systolic BP for the intervention group dropped from 154.2 to 139.5 mm Hg; for the control group, from 146.3 to 140.2 mm Hg. Diastolic BP for the intervention group dropped from 75 to 69 mm Hg; for the control group, from 72.2 to 73.5 mm Hg.
- **LDL cholesterol.** LDL cholesterol level for the intervention group dropped from 106.0 to 96.3 mg/dL, while for the control group, it increased from 95.0 to 99.0 mg/dL.

Greene credited the teaching methods, which taught the intervention group how to resolve conflicts over food preparation with real-life scenarios. "We asked them to think about it and work it out," she said.

> *"We emphasized that this was something that was for the family and about the family." To get spouses to take part, they were told, "It's so that you can be healthier, too."*
>
> —NATASHA GREENE, PHD, FNP, BC

The results show that for the African American community, having persons with T2DM attend diabetes classes with a family member can be "feasible, acceptable, and more beneficial" than having patients take classes alone.

But did the participants gain knowledge about diabetes? Well, yes, Greene said, but the data are problematic. As she went through the test results, it became apparent that the couples in the intervention group were sharing answers, as their results "correlated perfectly." Going forward, Greene plans to separate couples during the test—"I call it 'new investigator learning curve.'"

Funding for the Diabetes Family Project comes from the National Institute of Minority Health and Health Disparities P20 grant. **EBDM**

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Medicare's Failure to Cover CGM at Odds With Other Health, Research Agencies
(CONTINUED FROM COVER)

Patient Surveys Point to Cost Savings, Quality-of-Life Benefits From CGM Use

MARY K. CAFFREY

Use of continuous glucose monitoring (CGM) technology can save money in ways large and small, while reducing the fear of hypoglycemia episodes among those with diabetes, according to a pair of patient surveys presented at the 75th Scientific Sessions of the American Diabetes Association (ADA), held June 5-9, 2015, in Boston.

While results were not limited to those with type 1 diabetes mellitus (T1DM), concerns about access and payer coverage for CGM devices and supplies is a more universal concern among this group than in the population with type 2 diabetes mellitus (T2DM).

A study of a small group of patients using Dexcom's G4 device (See **FIGURE**) found that after a year of regular use, patients who relied on CGM cut in half the number of daily blood glucose tests they needed to maintain glycemic control. What's more, this group also reported dramatic reductions in the number of hospitalizations, trips to the emergency department (ED), or visits by paramedics, events that are major cost drivers in managed care.[1,2]

How often patients test their blood sugar each day depend on a number of factors, including overall health, what they eat, and how much exercise they get on a given day. CGM technology reveals not only a blood glucose reading, but its pattern throughout the day, giving the patient more valuable information than a meter alone.

While coverage for CGM technology has become standard among many commercial insurers, patients often face limits on the daily coverage of test strips. Meanwhile, Medicare does not cover CGM technology too hard to explain, causing patients to return to less reliable finger-stick testing, which does not provide the warning that blood glucose levels are rising or falling.

FIGURE. Dexcom G4

SOURCE: Dexcom

Results published at ADA involved the use the Dexcom G4 device. The study included 74 patients receiving intensive insulin therapy. The average age was 42.9 years (from a range of 23 to 71 years). The group was 49% male and 76.6% had been diagnosed with diabetes for at least 10 years. Most (79.7%) received insulin through a pump rather than injections.[1]

Study participants completed a questionnaire that examined how often they used the Dexcom G4 device and why they did (or not did) keep using it. Of the 74 participants, 58 (78.3%) reported CGM use on most days. Patients reported a 50.0% reduction in their average number of daily blood glucose tests after using the device for 1 year. The study group also reported an 85.7% reduction in the number of emergency hospitalizations or paramedic visits compared with the prior year. Thus, the researchers concluded, the cost of CGM technology can be easily offset by the savings that occurs if patients stay out of the ED.[1]

The Dexcom G4 Platinum system reportedly cost $1198 (without sensors) in 2012, when it received FDA approval.[3] By comparison, a study that appeared in *The American Journal of Managed Care* in 2011 found that the mean costs for hypoglycemia visits were $17,564 for an inpatient admission, $1387 for an ED visit, and $394 for an outpatient visit.[2] While this study involved patients with T2DM, it is frequently cited by the JDRF and other advocacy organizations when calling for Medicare to fund CGM technology.

Quality of life. Use of CGM technology can reduce patient fears of having an episode of hypoglycemia, and limiting anxiety has a positive effect on glycemic control, according to authors of a second abstract involving the Dexcom G4.[4]

The same 74-patient group was also asked about their concerns with hypoglycemia, both prior to using a CGM device and after a year of use. At the start of the study, a majority of respondents who ended up using CGM on most days (45 out of 58) reported worrying about hypoglycemia; either "most of the time" (20 respondents), or "frequently" (25 respondents). After a year of use, no respondents reported worrying about hypoglycemia "most of the time," and only 1 reported worrying frequently.[4]

James J. Chamberlain, MD, medical director for diabetes services at St. Mark's Hospital in Salt Lake City, Utah, and the lead author of the study, said creating peace of mind among those who depend on insulin delivery brings health benefits beyond what can be easily measured. Patients feel safer sleeping through the night, and so do family members, he told *Evidence-Based Diabetes Management* in an interview at the ADA sessions.

"The biggest fans are often spouses," he said, especially with advances that allow CGM data to be sent to a family member's iPhone. While the study group was too small to glean any differences among age groups, he said the arrival of CGM technology offers opportunities for young patients with T1DM to participate fully in team sports, and for all age groups to experience greater safety while exercising or traveling. **EBDM**

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SENATOR SUSAN M. COLLINS

US Senator Susan M. Collins is a Republican from Maine. She has served in the Senate since 1997.

with type 1 diabetes mellitus (T1DM).[1] Advances in technology, such as continuous glucose monitors (CGMs), are helping patients control their blood glucose levels, which is key to preventing costly and sometimes deadly diabetes complications. We are also moving closer and closer to our goal of an artificial pancreas, which would control blood glucose levels automatically and revolutionize diabetes care.

The NIH and the FDA have been extremely supportive of these innovations in diabetes care. As chairman of the Senate Aging Committee, I was surprised and troubled to learn that insulin-dependent Medicare beneficiaries with T1DM are being denied coverage for CGM technology because CMS has determined that they do not meet the Medicare definition of durable medical equipment and do not fall under any other Medicare category. As a consequence, we are seeing situations—similar to what we saw with insulin pumps in the late 1990s—in which individuals with T1DM have had coverage for their CGM on their private insurance, only to lose it when they age into Medicare.

A CGM is a physician-prescribed, FDA-approved medical device that can provide real-time readings and data about trends in glucose levels every 5 minutes, thus enabling someone with insulin-dependent diabetes to eat or take insulin and prevent dangerously low or high glucose levels. As demonstrated by extensive clinical evidence, adults using a CGM have had improved overall glucose control and have reduced rates of hypoglycemia. Professional medical societies, including the American Association of Clinical Endocrinologists (AACE) and the Endocrine Society, recognize this clinical evidence and have published guidelines recommending CGMs be used in appropriate patients with T1DM.[4] Today, about 95% of commercial insurers provide coverage for CGM devices.

I recently heard about this issue from one of my constituents, a 74-year old woman in Portland, Maine. Diabetes treatments have dramatically changed since she was diagnosed with T1DM in 1954. Testing her glucose levels back then involved test tubes and urine sticks—inaccurate tests that provided 4-hour-old results. Today, she checks her blood sugar with a blood glucose meter, which shows current glucose levels and is significantly more accurate.

While she has led an active and fulfilling life, living with T1DM for more than 60 years has taken its toll. Today, she can no longer feel when her blood glucose is dropping dangerously low; as a result, she loses consciousness and suffers seizures more frequently. Nighttime low sugars are particularly concerning, and she fears the possibility of her blood sugar dropping so low during the night that she never wakes up.

The CGM is a potential lifesaver for diabetes patients because it alarms the wearer when blood glucose levels fall or rise to dangerous levels.

Still, even though 95% of private insurers cover CGM technology, Medicare does not. As a consequence, many older Americans do not have access to this potentially lifesaving device because they can't afford to pay for it out of pocket. Thousands of seniors with T1DM are denied access to the CGM technology that would keep them healthy and safe.

Ironically, it is only because of advances in diabetes care such as the CGM that people with T1DM can expect to live long enough to become Medicare beneficiaries. I am particularly concerned about the implications this coverage decision has for the artificial pancreas systems, which will combine a CGM, insulin pump, and sophisticated algorithm to control high and low blood sugar around the clock.

This coverage decision by CMS—which, after all, is also part of HHS—is in direct opposition to all of the work that the NIH and the FDA are doing to get new innovative treatments and technologies to patients. At a recent Senate Health, Education, Labor, and Pensions Committee hearing, I had the opportunity to ask outgoing FDA Commissioner Margaret Hamburg whether CMS consults with her agency when making these kinds of coverage decisions. In response to my question, Commissioner Hamburg expressed regret that her agency does not routinely consult with CMS about payments for FDA-approved drugs and devices, saying that the FDA should "look at the whole ecosystem of

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biomedical product development and use, and recognize that all of the different components that often operate in silos actually are very interdependent." I completely agree with her assessment.

It is for this reason that I have joined with Senator Jeanne Shaheen, my colleague from New Hampshire and co-chair of the Senate Diabetes Caucus, in introducing the bipartisan Medicare CGM Access Act of 2015, to create a separate benefit category under Medicare for the CGM and require coverage of the device for individuals who meet specified medical criteria.[5]

Our legislation is strongly supported by a coalition of organizations, including the AACE, the American Association of Diabetes Educators, the Endocrine Society, and the JDRF. We must change our country's future with regard to diabetes by immediately addressing the explosive growth in the financial toll and human toll of this epidemic. By including CGM under Medicare, we can help transform the lives of older Americans living with this devastating disease. **EBDM**

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mHEALTH RESEARCH

Can mHealth Revolutionize Evidence-Based Practice in Diabetes Care?

(CONTINUED FROM COVER)

producing high-quality evidence to demonstrate the clinical and economic outcomes enabled by mHealth.

This article reviews mHealth's promises and challenges in the context of multiple US healthcare system stakeholders. We include specific commentary and examples for mHealth application in evidence-based diabetes care.

INTRODUCTION

Digital health devices, as defined by Accenture, are "Internet-connected devices or software created for detection or treatment of a medical indication."[1] Mobile health (mHealth) is a form of digital health that specifically includes the use of mobile technologies within healthcare. Data from mHealth can be used to inform, assess, anticipate, and aid in interventions while monitoring and coordinating patient health status and care. This use of real-time patient data will facilitate evidence-based practice, which is a research-informed, interdisciplinary approach to coordinating clinical care.

This paper is the result of a multiple stakeholder issue panel on the promise of mHealth presented at the 19th Annual International Society of Pharmacoeconomics and Outcomes Research (ISPOR) congress. The authors reflect the panel membership encompassing the perspectives of US decision makers in the life science industry, health service providers, and regulatory and payer communities. This review was augmented with specific mHealth examples relevant to diabetes care. To the best of our knowledge, there has been no comprehensive survey of where and how mHealth is being used to execute health services research and deliver evidence-based practice. This paper includes expert opinion and information gathered from a non-systematic scan of the peer-reviewed literature, government reports, news releases, and intelligence gathered at or after our issue panel. No attempt was made to include a comprehensive list of citations and sources.

THE STATE OF THE ART: 2015

The field of mHealth is experiencing rapid growth, with the market expected to reach $26 billion by 2017.[2] Overall, the digital health industry is projected to save $30 billion from improvements in medication adherence, behavior modifications, and fewer emergency department visits within the US healthcare system.[1] Multiple stakeholders are engaged in realizing this promise, and a majority (59%) of physicians and insurers view mHealth as an integral piece of the future of healthcare, believing that widespread adoption of such technologies and applications is unavoidable.[3]

While some healthcare applications may require dedicated mobile devices, the more common forms of mHealth requir=e only modest hardware augmentations or application downloads using general purpose devices. In fact, the adoption of the types of enabling technologies required for mHealth applications is currently nearly universal in the United States, where 90% of American adults own a cell phone, followed closely by access to tablets and personal computers.[4] Building off of this broad technology access, innovators in the mHealth field have been engaged in developing location- and platform-agnostic validated instruments for patient-centric real-time data capture using mobile technology. Captured data can be integrated with existing patient and guidelines information, and systematically analyzed via clinical algorithms, to provide timely and customized evidence-based care, often self-directed, to the patient.[5-6] This is noteworthy because many stakeholders believe that savings in the healthcare system can only be realized by taking providers out of the equation where possible and appropriate.

Arguably, the well-developed applications of mHealth have been in epidemiology and general public health—often in remote areas where traditional means of disease monitoring, response, and in-person examinations are lacking.[7] Diabetes is a disease area in which mHealth applications may be particularly relevant given the demographics, the public health challenge, and the fact that it is a condition that relies largely on self-management. This space is rife with potential for realizing the health efficiency promise, as $176 billion is spent annually on diabetes care, based on 2012 estimates.[8] Further, multiple researchers have documented an inverse relationship between diabetes patient adherence to treatment and annual healthcare costs.[9,11]

Increasing access to healthcare may highlight an even greater need for care coordination support; for instance, in the past year, researchers observed that 23% more Medicaid patients were diagnosed with diabetes in states that adopted Medicaid expansion as permitted under the Affordable Care Act, compared with 0.4% in states that did not expand Medicaid programs.[10] The prevalence of diabetes is especially high in rural areas—estimated to be about 17% greater than in urban areas.[11] Consequently, remote monitoring technologies, telehealth, and other digital health tools are increasingly being used in the attempt to improve diabetes care in these communities.[12] Although some evidence exists that these tools are improving health outcomes and reducing costs among persons with diabetes, limited data and uncertain findings persist. Further, research specifically calls for optimal care coordination in this population, which mHealth may support.[13,14]

Multiple stakeholders may hold a key to unlocking the potential of mHealth to revolutionize evidence-based practice in critical areas such as diabetes care, including the life sciences industry, providers, regulators, payers, and policymakers. The following commentary will explore each of these stakeholder perspectives in terms of the mHealth promise and challenge as it relates to the US health system's ambitious goals and evidence-based practice.

LIFE SCIENCES INDUSTRY

Evidence for Registration and Marketing

Life sciences industry stakeholders often consider using mHealth applications to augment the disease monitoring and tracking required in clinical trials. Much of the documentation associated with clinical trials can be transmitted by electronic, if not mobile, means. Automation facilitates the potential of lower-cost and higher-quality trials through enhanced data elements, superior accuracy, reduced risk of bias, and other technical improvements to research techniques. Although mHealth is still in its infancy, most frequently cited opportunities include incorporation of patient reported outcomes (PROs) into pre-, peri-, and/or post clinical research (within or outside of registries). Examples of PRO measures include symptoms, quality of life, health states, patient experience, patient satisfaction, perceived "value" of treatment, activity improvement or limitations, and therapy adherence tracking.[15]

Using the medical product development process (as adapted in **FIGURE 1**), mHealth can be applied to research and marketing in at least 8 different aspects of a product life cycle.

In addition to registration requirements, industry stakeholders have a strong mandate to market the effectiveness of healthcare technologies (traditionally drugs, devices, and diagnostics) from both a clinical outcomes and and an economic point of view. Toward this

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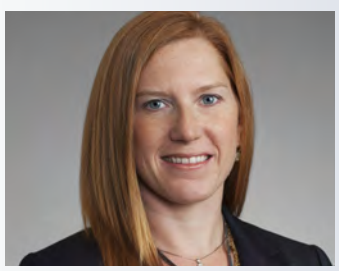

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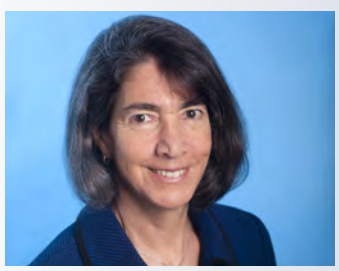

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end, longitudinal data series are being created as additional "extensions" of current warehouse data sets become available through mobile device–facilitated transmissions. In selected instances, data professionals are reporting "cyber" comparative effectiveness based on mobile transmissions of real-world evidence.[16] As an example, in single data warehouses, researchers are compiling clinical and administrative data, clinical trials and research information, molecular and biological data, and PROs. Professionals also report that they can connect processed information in the warehouse to clinical care outputs transmitted by mobile means to the patient. For instance, the algorithms developed to provide patients with diabetes or their providers with specific and relevant information related to a device, treatment, or recommended intervention are based on patterns seen in large public data sets coupled with proprietary patient-level information facilitated by mHealth tools and data linkages.

Various applications of this real-time information are now emerging in the diabetes care and population health space. For example, mHealth technologies and tools have been incorporated into patient wellness and disease prevention plans. These include smartphone apps that record food intake or exercise activity as well as text message services with healthy living reminders.[17] For patients with type 2 diabetes mellitus, a mobile application can be prescribed that continuously monitors the patient's key health metrics and behaviors in real time and adapts prescription therapy intervention recommendations based on these data. This demonstrates a potential place for mHealth in patient care as well as the advancement of knowledge on best practices in abetting self-care.[18] Another mHealth device that measures the patient's key health metrics is the continuous glucose monitor. This device provides the capability for patients to actively and continuously monitor their own health status, and some have the added capability of sharing data with their caretakers and physicians through connected mobile applications, supporting care integration (see stories, **SP374, SP378**).[19,20] With the growing innovations and possibilities in mHealth technologies, life science and other consumer product companies can explore opportunities to market solutions that inform, assess, anticipate, and aid in interventions with the purpose of delivering evidence-based management, driving better outcomes, and delivering value to various customers.

PROVIDERS

Evidence-Based Practice Considerations

Healthcare providers are critical stakeholders in the integration of mHealth into evidence-based practice.

Health services research is a multidisciplinary field that examines patient access to health services, cost of care, and patient outcomes following care delivery. Evidence-based practice can take years to transition from academic health service research to widespread application in clinical guidelines. Leveraging mHealth's access to real world data (data collected outside conventional randomized controlled trials or other clinical studies), researchers can identify gaps in population health and areas of focus for intervention; collect data (including resource use) during implementation in different settings (with and without intervention); monitor health outcomes and compliance to interventions over time as well as costs; and evaluate policy changes for screening or other key questions. The use of mHealth has the potential to revolutionize the uptake of evidence-based medicine by providers due to rapid insights and the ability to integrate health services research analytics into care algorithms. For example, mHealth applications can align prompts for patient behavior modification and clinical decision making with best practice guidelines. These prompts hold the promise of optimizing patient outcomes and streamlining care services in near real time.

Information Systems and Privacy

Health system stakeholders often contend that the triple aim promises of high-quality care, improved outcomes, and lower costs will be unattainable until mHealth can integrate into the existing technology infrastructure. Taken literally, this challenge means that mHealth has to be interoperable with existing technologies such as electronic health records and similar tools—which it must be. The diversity of existing electronic hardware, software, and telecommunication systems in developed countries lead to interface and interoperability difficulties within mHealth programs, as there is a seemingly unlimited number of platforms to choose from, each claiming a unique value-add to the patient care continuum. Despite the small-scale progress in developing platform-agnostic software to circumvent interface difficulties, interoperability will continue to pose challenges until more uniform information technology standards, "open systems," or other work-around solutions emerge.

As mHealth becomes more "personal," challenges of privacy, security, and data control increase. At minimum, mHealth devices must protect patient privacy while retaining the data quality and accessibility for research. Patients must have control over their data, regardless of the device. An extensive discussion of patient privacy and data security is beyond the scope of this paper. Of note, the Office of the National Coordinator for Health Information Technology (ONC) released a Privacy and Security Framework in December 2008, outlining principles that should be incorporated into the mHealth architecture: openness and transparency; individual choice; collection, use, and disclosure limitation; data quality and integrity; safeguards; and accountability.[21] Public and private sector entities alike will be challenged to consider all of these principles as they create mHealth systems that will assure patient privacy and data security.

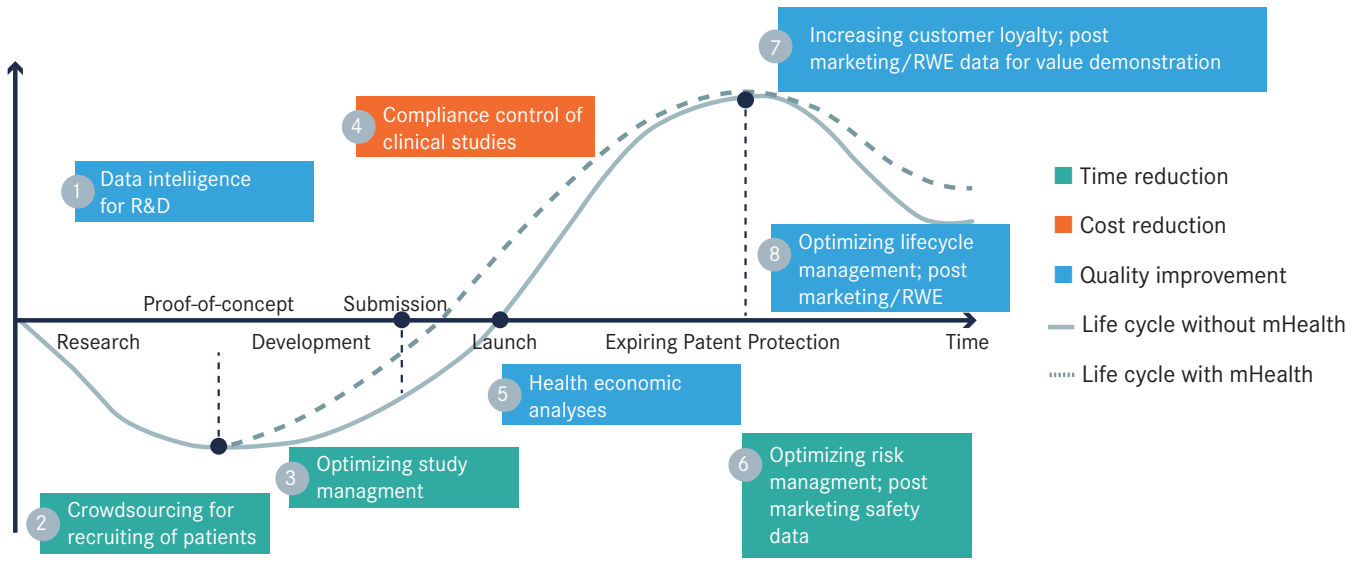
REGULATORY

Frameworks for mHealth Technology Approval

The FDA regulatory framework for medical devices is applicable to many mHealth products. The FDA requires clearance (through a process known as the "510k" process) or pre-market approval (PMA) of mHealth products that meet the definition of a medical device. The FDA uses historical precedent and paradigms to approach the regulation of mHealth, while also incorporating concepts of "enforcement discretion" for low-risk products to encourage innovation in this area. The agency is grappling with regulating novel mHealth technologies that do not fit squarely into the existing regulatory pathways, yet providing guidance documents to industry that communicate the FDA's policy and enforcement priorities. Examples include the FDA's January 2015 guidance documents: "General Wellness: Policy for Low Risk Devices"[22] and "Medical Device Accessories: Defining Accessories and Classification Pathway for New Accessory Types."[23] Other movements include strides to "down-classify" or deregulate products with low risk, such as the Medical Device Data Systems category of products that are now essentially unregulated after release of the FDA's February 2015 final guidance.[24,25] Assessing the regulatory classification and the level of regulation that will apply to mHealth products will continue to pose challenges for the evolving FDA policy.

The safety and efficacy of regulated products continue to be the chief concern of the FDA. However, new models of regulation and adaptive regulatory policy will become necessary, as innovation in technology always seems to outpace the ability of a regulatory framework to adapt. The FDA has available an alternative product approval pathway, referred to as the "de novo" process, whereby an innovative product that fits a "less than

FIGURE 1. mHealth Use in Research and Marketing Associated With Medical Product Development[2]



R&D indictes research and development; RWE, real-world evidence.

high risk" profile can be reviewed and approved without a predicate device yet without a full PMA. In order to deal with innovation, the FDA does at times take an approach that is customized to the product. This novel approach can be extremely frustrating to mHealth developers due to a lack of predictability in evidentiary standards and the uncertain nature of the regulatory pathway.

Many issues around gaining regulatory approval for mHealth products are the result of the FDA's very limited experience with the broad portfolio of devices (many targeted at the consumer market), mobile applications, and other novel technologies.[26] A broad range of regulatory bodies are responsible for regulating mobile medical applications, including the Federal Trade Commission (FTC), the ONC, and the Federal Communications Commission. And while the April 2014 FDASIA Health IT Report proposed a strategy for risk-based regulation of mHealth,[27] the recommendations are being implemented by each independent agency and full Federal coordination has not yet been achieved. As a result, there are circumstances where the jurisdiction and authority of one agency may overlap with (or compete with) another. For example, the FTC has required removal of some mobile medical applications from the market for false and misleading medical claims. Most recently, the FTC targeted a mobile app for which the manufacturer had made unsupported claims that it could help diagnose melanoma or assess consumers' melanoma risk.[28]

Frameworks for Research

In terms of data and research methods used in mHealth approvals, the FDA has also largely held to historical precedent on the type of information accepted for product clearance. As the field evolves, product developers may be challenged to convince the FDA that new data collection methods produce data that is standard-compliant. Of great interest to researchers and health providers may be whether any of the "randomized clinical trial alternatives" and data derived from them will be acceptable for product approval. Within or outside of clinical trials, the variability of file types, formats, and other particulars will continue to pose challenges to integrating mHealth data with those collected by other means in health services research projects. Another challenge is the volume of data and the ability for reference databases to be dynamic, collecting new data regularly and adjusting software analysis of the data accordingly. This dynamic nature of data and software algorithms presents a challenge to researchers and regulators alike.

PAYERS

Most healthcare stakeholders agree that payers will not advance coding, coverage, and payment policies in support of mHealth until higher-quality evidence shows clearer clinical utility. Researchers are calling for stronger evidence for mHealth to support integration into public health programs, particularly in developing countries where the need for infusions of funding is also dependent on amassing the right evidence.[29] A systematic review and meta-analysis of mHealth interventions concluded that even well-designed studies of healthcare delivery process interventions showed only "modest benefits" and called for more high-quality trials to measure clinical outcomes.[30] This lack of real-world evidence is a common criticism of medical device technologies, as the regulatory frameworks often dictate greater focus on efficacy and clinical evidence rather than the effectiveness outcomes payers demand. With the growth and increased demand for improved technology, further research will be required to support payer decision making.

In considering the path forward, the authors posit that evidence of the benefits of mHealth technologies in diabetes care and remote patient monitoring through telehealth technologies creates a precedent for reimbursement in the digital health space. As an example, CMS' October 2014 physician fee schedule expands coverage of procedures that can be reimbursed for telehealth, specifically for activities such as remote patient monitoring, reviewing patient data, and live video consultations.[31] Recently, a mobile prescription platform documented reduced average blood sugar levels in patients, which resulted in reimbursement for this specific platform from several self-insured companies[26]; the platform developer is currently in negotiations with pharmacy benefit managers.[21]

POLICY MAKERS

Even with the recent success of select diabetes care mHealth products in gaining FDA approval and payer reimbursement, when pundits look at the skills and expertise needed to develop end-to-end patient care solutions that can provide desired population-level impact on outcomes and costs, it is clear that bringing these solutions to market and integrating them into care requires a diverse team. A coordinating body has been proposed that could lead the way to overcome existing obstacles and provide standards in an intense and unified fashion. Others disagree, claiming that even the federal government (if it were inclined to do so) could not play the role. As the field of mHealth applications evolves, it is essential that the multiple stakeholders work together to ensure a robust body of evidence that can inform health policies and reimbursement appropriate to these new tools, in addition to regulatory and clinical practice requirements. Most agree that a policy framework combined with increased cooperation among companies and political or regulatory decision makers, among other stakeholders, is needed to realize mHealth's potential. For high-burden diseases, we can imagine a call to action across multiple stakeholders that brings together the evidence, data systems, clinical policies, and collaboration frameworks (including patients) to accelerate integration of mHealth into evidence-based practice.

CONCLUSION

Reasons often cited as barriers to mHealth realizing its potential in the US healthcare system include:

1. Industry. This is a complex, tightly regulated market with various stakeholders and conflicting interests.

2. Providers. Clinical practice changes at a slow pace, and the application of information technology and focus on interoperability have been disproportionately slow and small in healthcare in general.

3. Regulatory. The legal or regulatory framework surrounding mHealth services remains ill-defined.

4. Payers. There is limited evidence of mHealth's benefits, hampering remuneration from third-party payers and causing some skepticism about the fraudulent substitution of mHealth for in-person provider services.

5. Policy makers. Incentives for multiple stakeholders to work effectively toward a common goal are lacking.

As more mHealth products come to market, challenges will undoubtedly arise in regulation, implementation, and adaptability of mHealth technologies. In pondering the future of mHealth in delivering evidence-based care, specifically in diabetes care, it is useful to think about its 4 aspects: regulatory pathway, software and hardware interoperability, payer policies, and reporting analytics standards.[35] On a more global level, mHealth cannot be seen as an end unto itself; it is a tool that can and should be used to coordinate or improve the delivery of higher-quality care for more people at an affordable price.

In summary, mHealth has great potential, particularly in diabetes, where there is a high clinical and cost burden, a need to accelerate efficient care in urban areas, and a need to supplement care for patients in rural areas who have limited access to healthcare. It is imperative that stakeholders across the con-

tinuum, from consumers to providers to regulators to payers, collaborate to build the infrastructure and policies that will drive high-quality personalized healthcare and improve patient outcomes through evidence-based practice. Today, we begin to see some of this potential realized with emerging technologies such as mobile medication therapies. Diabetes stakeholders are pioneers in adopting mHealth into the entire patient care pathway, and one could argue that mHealth's promise is poised to deliver in this complex disease area where patient engagement is critical to achieving better outcomes at a lower cost to the healthcare system. **EBDM**

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ARTIFICIAL PANCREAS

Multiple Teams Move to Testing Phase of the Artificial Pancreas

(CONTINUED FROM COVER)

earlier phases (see **FIGURE**).[1]

Medtronic Inc hopes to be the first company to bring such a product to market. The California-based company has long sold the only system that combines a pump and continuous glucose monitor (CGM) with software that automates any aspect of insulin delivery. (This advance led the FDA to dub Medtronic's MiniMed 530G an "artificial pancreas device system,"[2] but limitations in the automation—which begins and ends with the ability to pause insulin delivery after blood sugar falls below a preset threshold—underwhelmed some opinion makers in the T1DM community). Now, Medtronic is beginning a pivotal study of a far more ambitious device.

The company's Hybrid Closed Loop system uses data from a CGM and information that patients provide to pump the right amount of insulin at the right time. Patients still need to calibrate the CGM sensor with periodic finger sticks, tell the system how many carbohydrates they eat, and perform maintenance tasks such as replenishing the insulin in the pump, but the machine takes care of all the calculations and automatically adjusts basal insulin.

Medtronic announced this month that it would enroll 150 patients, aged 14 to 75 years, in a yearlong trial that would, if successful, provide all the data the company would need to ask the FDA to approve the system, which uses a Medtronic pump, a third-generation Enlite monitor, and proprietary software that performs the calculations.[3]

The company has already conducted a number of feasibility studies of its Hybrid Closed Loop system. Most of these studies have tested prototypes on small numbers of patients over short periods of time. Medtronic has not published complete data from any of these tests, but the research has helped the company optimize the underlying technology for the pivotal trial it just announced.

"The trial will measure not only A1C [glycated hemoglobin] levels but also the device's ability to deliver small packets of insulin every few minutes to keep the patient's blood glucose at or near a target. Maintaining blood sugar in this narrow band mimics what the body naturally does and may reduce the complications associated with diabetes to a greater degree than just reaching long-term A1C targets," said Francine R. Kaufman, MD, chief medical officer of Medtronic Diabetes.

"We'll also be using questionnaires to measure patient satisfaction with the system, and we expect enthusiastic responses. The Hybrid Closed Loop certainly doesn't automate everything and leave the patient to forget about diabe-

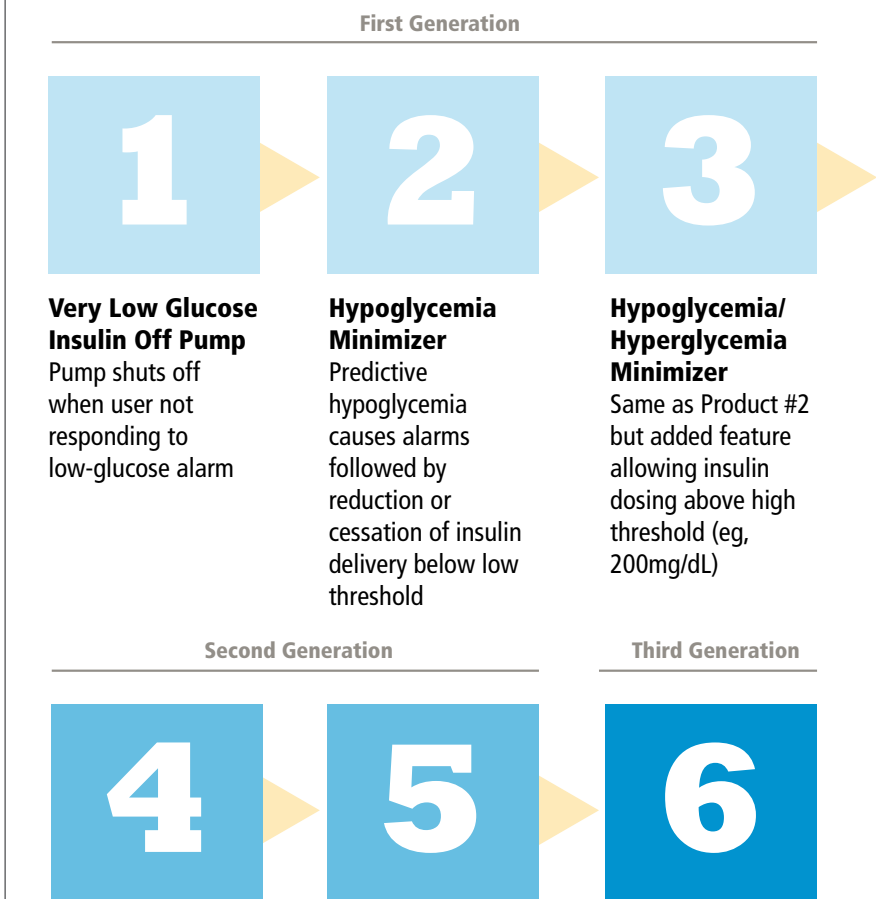
tes, but it does transform the condition from something that's primarily managed by patients to something that's primarily managed by the device. As someone who started out teaching patients to treat themselves with urine tests and animal insulin, I find the progress amazing. It's truly exciting to be launching this trial."

If all goes according to plan, Medtronic's Hybrid Closed Loop system will reach American patients in the first half of 2017, just about a year after the introduction of a simpler Medtronic system that uses intelligent software to reduce hypoglycemia.

The MiniMed 640G system is a successor to the 530G. Instead of waiting for blood sugar to drop below a preset level before pausing insulin delivery, the 640G uses software to predict when blood sugar is likely to drop below the threshold and pauses insulin delivery in advance. The MiniMed 640G is already available in Europe and Australia, where it could come to market without trial data, and it is undergoing the pivotal trial required for FDA approval.

Medtronic has announced preliminary 640G trial data, and the system's predictive low glucose management technology appears to significantly reduce hypoglycemia. Indeed, a study of 22 T1DM patients, published in *Diabetes Technology & Therapeutics*, found that it reduced hypoglycemia associated with manually controlled systems by 26.7%. (The low glucose suspend technology of the 530G reduced hypoglycemia by 5.3%). The predictive technology also reduced the duration of each hypoglycemic episode. The average duration was 101 minutes with the threshold suspend technology but only 58 minutes with the predictive technology ($P < .001$).[4]

FIGURE. Steps Toward the Artificial Pancreas



As outlined by the JDRF, progress toward a "closed loop" artificial pancreas is expected to come in steps, with 3 distinct generations of technology before patients are completely freed from the need to make adjustments to maintain blood glucose levels.

SOURCE: JDRF

Medtronic has divulged much more about its plans for artificial pancreas technology than its main competitors, but several of those companies have given investors and patients some guidance.

Kim Blickenstaff, CEO of Tandem Diabetes Care, outlined his company's plans during an earnings call in February: "In 2014, we initiated the R&D concept phase of our artificial pancreas offering. Our first AP [artificial pancreas] product will utilize Tandem's proprietary technology platform and will partially automate insulin delivery based on CGM information and predictive algorithms to aid a user. [It will] maintain their targeted blood glucose level and may reduce the frequency and severity of a hyper- or hypoglycemic event. In the second half of 2015, we plan to file an Investigational Device Exemption or IDE with the FDA for a clinical study in rolling out our first AP product."[5]

Insulet Corp's president and CEO Patrick J. Sullivan provided a similar level of guidance concerning his company's plans when he spoke to investors that same month: "We are putting together strategy so that OmniPod is a very significant part of the artificial pancreas product offering in the future. We have been working internally on our own CGM development, which continues, but we also have an agreement with Dexcom to use their CGM sensor along with our new [personal diabetes manager] to integrate those 2 products together. I'd also say that we would evaluate and look at opportunities with Abbott and others that would have potential CGM integration opportunities for us. So in the short term we're looking at other people that have CGM capabilities and algorithm capability, but at the same time we are continuing at a low level our own efforts in our own CGM product development."[6]

While Animas released periodic updates about its "HHM" (hypoglycemia-hyperglycemia minimizer) between 2011 and 2013, there haven't been many recent announcements from this Johnson & Johnson subsidiary, but work has continued.

"Since 2010, Johnson & Johnson Diabetes Solutions Companies has collaborated with the JDRF, industry, academia, and regulatory bodies to develop a first-generation automated insulin delivery device (what some call an "artificial pancreas") based on predictive closed-loop technology," wrote Johnson & Johnson spokeswoman Bridget Kimmel in response to inquiries about the project's progress.

"As part of the program, 3 clinical research center–based studies have been successfully completed which clearly demonstrate the ability of the system to decrease and increase insulin delivery in order to avoid, or mitigate, potential hypo- and hyperglycemic excursions. Two related peer-reviewed articles have been published in the *Journal of Diabetes Science and Technology*, and a third is due for publication this year. Johnson & Johnson remains committed to introducing this important next generation pump to people living with type 1 diabetes."

Another company that hopes to be among the first to bring artificial pancreas technology to the US market is a small start-up that has yet to sell any products commercially.

Bigfoot Biomedical is less than a year old, but it raised more than $15 million in venture capital this year to pursue its plan for radically disrupting the diabetes device market. Its initial intellectual property stemmed from software that a company founder had developed to make existing products into the artificial pancreas products that his wife and son have worn for years. In June, Bigfoot bought the pump-making business that Asante had just shut down. Looking forward, Bigfoot's goal is to begin pivotal trials by the end of next year and bring a closed-loop system to market by 2018.

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Dr Kowalski is chief mission officer of JDRF.

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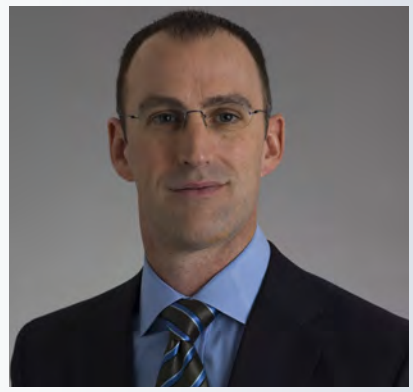
Dr Kaufman is the chief medical officer of Medtronic Diabetes.



JEFFREY BREWER

Jeffrey Brewer is CEO of Bigfood Biomedical.

"Everything about using an insulin pump is incredibly complex. Calculating basal rates and bolus infusions several times per day, putting insulin in the pump, ordering new supplies, getting insurance coverage: it's all complex. Most general practitioners won't even get involved, so patients who want to try pumps have to go to endocrinologists," said Bigfoot CEO Jeffrey Brewer.

"We aim to simplify every single step in the process. Current technology won't let us dispense with some notification at mealtimes, but other than that, the system itself will pretty much run on autopilot. Our pump technology eliminates the need to mix insulin and spend hours each month getting rid of air bubbles. Our supply-order process will be automated because the system will track what patients have ordered in the past and what they have used. As for payments, we plan to charge users a flat monthly fee to simplify that as well. Our goal isn't to attract the tiny percentage of medical specialists and tech-savvy patients who have always used pumps. It's to attract the overwhelming majority of doctors and patients who have always thought them too complicated to use."

The biggest limitations on artificial pancreas development in recent years have probably been the speed with which the insulin acts and the accuracy of glucose monitors. Many researchers are working on a faster-acting (and shorter-acting) liquid insulin, but progress has been slow. Glucose monitors, on the other hand, have been improving rapidly. Dexcom recently won FDA approval for an algorithm that improves the accuracy of its Gen 4 Platinum monitor from a mean absolute relative difference (MARD) of 13% to an MARD of 9%. Dexcom Chairman Terry Gregg says that level of accuracy is right on the edge of making CGMs a true replacement for finger sticks, if the product could maintain it without recalibration.[7]

The company is working with the FDA to demonstrate sustained accuracy, and of course, it is also working on new monitors. Dexcom has already filed for approval of its Gen 5 Platinum monitor, which should reach consumers later this year. It's unclear whether that product will offer improved accuracy, as it uses the same sensor as the Gen 4. The Gen 6 monitor, on the other hand, is being developed with new sensor technology that should reduce (or even eliminate) the need for recalibration after initial installation at a new site.[8]

Dexcom expects to have this device to market as early as late 2016,[9] so subsequent artificial pancreas systems that use Dexcom monitors (and most aspiring pancreas makers other than Medtronic do use Dexcom monitors) could greatly reduce or entirely eliminate the need for routine finger sticks. Moreover, Medtronic is also working to improve its CGM technology, though it has released less information than Dexcom about current performance and upcoming releases. (The technology used in the pivotal trial of Medtronic's Hybrid Closed Loop asks users to recalibrate their sensors every 12 hours.)

Other companies are working on glucose-sensing technology as well. Abbott, for example, has already won approval from European regulators for a CGM that can be worn for 14 days at a time with no calibration.[10] Some companies are also reportedly working on monitors that would never need to be moved because they detect blood glucose through the skin. Indeed, some observers expected the Apple Watch to launch with such technology.[11]

As commercial device makers such as Medtronic and Bigfoot work to bring their devices to market, academic research groups are working to develop and test the next generation of artificial pancreas technology. Significant efforts are under way in England, France, Israel, Australia, the United States and other places that have won substantial funding from governments and research advocates such as JDRF.

That said, the most advanced and best known of the academic development efforts—at least to American readers—are probably those ongoing at the University of Virginia and Boston University-Massachusetts General Hospital.

The Virginia project has published several studies over the past few years, all with positive results, with the most recent unveiled at the American Diabetes Association (ADA) meeting in Boston. At ADA, one of the project's leaders announced that in a study on 36 adults with T1DM, overnight use of the Virginia system controlled glucose far better than a conventional insulin pump in both outpatient and inpatient settings[12]

The current iteration of the Virginia system has also been tested in patients who wear the system 24 hours a day in outpatient settings. It requires users to enter information about meals but is otherwise automated for users who choose to take a hands-off approach. (Users who wish to take some control over the system can do so.)[12]

The Virginia system, like every other system described above, uses nothing but insulin to control blood sugar. The Boston University-Massachusetts General system uses both insulin (to lower blood sugar) and glucagon (to raise it). Many believe this 2-hormone solution is impractical for reasons that range from the instability of glucagon to the extra expense of 2-hormone pumps, but the team in Boston believes it gives them much finer control over blood sugar levels and that it better mimics how a functional body controls its own blood sugar.

Trial results have been very impressive, but the only results published to date have come from small, short studies.[13] Results from larger trials should appear soon, as the trials had been scheduled to be completed this spring,[14] and the leaders of the Bionic Pancreas team say they hope to bring the technology to market by 2017.[15]

"The exciting thing is that it isn't just 1 group that has produced great results in early trials. It's a whole bunch of groups that have demonstrated technology that can control blood sugar better than current standards of care and do it with a lot less effort than current standards of care," said Kowalski.

"If it were just 1, then there'd always be the worry that it would fall through, but what we see now shows that the technology is ready." **EBDM**

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EYLEA® (aflibercept) Injection For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.5 Diabetic Retinopathy (DR) in Patients with DME. The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.6 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

2.7 Injection Procedure. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad–spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay (*see Patient Counseling Information*).

Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye. After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
- Active intraocular inflammation
- Known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as severe intraocular inflammation

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments (*see Adverse Reactions*). Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately (*see Dosage and Administration and Patient Counseling Information*).

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA (*see Adverse Reactions*). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular edothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (*see Dosage and Administration*).

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the *Warnings and Precautions* section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

6.1 Clinical Trials Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg. There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist (*see Warnings and Precautions*). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (*see Adverse Reactions*). Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

U.S. License Number 1760

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Initial U.S. Approval: 2011

Regeneron U.S. Patents 7,070,959; 7,303,746; 7,303,747; 7,306,799; 7,374,757; 7,374,758; 7,531,173; 7,608,261; 7,972,598; 8,029,791; 8,092,803; 8,647,842; and other pending patents. LEA-0721

Discover Strength in efficacy

As demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in patients with DME

Choose EYLEA® (aflibercept) Injection from the start

Learn about EYLEA at EYLEA.us/op

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

- EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Please see brief summary of full Prescribing Information on the following page.

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REGENERON

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(aflibercept) Injection
For Intravitreal Injection

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