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Evidence-Based Diabetes Management™

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Diabetes, Mental Health Connection

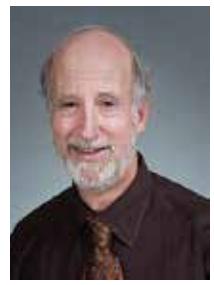
Integrated Treatment for Diabetes, Depression Gains Notice, With Help from ACA

Mary K. Caffrey

For decades medicine's divide between psychiatrists who cared for the mind and primary care physicians (PCPs), who treated "from the neck down," worked against both patients and the healthcare system. The arrival of the Affordable Care Act (ACA), coupled with a federal parity law for mental health coverage, offers hope for those with multiple chronic conditions.

Persons with diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), stand to gain, if the offerings at recent medical meetings are any sign. Both, the May gathering of the American Psychiatric Association (APA) in New York City,[1] and the June Scientific Sessions of the American Diabetes Association (ADA) in San Francisco,[2] featured sessions on the link between diabetes and depression.

The message at both meetings: coordinating care between PCPs and mental health providers is an idea whose time has come. Not only does this approach work better for patients, but evidence shows it saves money, too.



Wayne J. Katon, MD

Both meetings and several studies published in recent years have explored the connections between diabetes and depression. Among the observations: persons with depression account for more healthcare spending on diabetes and cardiovascular disease than those without mental health problems; depression that starts during adolescence causes sufferers to eat poorly, be less active, or smoke and drink, contributing to obesity and other comorbidities; and, managing diabetes over a lifetime is stressful and time-consuming, which wears patients down.[3,4]

(continued on page SP304)

Cognition and Diabetes

Aging and Cognitive Decline in Diabetes

Surabhi Dangi-Garimella, PhD

The association between diabetes and cognition has been known for a while. However, until recently, the primary focus of diabetes-related complications has been on hypertension, renal failure, vision loss, autonomic and peripheral neuropathy, myocardial infarction and cerebrovascular disease, including stroke. Neuropathy, in particular, is responsible for additional comorbidities, resulting in a significantly increased cost of treatment.[1] Of late, the effect of hyperglycemia on the cognitive ability of patients has been regaining interest, after research efforts were abandoned in the United States by 1970.[2]

> *"There is a big gap in the knowledge base–not just among patients and caregivers, but also providers themselves."*
> –Medha N. Munshi, MD

Global Numbers of the Cognitive Syndrome

According to the World Health Organization, dementia—a cognitive degeneration syndrome—affects 35.6 million people globally, with about 7.7 million added every year. Almost 60% to 70% of dementia cases are a result of pathological degeneration caused by Alzheimer's,[3] and recent data suggest that diabetes could be one of the causative factors for the remaining 30% of cases.

In the United States, 16 million people were estimated to be living with cognitive impairment in 2010. With the baby boomers fast approaching and crossing 65 years of age, that number is expected to increase significantly.[4] The cost of patient care can be an enormous strain on the healthcare system, both in direct healthcare costs and indirect costs, such as the loss of income for a caregiver within the family. Treating patients with Alzheimer's and other related dementias were estimated to cost Medicaid nursing facilities an average of $647 million in 2010, which did not include prescription drug costs or home- and community-based care.[4] The direct costs of Alzheimer's alone are estimated at $214 billion in 2014, $150 billion of which would be Medicare and Medicaid expenses. In terms of indirect costs, 15.5 million caregivers provided unpaid care to Alzheimer's patients in 2013, valued at a whopping $220 billion.[5]

(continued on page SP307)

Commentary

Value-Engineered Translation: Developing Biotherapeutics That Align With Health-System Needs

Tania Bubela, PhD, JD, and Christopher McCabe, PhD

Research and development (R&D) of novel biotherapeutics must be driven by considerations of value to healthcare payers. In an era of cost-constrained health systems, those who make investment decisions in R&D for novel biotherapeutics must closely consider market needs and the necessity to clear market access hurdles. Even in the United States, developers can no longer assume that the products and services they develop will be adopted and funded; payers may not reimburse innovative technologies at a price sufficient to generate a competitive return on the investment in R&D.

It is no longer sufficient for developers to focus on clearing safety and efficacy regulatory hurdles. Meeting

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Also in this issue...

PEER EXCHANGE

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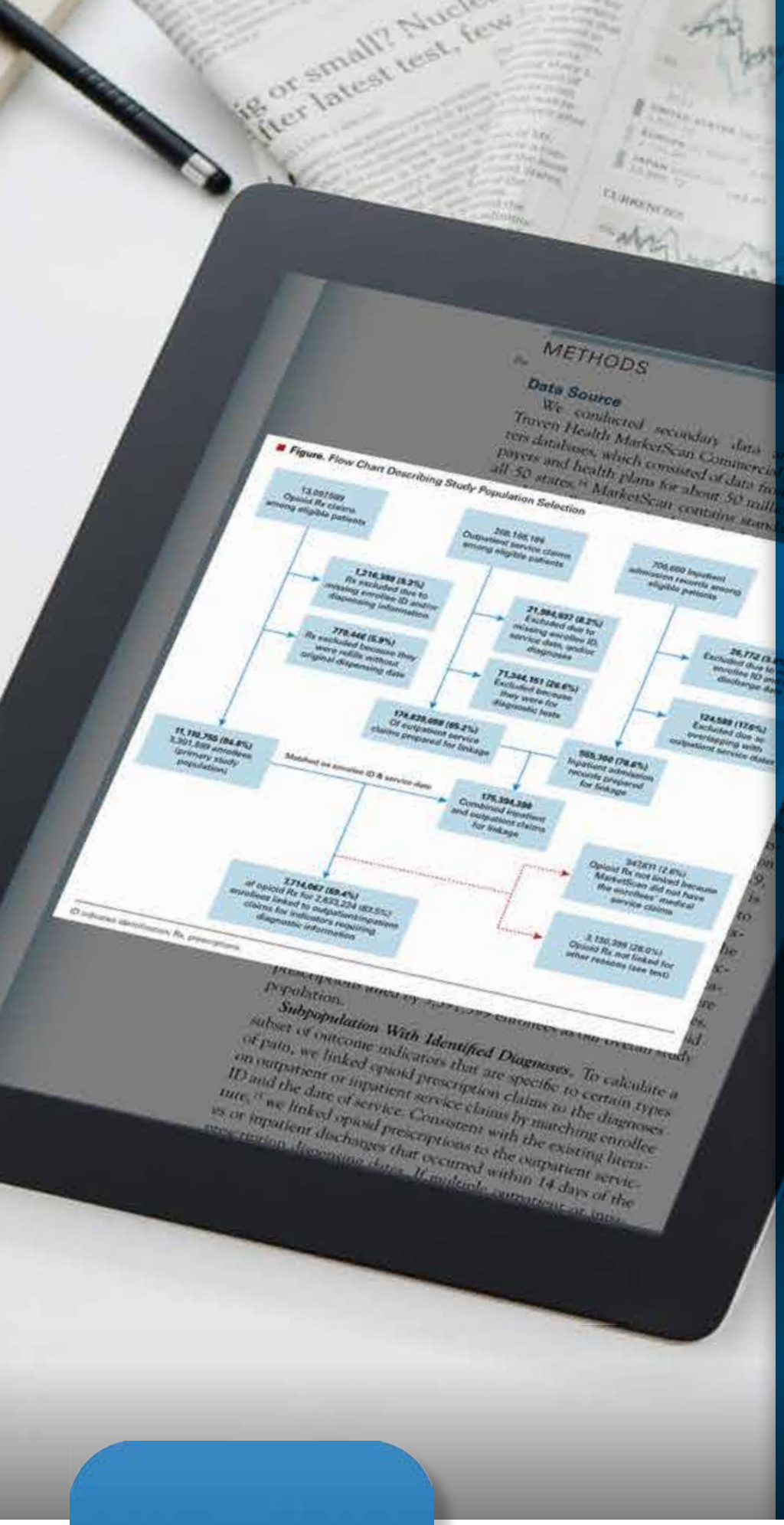

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In This Issue...

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How does bariatric surgery influence the physiologic processes, resulting in improved glycemic control or even remission? The most obvious answer would be that the insulin resistance associated with excess adipose tissue dissolves away with the decrease in weight. This could spare the beta cells. However—although the precise mechanism of action in bariatric surgery's effect on glycemic control is not yet known—investigators suspect the answer may be more complicated than that.

"Diabetes is a lot of work. The day someone is diagnosed, they've just been given a new job for the rest of their life."
William Polonsky, PhD, CDE

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This issue of *Evidence-Based Diabetes Management* continues our evaluation of the relationship between mind and body. There's an increasing level of scholarship on connections between mental health—especially depression—and the management of diabetes, metabolic syndrome, and cardiovascular issues. Some of what clinicians are learning seems so obvious, it's a wonder these links have not been explored before now. But there's a reason, and it's rooted in the way we have been paying for healthcare. For years, insurers have limited an individual's number of covered visits to mental health professionals and walled-off reimbursement for psychiatric care from medical payments for treatment "from the neck down." This has caused patients and providers alike to think of mental health care as the stepchild of the system, with catastrophic results. A groundbreaking actuarial report commissioned by the American Psychiatric Association (APA), unveiled this spring, tabulated what emergency department professionals have known for years: those with untreated mental health problems account for a disproportionate share of the nation's medical costs. This is especially true in diabetes. As pioneers such as those at the University of Washington tell us, when depression sets in during the teenage years, it causes its victims to eat poorly, exercise less, and fail to follow medication schedules that would stop prediabetes from turning into something worse. Treating the continuum of depression and diabetes, and understanding how each condition affects the other, is the key to avoiding the worst of each. It's an idea that received plenty of attention at major meetings of both the APA and the American Diabetes Association (ADA), and it's an idea whose time has come. The 2014 ADA Scientific Sessions featured plenty of news, including updates on SGLT2 inhibitors, reports of progress on the artificial pancreas, and ideas for early use of insulin to halt diabetes progression. But perhaps the most interesting news came a few weeks later when the FDA at long last approved Afrezza, an inhaled insulin for mealtime use, giving both type 1 and type 2 patients a new treatment option. Unlike an earlier effort, Afrezza's delivery system appears to offer the portability that patients desire. There's plenty more in this issue of *Evidence-Based Diabetes Management*.

For years, insurers have limited an individual's number of covered visits to mental health professionals and walled-off reimbursement for psychiatric care from medical payments for treatment "from the neck down." This has caused patients and providers alike to think of mental health care as the stepchild of the system, with catastrophic results.

As always, thank you for reading, and look to www.ajmc.com for updates.

Brian Haug
Publisher

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.

evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions such as urticaria and rash have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction or angioedema, and to take no more drug until they have consulted prescribing physicians.

Urinary Tract Infections: Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

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A Novel Pharmaceutical-ACO Collaboration: the Merck/Heritage Provider Network Open Innovation Challenge

Aman Bhandari, PhD; Arnaub Chatterjee, MHA, MPA; Sara Holoubek, MBA; Brian Powers, BA; Jonathan Gluck, JD; and Sachin H. Jain, MD, MBA

Accountable care is forcing providers to develop new capacities and strategies for managing cost and quality trends. Prospectively managing the health of populations requires shifting the focus of care delivery from episodic interventions to continuous population management. As a result, accountable care organizations (ACOs) are dedicating considerable focus to developing the infrastructure and tools needed to help patients manage their chronic conditions. This is a significant departure from traditional care-delivery models and will require provider organizations to develop new partnerships and embrace new methods.

The enhanced focus on patient outcomes and value for ACOs in general will mean that pharmaceutical companies will have to reshape their relationships with ACOs along these lines. Refocusing these relationships around value will require (1) collaborative measurement of patient outcomes; (2) new commercial models that enable value-based payment; and (3) a broadening of the relationship to develop solutions and services that enhance outcomes independent of the pharmaceutical companies' products. It is this latter requirement that prompted Merck & Co, Inc, a global pharmaceutical company, and the Heritage Provider Network, Inc (HPN), a Southern California based managed care organization with affiliates in Arizona and New York, and the largest of the Pioneer Model ACOs, to engage in a collaborative process to identify novel solutions in disease areas of considerable shared epidemiological interest: diabetes and heart disease.

During the fall of 2013, Merck and HPN launched an open innovation challenge around care plan adherence for patients with diabetes and heart disease. To our knowledge, this is the first collaboration between a pharmaceutical company and an ACO.

This article describes this collaboration, the innovation process, and implications for further collaborations between ACOs and other healthcare stakeholders.

Defining the Problem

As we transition to a clinically integrated system that incentivizes quality and better health outcomes, care plans are critical patient engagement tools that will be invaluable in helping patients become informed and educated.

Care plans serve as road maps for patients, because they outline diagnosis and treatment, schedules for follow-up, and vital information and resources postvisit. Additionally, they serve as a lifeline, allowing providers to monitor their patients and ensure coordination among the healthcare team. But there are significant challenges associated with creating and delivering successful care plans between the provider and the patient. More than 40% of patients misunderstand, misinterpret, forget, or ignore healthcare advice given by their providers.[1] Factors associated with patient compliance to provider-recommended care plans include patients' knowledge and understanding of treatment and effective communication between the patient and provider.

HPN has a long history of providing coordinated care, and both Merck and HPN realized that adherence to care plans for patients with chronic diseases is an underutilized lever for improving a patient's quality of life, while also potentially creating cost reductions in healthcare. Together, leadership from the 2 organizations decided to use an open innovation process to identify and incubate ideas that would advance shared aims around improving adherence to care plans for patients with these conditions.

Structure

Many sectors have looked to "the wisdom of the crowd" or the phenomenon that the collective knowledge of the community is greater than the knowledge of the individual[2] to devise novel solutions to complicated problems. The use of challenge competitions and an open innovation process to drive breakthrough results has a very long history, going back hundreds of years.[3] For example, Charles Lindbergh's flight across the Atlantic can be traced back to a challenge famously titled The Orteig Prize, a $25,000 reward offered to the first aviator to fly nonstop from New York City to Paris. While this mechanism has been well defined in other sectors, it is relatively new to the healthcare services arena. Challenge-based competitions have proved to be successful frameworks for addressing fundamental research questions by presenting difficult problems and data to the community and enabling the open exchange of ideas and methodologies. Merck and HPN quickly realized that the long-standing problem of treating chronic diseases could benefit from a community approach, and as a result, the 2 organizations collaborated on devising an open innovation challenge competition that aimed to source and incorporate novel care plan products or services to support providers and patients in the area of chronic disease management.[4] (HPN has sponsored a number of other prizes, including prizes related to hospitalization prediction and cancer cell networks, but this is the first nondata, nontechnology challenge in which HPN has participated.)

Merck and HPN's aim was to apply the best practices of open innovation to identify novel solutions for managing patients with chronic diseases. There has been some experimental research indicating that traditional approaches like "winner-take-all" prizes are suboptimal for generating solutions.[5] We therefore opted for a staged process, with the opportunity for multiple prizes across teams.[6] Additionally, other inno-

Table 1. Select Finalist Concepts

Concept	Description
Personalized diabetes coaching	Using a platform that synthesizes work flow, data capture, device integration, and reporting-enabling personalized service delivery via coaches.
Comprehensive patient adherence profiles	Using a personality characteristic database. In a 6-minute session, the platform determines the psychological triggers that will be most effective to attain medical adherence with each patient.
Messaging support via SMS	Crafting interactive conversations so providers can better support patients between appointments. This concept helps providers create and monitor care plans (and thus patient progress) while delivering SMS support.
Care plan reinvention and reformulation	Using mobile devices, artificial intelligence, and human-centered process design. A clinically proven proprietary method of delivering care plans to patients was developed as dynamically generated personalized multimedia daily to-do lists on mobile devices.

Challenge Winner Sees Promise in Daily App Check

Mary K. Caffrey

If doctors could see their patients with chronic conditions every day, what would they check?

That, essentially, is the question that the collaborators at Wellframe asked when they developed Heart Coach, a smartphone-based application that gives patients undergoing cardiac rehabilitation a series of daily tasks, such as taking medication, walking, doing an eye check, watching an instructional video, or completing a survey.[1]

Trishan Panch, MD, MPH

Trishan Panch, MD, MPH, co-founder and chief medical officer for Wellframe, described the technology, which won the challenge set forth by Merck and the Heritage Provider Network (HPN): to develop a system for managing population health. The application will prove quite valuable as healthcare moves away from the traditional fee-for-service model.

Wellframe's mission is to use technology to help patients recover from acute health crises and avoid repeat episodes.[2] Of course, heart attacks and strokes typically do not happen out of the blue–they are often the result of failing to manage a chronic condition, such as diabetes or hypertension. In an interview with *Evidence-Based Diabetes Management*, Panch described the well-known challenge of managing these conditions: "It requires sustained coordination and action," between doctor and patient, he said, and it can be really hard for doctors to motivate patients every day.

Technology's role, as Panch explained, is to provide not only that between-visit monitoring but also the motivation. What Wellframe has found, he said, is that the technology helps, but what really matters is the relationship that develops over time as patients check-in daily. Of course, the check-ins also catch things that go awry and require immediate attention, Panch said.

The model shifts the definition of who is the "provider," he said. "Patients provide their own health," he said. People like physicians, nurses, or diabetes educators "provide the raw materials."

Wellframe recently published results for 26 patients enrolled in cardiac rehabilitation who used the Heart Coach for 30 days. Researchers found that patients engaged with the application for 90% of the days during the study period, with "uniformly favorable impact on compliance and adherence."[1] The authors reported that 83% of patients reported a positive or very positive experience with the Heart Coach; providers reported improved communication and patient participation, and that the application "enhanced their provision of therapy."[1]

Panch noted that patients aged 65 years and older responded very well to the smartphone application, and those aged 75 years and older felt especially strong about its usefulness. Panch said this reflects the patients' knowledge that "they need to be on top of this on a day-to-day basis." **EBDM**

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2. Wellframe website. http://wellfra.me/. Accessed July 7, 2014.

vation processes, such as lean methodology and design thinking, were embedded into the structure of the challenge. Drawing on established principles for open innovation challenges, Merck and HPN designed an innovation challenge with several phases.

Challenge Launch and Submission Phase

Outreach is essential for open innovation challenges. Merck and HPN partnered closely with Luminary Labs, an innovation and strategy consultancy, for the operational components of this challenge, and to ensure that the right community of solvers was involved.

Following announcement of the challenge, there was a 1-month open call to the public for submissions. To spread awareness of the challenge and ensure that there would be broad outreach, Luminary Labs notified key media outlets in technology, big data, and healthcare.

Overall, 90 teams submitted solutions for consideration. These submissions spanned from initial concepts to fully mature products or services: 17 in the idea phase, 33 in the early prototype phase, 14 in the full prototype phase, 14 in the beta phase, and 12 that were publicly available. Concepts included hardware, stand-alone care planning solutions, communications platforms, and comprehensive integrated care systems. Eighty-four percent (84%) of submitted solutions were patient-facing; the remaining submissions aimed at multiple segments of the ecosystem. With over 17,000 visits to the challenge website, there was wide-ranging interest and geographic reach. Visitors drew from academic, government, and private-sector spheres that included the Broad Institute, the Bill and Melinda Gates Foundation, Facebook, the Centers for Disease Control and Prevention, and the White House.

Virtual Accelerator and Finalist Selection

An independent panel of judges from the healthcare, innovation, development, and design communities selected 5 teams to proceed on to the virtual accelerator process. Submissions were then evaluated on several dimensions.

The 5 semifinalist teams were composed of clinicians, scientists, patient-entrepreneurs, media producers, and technologists, and the solutions ranged from early prototype to established startup.

Accelerators are designed to support .the successful development of entrepreneurial companies and are aimed at increasing the likelihood of success for those companies and iterating their concepts. The 5 semifinalists took part in rigorous design, prototyping, and business modeling sessions tailored to the strengths and weaknesses of each team. The virtual accelerator process consisted of 3 core modeling sessions.

Modeling session 1 focused on an introduction to design thinking also on need-based solution development. These exercises functioned as primers on cultivating empathy, end-user focus, and rapid prototyping. The semifinalists were also exposed to interview-based ethnography, where they simulated exercises in patient engagement and were asked to reconsider care coordination from new angles. The sessions were designed with the patient in mind—and more specifically, how entrepreneurial companies can refocus their solutions to ensure that patient and provider needs are met.

Modeling Session 2 commenced with a stronger emphasis on patient interaction and learning how to complement technology with disease self-management. Semifinalists met with 2 panels of patients living with diabetes and/or heart disease, and gained insights by simulating the complex experience of learning to live with chronic disease from the perspective of a patient and of a caregiver. Clinicians provided their observations from the field, noting best practices and pain points regarding increasing adherence and patient engagement to improve health outcomes.

Modeling Session 3 gave semifinalists the opportunity to access experts in different fields, ranging from business modeling and capital acquisition to design and public speaking. Teams

Figure 1. Overall Challenge Timeline

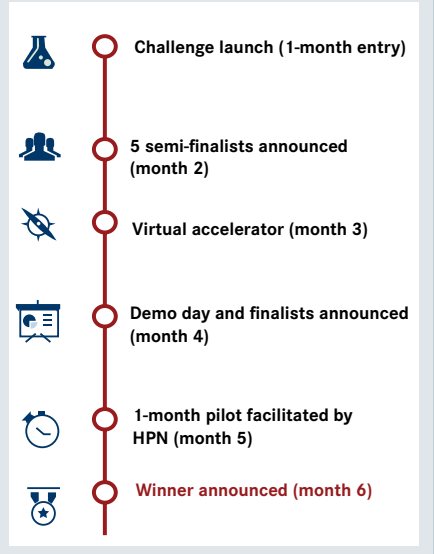

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Table 2. Judging Criteria and Constraints

Concept maturity	Early prototype, full prototype, beta, publicly available product/service
Target audience	• People living with diabetes • People living with heart disease • People living with both diabetes and heart disease • Healthcare providers and members of the clinical patient ecosystem (physicans, nurses, pharmacists, etc) • Members of the nonclinical patient ecosystem (family, friends, caregivers, social service providers)
Does concept address the core needs of its target audience?	To what extent does the concept respond to issues that impact care plan success? (eg, life stage, education, familiarity with terminology, support systems, financial and professional circumstances)?
Methodology for design and development	Cascade, design thinking, lean startup, etc
Market readiness	How do you propose to take your concept to market?
Business model	Who will provide funding, how will the concept be distributed, how will engagement be sustained over time, etc?
Is concept data-driven?	What data and analytic aspects are part of the concept?
Probability of success	To what extent will the team's skill sets, experience, and ability to collaborate bring the concept to life?

were provided hands-on mentorship from industry experts and continually crafted their solutions to focus on the problem at hand.

Lessons Learned

Several insights have emerged from this collaboration. First, by placing a dedicated focus on the challenge announcement and community outreach, Merck and HPN were able to develop a landscape view of the marketplace for care plan adherence solutions. The process also gave both parties proximity to the innovator community, opening up a new opportunity for identifying and harvesting talent from a diverse group of forward thinkers offering fresh ideas and a unique perspective. Second, Merck and HPN were able to successfully source solutions that proactively engage patients to promote lifestyle changes around healthy behaviors and medication management, as well as bridge the communication and coordination gap between patients and providers. This collaboration initiative serves as a model for engaging entrepreneurs and key health stakeholders to work across the care continuum.

As we move toward an increased focus on patient engagement, there is an opportunity for organizations to create dynamic and effective programs that facilitate the exchange of information. Shifting to new models will require an increased focus on identifying clinical gaps to uncover every opportunity and implement patient-centric care plans.

Conclusions

Open innovation, while common in other industries, is still relatively new to the healthcare field. This approach provides a pathway for collaboration, rapid identification of solutions, and access to the broader marketplace. The aim of both Merck and HPN was to apply the best practices of open innovation to identify novel solutions for managing patients with chronic diseases. The quality and quantity of submissions showed notable interest from entrepreneurs to data scientists to clinicians and provided a diverse set of solutions. The challenge allowed both Merck and HPN to look beyond their own walls and gain access to non-traditional partners and products. Additionally, this first-of-its-kind pharmaceutical-ACO collaboration demonstrated how challenge competitions can set in motion communities of innovators to develop sophisticated tools for care management, lay the groundwork for future collaboration, and offer a mechanism for stakeholders like Merck and HPN to collaborate. **EBDM**

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Pharma-Payer Partnerships Seek to Prove Effectiveness of Care

Milly Dawson, MS, MPH

As the healthcare industry moves toward outcomes-based payment models, pharmaceutical manufacturers find themselves in a new, less comfortable position than they once occupied. In earlier decades, drug makers were asked only to prove the safety and efficacy of a new product. Today, they face powerful pressure to also demonstrate both cost-effectiveness and comparative effectiveness, which means they must show their agent is not only better than placebo but also better than other agents.

Comparative effectiveness research is now included in the Affordable Care Act (ACA),[1,2] and pharmaceutical manufacturers that fail to prove their products' value on this expanded set of measures will probably suffer by not cementing trust with physicians, hospitals, and health plans, according to accounts from industry and academia.[1,2]

"Today many pharmaceutical companies talk about being health-solution or patient-solution companies," says Judith Goodwin, MBA, a senior vice president at Joslin Diabetes Center. It's a whole new approach for them, she says, that speaks to their current eagerness to join in shared efforts to improve quality and outcomes by working with various healthcare stakeholders, including payers.

By partnering with payers, pharma can gain access to medical, pharmaceutical, and laboratory claims data. Such data, once identifiers have been removed, can be used to create profiles of the kinds of diabetes patients whose care most drives cost. That knowledge can in turn be used to target patients with certain traits early on, by offering them behavioral and other interventions to reduce costs and improve their health.

Pharma's New Attitude

A 2009 report by Deloitte, "What Payers Want—Viewing Payers as Customers," highlights the shift that began the year before the ACA passed. In the years

prior, pharmaceutical companies enjoyed "the most desirable position" in healthcare.[3] Drug manufacturers generated a steady stream of highly profitable products, maintaining nearly full control over the data about the safety and efficacy of those products and facing fairly low barriers to approval and access to customers. The pharmaceutical sector held considerable pricing power over payers, whom drug company leaders viewed as administrators and intermediaries. In short, Deloitte reported, "If pharma products were safe and effective, physicians could prescribe them, patients could fill their prescriptions, and payers would reimburse."[3] Today, the balance has shifted, and payers have gained bargaining power.

Healthcare today is marked by more transparency of information, more crowded therapy areas, and a focus on shrinking pharmacy spending. Payers, who also face new sorts of pressures, are nonetheless gaining unprecedented standing. The pressures on payers include movements to address rising costs, demands for openness, and the prospect of more government involvement. Payers are increasingly establishing evidence-based clinical guidelines, managing access more tightly, and examining drug pricing.

As Chernew, et al, wrote last year in *Evidence-Based Diabetes Management*, diabetes in particular presents a strong opportunity to gain value for what is spent on treatment. Benefit design has been tied to patient behavior, especially adherence; thus, the authors note, payers, including pharmacy benefit managers, have an important role in improving the value of spending on diabetes care.

Ultimately, it is proving to be in the pharmaceutical sector's best interests to view payers as both customers and collaborators with whom they can work to ensure that new drugs are not only safe and efficacious but that they also fulfill other key requirements. As John LaMattina wrote last year in *Forbes*, "The commercial landscape has shifted dramatically." A firm bringing out the fourth or fifth agent in a class, years after the first appeared, must, in its new drug application (NDA) package, demonstrate not only safety and efficacy for the FDA, "but also significant improvements over existing agents to justify formulary acceptance and pricing for payers."[4]

Pharmaceutical executives acknowledge these new requirements. In the 2009 report by Deloitte, 75% of the executives surveyed agreed that "major changes are needed by some or all parts of their organizations to address future risks." Thirty-eight percent said their companies would be dedicating "more resources to proving products' economic value." Forty-one percent said that their organizations planned to develop "partnerships in diagnostics, treatment, and prevention…with academics, providers, payers, and regulators."[3]

Janice Murphy, JD, director of national affiliated programs at Joslin Diabetes Center, says that pharma today has to demonstrate why a particular new diabetes drug is really better than similar predecessors, and partnerships with payers can help. "What will be the lift in terms of outcomes?" is the key question, she says. Answering that question means looking closely at clinical efficacy and doing cost-benefit analyses to determine the most efficient use of dollars and to ensure that payers have essential data.

Humana and Lilly Team Up

Humana and Eli Lilly will use claims data to study how drug interventions affect patients' outcomes, adherence, and total costs. The firms have signed a multiyear agreement to run diverse studies of various disease conditions, starting with type 2 diabetes mellitus (T2DM). The partnership may also pursue research in the areas of oncology and osteoporosis, according to Lewis Wilkerson, PharmD, collaboration account manager, and Lane Slabaugh, PharmD, MBA, research leader, both with Comprehensive Health Insights at Humana.

The partnership's efforts will include pharmacoeconomic studies, as well as studies to examine the impact of various clinical interventions on outcomes. Studies will also assess disease management programs and programs meant to increase adherence. An early research project will investigate the types of patient characteristics that are associated with increased healthcare costs in patients with T2DM.[5]

"Diabetes is a very complex disease," says Dara Schuster, MD, an endocrinologist and a medical fellow at Lilly Diabetes, adding that some of that complexity is positive. "We have more medications and medications that act differently, so the options are greater for patients. Making the right decisions demands that much more depth of knowledge." She adds that prescribing wisely for a given patient involves not only clinical decisions but also ones about that patient's lifestyle and ability to pay for care. "Patients and payers are telling us clearly—help to make this all simpler."

The combination of today's growing demands for medical care that suits each patient's profile and the availability of massive data held by payers creates what Schuster calls "a perfect storm to allow us [payers and pharma] to achieve better insights," acting as partners.

Representatives of both companies agreed that the "lens" they will use to guide their partnership will be to continually ask what is best for the patients and what will make the healthcare provider's job easier. Merck and Pfizer are also incorporating input from payers in deciding which drugs will provide the most benefits to patients.[5]

Pressure From Government Payers

Today's pharma-payer partnerships confirm the 19th-century maxim first stated by writer Charles Dudley Warner: "Politics makes strange bedfellows."[6] Much of the pressure behind the new payer-pharma partnership reflects policy shifts expressed in the United States by the ACA, and in Western Europe by austerity measures sweeping the continent and in legislation promoting such alliances. For instance, in the United Kingdom, the Health and Social Care Act of 2012[7] has created a framework to promote joint efforts between the National Health Service and pharmaceutical companies to improve innovation and healthcare delivery through collaboration, according to Pascal King, a global director with the Access Partnership.

The new openness of pharmaceutical companies to work with other stakeholders, such as insurers and even with other drug companies, reflects their evolution as they face "a tsunami of change" in the post ACA environment, says Judith Goodwin. She notes that despite the still strongly divided opinion about the bill, everyone in healthcare must adapt to its demands. "The old paradigm of pharmaceutical reps calling on doctors' offices and taking them out for nice dinners and offering honorariums isn't happening anymore," she says. Now, she says, pharmaceutical companies must work with the larger healthcare system, including payers, and be "way more open to collaboration" than they once were.

Patients and Providers Should Benefit

Pascal King emphasizes that a "consideration of the complete patient's treatment journey" requires new ways of thinking from all stakeholders. His firm helps drug and device manufacturers develop strategies to enhance the value of their innovations, strategies that include partnerships with payers.

King cites many powerful forces accelerating the move toward partnerships. These include awareness among drug manufacturers that the blockbuster era is over; the sophistication of today's patients, who come in armed with knowledge from the Internet; and the shift towards even more serious consideration of costs than in the past.

Concerns About Competition

Murphy and Goodwin express concerns about the possibility that payer-pharma partnerships might solidify too much clout in the hands of too few healthcare stakeholders. "Combined power between payers and pharma might limit choices or drive up prices. The partners will be more powerful than any 1 patient or even any 1 patient within a provider organization," says Goodwin.

Nonetheless Goodwin expresses guarded optimism that the payer-pharma partnerships will help to maximize the usefulness and cost effectiveness of the therapies available to patients. "I would hope and imagine that these kinds of conversations will lead to the delivery of the best therapies to patients. I hope it would be a good thing," although, she adds, that remains to be seen. **EBDM**

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Can Gastric Bypass Surgery Be a Cure for Diabetes Mellitus?

Stanton R. Mehr

Sally G, a 38-year-old white woman from Atlanta, has type 2 diabetes mellitus (T2DM). She stands 64 inches tall and weighs 220 pounds. Her body mass index (BMI) is 38.2 kg/m^2 and her glycated hemoglobin (A1C) level remains 8.8%—results that persist despite the use of metformin and a sulfonylurea. Sally's BMI alone makes her a candidate for gastric bypass surgery. But how would the surgery affect her diabetes? It might be a cure, according to several groups of investigators.

Since 2012, studies of bariatric surgery's effect on diabetes have appeared at a furious pace. These evaluations cover how much glycemic levels can be reduced with the use of bariatric surgery, the link between bariatric surgery and complete diabetes remission, and the feasibility of this approach to other subpopulations.

Results from bariatric surgery studies have received prominent billing at the most recent meeting of the American College of Cardiology (ACC), which convened in Washington, DC, in late March, and at the 74th Scientific Sessions of the American Diabetes Association (ADA), held in San Francisco in June.

A Flurry of Research

A study highlighted on the last day of the ACC meeting, and simultaneously published in the *New England Journal of Medicine,* involved Brigham and Women's Hospital, Cleveland Clinic, and Harvard Medical School.[1] The researchers found that gastric bypass surgery plus intensive medical therapy for diabetes, in patients with BMIs >40 kg/mg^2, was significantly more effective in controlling glycemic levels after 3 years than intensive medical therapy alone.

In the intensive medical therapy group, only 5% and 18% of patients were able to attain an A1C level of ≤6.0% or ≤6.5%, respectively, after 3 years. In the Roux-en-Y gastric bypass combination group, however, 38% reached the ≤6.0% mark (P <.001) and 48% reached ≤6.5% (P <.003). In the sleeve gastrectomy combination group, 24% got to ≤6.0% A1C after 3 years (P <.01), and 47% achieved ≤6.5% (P <.003).

The results of this study demonstrate not only how hard it is to control glycemic levels in obese patients using only lifestyle modification and intensive medical treatment, but also show the possible combined benefit of lost weight and better control through bariatric surgery.

But does this apply to Sally G? She is not currently receiving intensive medical therapy. Will bariatric surgery improve her poor glycemic control sufficiently to justify the risk associated with surgery? In the study cited above, the mean baseline A1C level was 9.3%. Both of the combined bariatric surgery/medical therapy groups registered a mean drop in A1C of 2.5%, compared with a 0.6% drop for medical therapy alone. Perhaps of greater note, other researchers have found that diabetes mellitus *resolves* in a proportion of obese patients undergoing gastric bypass.[2-4]

In a study from Cleveland Clinic and Loyola University School of Medicine, Chicago, investigators revealed a mean excess weight loss of 55% after an average follow-up of 6 months in more than 200 patients who had undergone various types of bariatric surgery. The patients' mean A1C levels dropped from 7.5% at baseline to 6.5% after the follow-up period (P <.001), and they also registered a drop in fasting blood glucose levels of 41.1 mg/dL (P <.001) during that time. One-fourth of these patients experienced a long-term complete remission of T2DM during which they needed no hyperglycemic medications.[5]

Opening the Floodgates?

Investigators from Chile wanted to study the effects on T2DM of bariatric surgery in patients who were less obese, who had BMIs below 35 kg/m^2. They found even greater likelihood of T2DM remission: after a 36-month follow-up, more than 50% of 100 patients had complete remission of their T2DM, 10% had partial remission, and 25% showed significant improvement.[6]

Researchers from Genoa, Italy,[7] saw similar results in a smaller controlled study of 20 patients and 27 control individuals with diabetes. From a mean BMI of 32.9 kg/m^2 and an A1C of 7.5% despite intensive medical therapy before Roux-en-Y gastric bypass, the study subjects' mean BMI decreased to 25 kg/m^2 and mean A1C level dropped to 7.0% over 36 months. Five of the 20 registered complete diabetes remission; 9 achieved control with medications, with A1C below 6.0%; and the remaining 6 had improved control with medications.

Getting patients to a glycemic level below 7.0% (without factoring in an effect from continuing medical therapy) would be enticing for endocrinologists and bariatric surgeons, as well as patients. With that in mind, will gastric bypass surgery one day be considered a primary treatment for diabetes mellitus? Health plans have well-established requirements in place for the reimbursement of gastric bypass surgery. Payers must decide whether to make bariatric surgery available for T2DM patients with a lower BMI. Michael Fine, MD, medical director of Health Net of California told *Evidence-Based Diabetes Management*, "Our plan covers bariatric surgery for patients with BMI >35 kg/m^2 and a diagnosis of diabetes. It is unlikely we would lower that BMI [threshold] until there is long-term evidence that patients with BMIs between 30 and 35 do better with bariatric surgery than with medical management of their diabetes and weight."

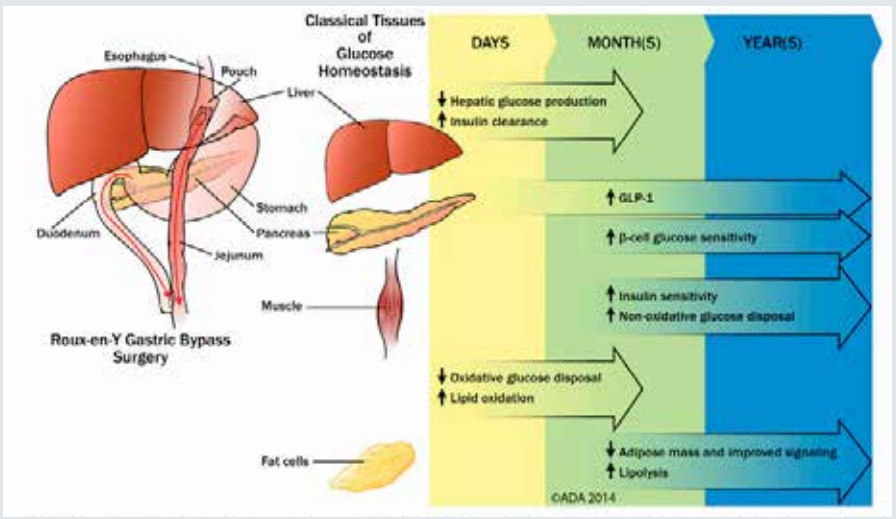
Glycemic Regulatory Changes After Bariatric Surgery

Allison Goldfine, MD, and Mary Elizabeth Patti, MD, from Joslin Diabetes Center, Boston, wrote in a commentary in *Diabetes Care*, "Understanding the physiologic processes and sequence of change may help inform optimal selection of candidates most likely to benefit from different surgical interventions for diabetes and weight management and [from] less invasive, safer alternative therapeutic approaches to manage obesity and T2DM."[8]

This seems to be the puzzling question: how does bariatric surgery influence the physiologic processes, resulting in improved glycemic control or even remission? The most obvious answer would be that the insulin resistance associated with excess adipose tissue dissolves away with the decrease in weight. This could spare the beta cells. However—although the precise mechanism of action in bariatric surgery's effect on glycemic control is not yet known—investigators suspect the answer may be more complicated than that.

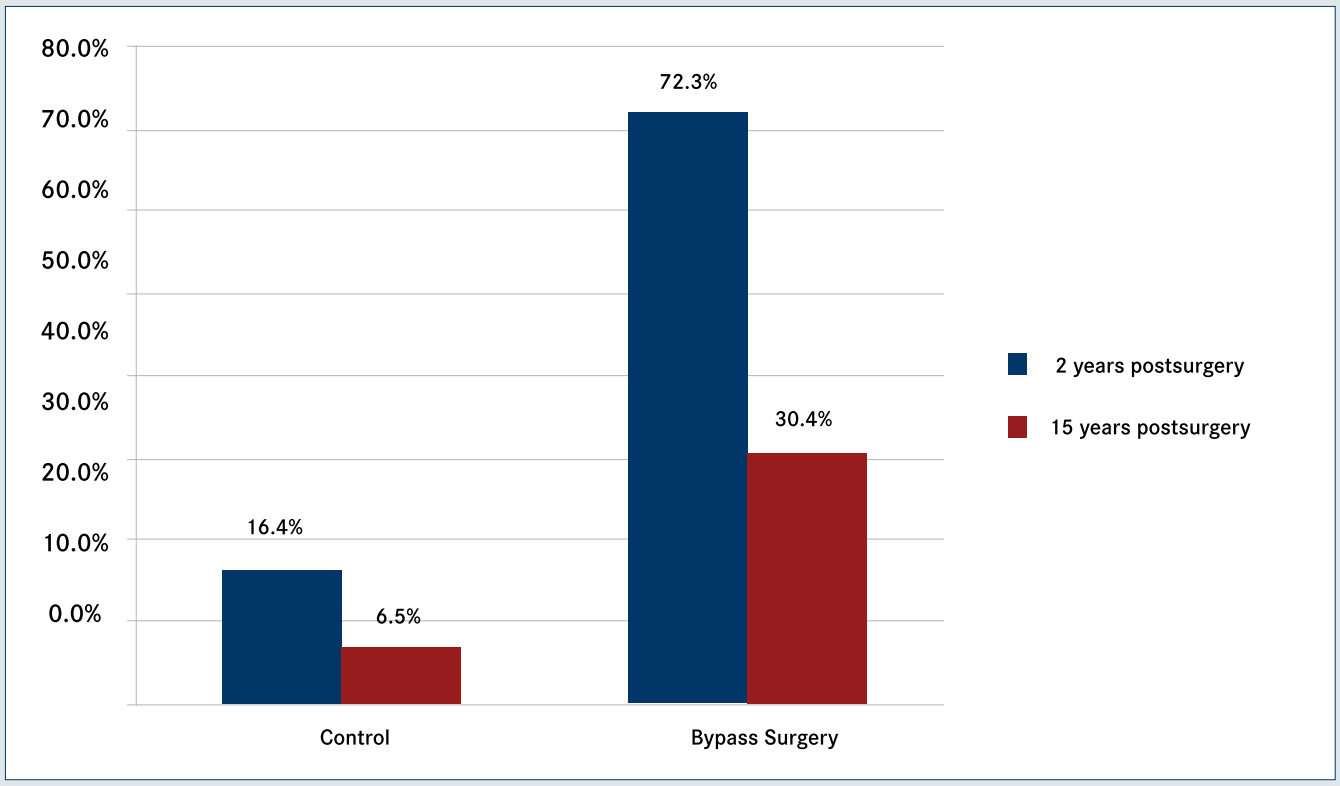
A study published in 2014 proposes that the effect may arise from altered hepatic insulin sensitivity, which then spreads to the peripheral tissues. The combination with increased postprandial insulin secretion may be respon-

Figure 1. Physiologic Effects of Roux-en-Y Gastric Bypass on Classical Pathways of Glucose Metabolism Over Time



GLP-1 indicates glucagon-like peptide-1. Source: Goldfine AB, Patti ME. Diabetes improvement following Roux-en-Y gastric bypass: understanding dynamic changes in insulin secretion and action. *Diabetes.* 2014;63:1454-1456.

Figure 2. Diabetes Remission Rates Post-Surgery[4]



The odds ratio for diabetes remission was 13.3 and 6.3 in the patients undergoing bariatric surgery, at 2 and 15 years post surgery, respectively (P <.001). Adapted from Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complication.

sible for the effect.[9] Researchers in that study also found that changes in other factors are involved as well, such as improved insulin secretion and a spike in postprandial glucagon-like peptide 1 (GLP-1) production.[10] Yet, many other mechanisms have been proposed, as listed below and illustrated in **Figure 1**[8]:

- Exclusion of inhibitory factors from the proximal intestine
- Morphological changes of the Roux limb with increased cellular size and mass, resulting in reprogramming of intestinal glucose metabolism
- Increased energy expenditure
- Changes in branched-chain amino acids
- Bile-acid composition
- Gut microflora
- Unfolded protein response in adipose tissue [11]

Using a pig model, Lindquist and colleagues performed Roux-en-Y or sham operations, fed the pigs low-calorie diets, and examined the changes in pancreatic tissue. They found that beta-cell mass had actually grown significantly in those undergoing Roux-en-Y, along with islet number and the number of extra-islet beta cells. These investigators also observed greater pancreatic expression of insulin and glucagon as well as a greater number of cells with the GLP-1 receptors in pigs undergoing gastric bypass surgery.[12]

It seems that many different pathways may be responsible for the change in glycemic control. It also seems clear that whereas some changes, like increased hepatic insulin sensitivity, happen rather soon, the others likely occur over greater timespans, as the body adapts to its new anatomy.

And these positive changes may not be limited to patients with T2DM. Patients with type 1 diabetes mellitus (T1DM) seemed to experience a positive effect in a small study published earlier this year. Harvard investigators found that severely obese women with T1DM who underwent gastric bypass also had 2 positive short-term changes after a mean of 7.7 weeks postsurgery: Their A1C levels had dropped from 8.0% to 7.1%, and they experienced an 11% reduction in BMI.[13] Although both factors may help improve glycemic management, each of these patients will continue to need insulin supplementation.

Long-Lasting Benefit?

Although improvement or remission of T2DM is a potential positive side effect of bariatric surgical procedures, the procedures are not without serious risk and negative side effects. Perioperative mortality and morbidity are serious concerns, for providers, patients, and payers. As discussed in a previous issue of *Evidence-Based Diabetes Management*, Roux-en-Y surgery is associated with a risk of substance abuse, including alcohol abuse, after surgery.[14] In addition, the longer-term effects of bariatric surgery on T2DM are not yet completely known.

However, a truly long-term study of patients who had undergone gastric bypass (using various methods), the Swedish Obese Subjects (SOS) trial, may serve as a guide to the diabetes outcomes of patients decades after bypass surgery.[4] This prospective, matched-cohort study recruited and followed thousands of patients from 25 surgical departments and 480 primary healthcare centers in Sweden. In a study published in June 2014, the investigators followed the outcomes of those with T2DM: 260 control patients who did not undergo gastric bypass and 343 patients who did. The patients entered the study between 1987 and 2001 and were followed through 2013. The median follow-up time for glycemic status in patients in the control and surgery groups was 10 years. The researchers also assessed patients' T2DM complication outcomes, and the median follow-up time for this evaluation was roughly 18 years in both groups.[4]

The T2DM remission rates have been considerably higher in the gastric bypass group in both the 2-year and 15-year analyses **(Figure 2)**. The improved glycemic control seemed to translate over the long term to fewer T2DM complications: The cumulative incidence of microvascular complications was 41.8 events per 1000 person-years for controls and 20.6 per 1000 person-years for those in the surgery group, yielding a hazard ratio (HR) of 0.44 (P <.001). For macrovascular complications, controls experienced 44.2 events per 1000 person-years compared with 31.7 per 1000 person-years for the surgical group (HR, 0.68; P = .001).[4]

It is not yet known what happens to glycemic levels in patients who undergo gastric bypass but fail to maintain their initial weight loss. Although this is a concern, the SOS trial and other population-based studies consider this in their overall evaluations.[4,15] Overall, control of patients' T2DM is better. More research is needed into the effect on T2DM in those whose weight loss is not maintained, as this may help to better define prior authorization criteria for gastric bypass surgery and to clarify the mechanism of glycemic regulation after surgery.

Predicting Who Will Experience Remission of Diabetes

As the studies discussed above confirm, not every patient undergoing bariatric surgery will be able to discard their T2DM medications. Currently, no mechanisms exist to predict who will or won't benefit most from such surgery, in terms of T2DM improvement. Still, colleagues from the Geisinger Health System conducted a retrospective analysis to try to determine the factors that favor a T2DM remission. They evaluated the medical records of 630 Geisinger members with T2DM who underwent Roux-en-Y surgery between 2004 and 2011, for whom complete medical records were available.[16]

From this analysis, they developed a scoring system, dubbed DiaRem, which rates an individual patient from 0 to 22. The lowest scores seem to presage a clinical remission of T2DM within 5 years of the operation. The scores were determined based on 4 principal preoperative variables that they identified: insulin use, age, A1C level, and type of antidiabetic drugs used. Insulin use before surgery seemed to have the greatest (negative) effect on likelihood of remission.[16] Additional validation testing will need to be conducted before DiaRem can be incorporated into practice.

New research presented at the June

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2014 ADA meeting supported several components of the DiaRem formula. Stanford University researchers concurred that age, insulin use, and duration of insulin use were among several factors that seemed to differentiate those with partial versus complete remissions. Furthermore, some postoperative factors that seemed to be correlated with complete remission were greater weight loss, lower postop BMI, and lower triglyceride levels.[17]

Austrian researchers investigated a differentiation by gender, and determined that men may be more likely to experience full remission than women, although many more women undergo bariatric surgery than men. In this study's sample, 37.7% of men initially had T2DM, compared with 15.8% of women. Two years after bariatric surgery, only 1.6% of men had diabetes compared with 2.6% of women. The researchers also observed improved insulin resistance, low-density lipoprotein cholesterol, and triglyceride levels in men compared with women (P<.03). In this study, however, each subject had a starting BMI above 45 kg/m^2, so we cannot assume the results could be predictive for those with lower levels of preoperative obesity.[18]

The Value Proposition

The possibility of long-term benefit, including reduction or remission of long-term T2DM complications, is tantalizing. From a financial perspective, the chance to reduce the costs of treating T2DM, and of managing chronic kidney disease and heart disease common in patients with T2DM, may convince payers to cover bariatric surgery as an effective primary treatment for individuals like Sally G. But payers will likely move cautiously, especially in the short term, and still require initial treatment with intensive medical therapy. As Fine noted, "Assuming the long-term data demonstrates better outcomes on average with surgery than with medical management, we would [still] require a significant trial of participation in a program of supervised diet, exercise, and medication—including a GLP-1—without reaching an A1C goal <7%." He added that his organization would also seek "psychological profiles [of patients with T2DM] that indicated likely adherence to the post surgery diet restrictions."

Still, in the future, screening tools may help differentiate those patients who may experience the greatest glycemic benefit from this expensive and risky procedure. This would increase the value of bariatric surgery further to some patients with T2DM, perhaps even to some who are not morbidly obese. Answers to questions about the cost effectiveness of bariatric surgery for people with T2DM may well shift in coming years. **EBDM**

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FDA Update

Environmental Pollutants: A Risk Factor for Obesity and Diabetes

Surabhi Dangi-Garimella, PhD

Pollution has been associated with health complications that can have lingering effects. Air pollution, for example, not only affects the respiratory system, but is also associated with heart disease and stroke. According to a report by the American Heart Association, pollution, from traffic, factory exhausts, power generation, wildfires, smoking, and cooking on wood stoves, can lead to cardiac issues. Elderly heart patients experience the most impact, including the possibility of myocardial infarction. Additionally, pollution-mediated inflammation in the heart can also lead to cardiovascular (CV) complications.[1]

Surprisingly, environmental air pollutants also belong on the list of risk factors for obesity, along with the more familiar high-fat diet, lack of exercise, and agricultural policies. Prenatal exposure to polycyclic aromatic hydrocarbons (PAHs; carcinogens and endocrine disruptors produced as a result of incomplete combustion) was found to be associated with childhood obesity in a study that monitored children born to African American and Hispanic mothers living in the Bronx or Northern Manhattan.[2] By age 5 years, 21% of the children were considered obese, and by age 7 years, 25%, with the children's obesity found to be associated with the mother's exposure to airborne PAHs during pregnancy.[2]

An evaluation of PAHs in the urine of 3189 children and adolescents, aged 6 to 19 years, who participated in the 2001 to 2006 National Health and Nutrition Examination Survey, found total urinary PAH metabolites in those aged 6 to 11 years to be associated with higher body mass index, greater waist

circumference, and greater prevalence of obesity. In adolescents (aged 12 to 19 years), a positive but less consistent association was observed for all 3 indices.[3] In vitro and in vivo studies have identified the lipogenesis-promoting endocrine effects of PAHs, such as the regulation of PPAR in adipocytes and inhibition of the thyroid hormone receptor.[4]

Scientists at the Institut de Recherches Cliniques de Montréal (IRCM), Canada, found that persistent organic pollutants (POPs) can cause endocrine effects in metabolically abnormal obese (MAO) patients, but not in metabolically healthy but obese (MHO) patients. Serum analysis of these 2 types of patients revealed distinct POP profiles.[5] The study demonstrated that MHO patients are protected from the effects of POPs, and IRCM is directing ongoing efforts toward identifying the protective factors at work.

POPs—including polychlorinated biphenyls (PCBs), dichlorodiphenyl trichloroethane (DDT), and dioxins—are chemicals produced for use in agriculture, disease control, manufacturing, and industry, among them are. POPs are hard to contain–being easily transported by water and wind–and due to their lipid solubility can accumulate in the body fat of both people and wildlife. Their potential negative effects are multiplied via a process called biomagnification, whereby contaminants present in small amounts at the bottom of the food chain grow increasingly concentrated as they move from one creature to another, ultimately becoming a significant hazard to predators at the top of the chain.[6]

Researchers in Belgium have identified a correlation between POPs, obesity, and diabetes. Following evaluation of 28 different POPs among 151 obese and 44 normal-weight individuals, the authors concluded that exposure to environmentally relevant levels of POPs can be both diabetogenic and obesogenic.[7]

Efforts to Control Pollution-Related Diabetes

A workshop conducted by the National Institute of Environmental Health Sciences (NIEHS), a division of the National Toxicology Program, evaluated the available data on the association between environmental pollution and public health. The participating scientists concluded that several environmental exposures were associated with type 2 diabetes mellitus. Additionally, analysis of the existing literature supported the existence of the "developmental obesogen" hypothesis. According to this hypothesis, chemical exposures can alter adipocyte differentiation, or the development of neural circuits that regulate feeding behavior, and in turn increase the risk of obesity. When combined later in life with a diet that is high in sugar, fat, and carbohydrates, the effect of the chemical exposure may become more obvious.[8]

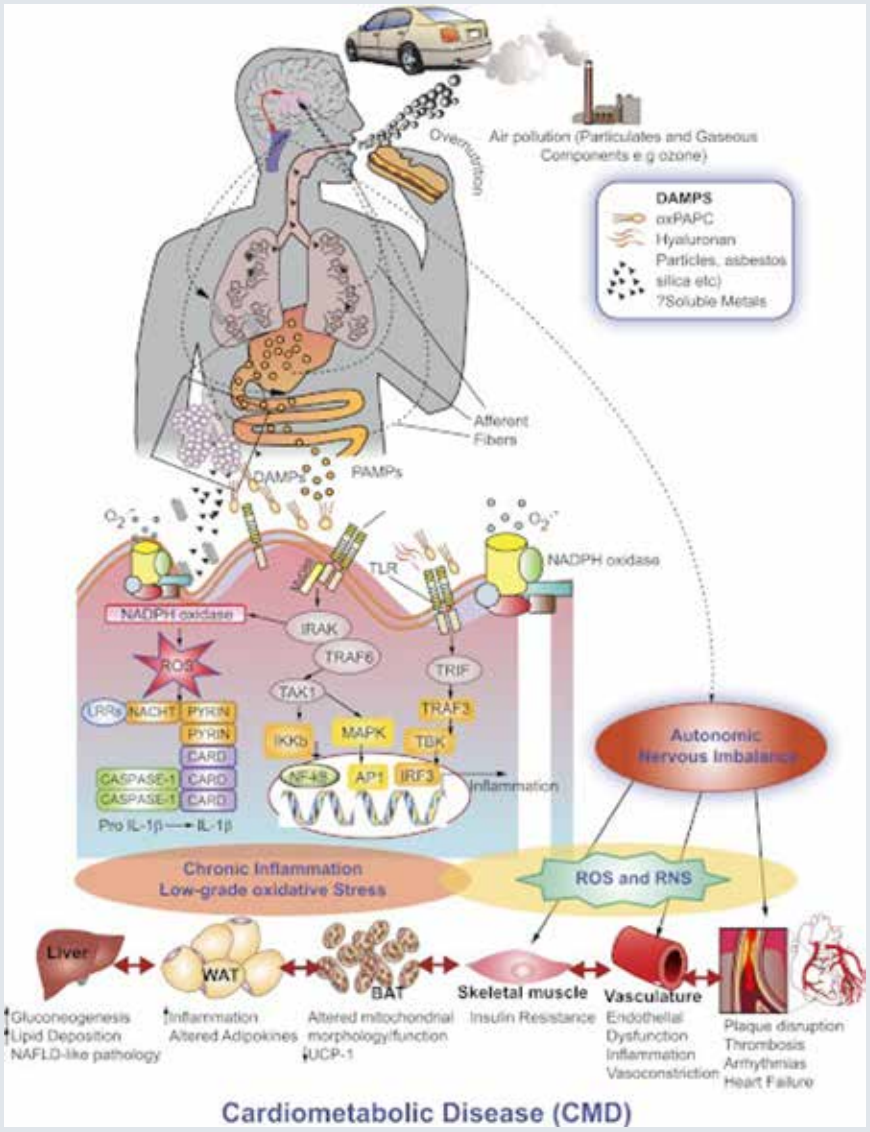
The workshop identified a critical knowledge gap in the understanding of the effects of pollution on type 1 diabetes mellitus. It also provided suggestions for appropriate end points or biomarkers and clinically accepted measures for diabetes and obesity.

With a mission to further the dialogue on environmental factors influencing human health, the Collaborative on Health and the Environment (CHE) facilitates collaborations that can prevent environmental atrocities and improve health.[9] The aim of CHE's Diabetes-Obesity Spectrum Working Group is to stimulate scientific efforts that demonstrate how environmental chemicals and other environmental or societal factors may contribute to the development and management of obesity, metabolic syndrome, and all types of diabetes.[10]

Despite the scientific community's extensive knowledge about the influence of environmental pollution on numerous disease states, there seems to be a lack of public awareness. When contacted by e-mail, representatives at both the NIEHS and the American Diabetes Association informed *Evidence-Based Diabetes* Management that there were no specific programs at either organization to draw attention to this growing risk in diabetes. Kristina Thayer, PhD, director, Office of Health Assessment and Translation, NIEHS, said in her e-mail that although federal agencies such as the FDA and the environmental health agency regulate environmental pollution measures, none have been regulated based on diabetes or obesity so far.

With obesity and associated metabolic disorders, diet and exercise are emphasized as risk factors, generally to the exclusion of all others. There is a need to adjust this perception to include the daily exposure to pollutants to our list of preventable causes of diabetes, among a host of other diseases. **EBDM**

Figure. Mechanism of Air Pollution–Mediated Cardiometabolic Effects



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Early Cellular Aging: Salt and the Telomeres

Surabhi Dangi-Garimella, PhD

Lowering sodium intake can slow down aging, especially in obese individuals, according to results presented at the recent American Heart Association (AHA) Meeting on Epidemiology and Prevention/Nutrition, Physical Activity and Metabolism Scientific Sessions 2014. The results were presented by Haidong Zhu, MD, PhD, assistant professor of pediatrics at the Medical College of Georgia, Georgia Regents University, and her research group.[1] The authors divided 766 teens (14 to 18 years old) into 2 groups, based on their reported sodium intake. The first group had an average intake of 2388 mg/day, and the second reported an average intake of 4412 mg/day; notably, both groups consumed more sodium than the 1500 mg/day recommended by the AHA.[2] The authors identified a significant impact of high sodium intake on telomere length (TL). Obese/overweight teens in the high sodium intake group had significantly shorter telomeres compared with normal-weight teens in the same group. This prompted the authors to recommend lowering the daily sodium intake as a first step in losing weight to lower the risk of heart disease.[1] The AHA website also has some heart-friendly tips to reduce daily salt intake (**Figure 1**).

Figure 1. **Salt Myths**

Source: American Heart Association website; http://bit.ly/1ICbbeP.

Telomeres and Obesity

The association between obesity and TL has been known for some time. Telomeres are nucleoprotein structures that cap the ends of eukaryotic chromosomes and prevent chromosome fusion, thereby maintaining genomic stability.[3] However, each cell division is associated with loss of a part of the telomere, such that as the telomeres shorten with aging, they reach a critical length and can no longer replicate.[4] The cells then undergo senescence or die (**Figure 2**). Thus, TL can serve as a biological clock to predict the lifespan of a cell or an organism. Independent of aging, TL is also driven by various disease conditions such as type 2 diabetes mellitus,[5] cancer,[6] metabolic syndrome,[7] and obesity.[8]

Expression of a telomere-binding protein, RAP1, was found associated with obesity. A RAP1 whole-body knockout mouse generated by scientists showed early-onset obesity, accumulation of abdominal fat, hepatic steatosis, and high fasting plasma levels of insulin and glucose. Thus, the transcription factor RAP1, which protects TL and regulates telomerase activity, also regulates metabolic signaling pathways, and in turn obesity. However, surprisingly, the authors did not find an association between RAP1 deficiency and short/dysfunctional telomeres in the setting of severe metabolic changes, leading them to conclude that these are 2 distinct functions of the transcription factor.[9]

Evaluation of 647 women (35 to 74 years of age) in the United States and Puerto Rico about a decade ago (2003 to 2004) identified that TL was inversely related to higher current body mass index (BMI) and hip circumference. A higher BMI in women who were in their 30s was associated with a shorter TL when they crossed 40 years of age. Further, weight gain and weight cycling in the 30s was inversely associated with TL. On comparing the women's existing BMI with their BMI when they were between 30 to 39 years old, shortest TLs were obvious among women who were obese or overweight at both time points in their life.[10]

A recent clinical trial, PREDIMED-NAVARRA, assessed the relation between TL and changes in adiposity indices after a 5-year nutritional intervention (Mediterranean diet) in 521 individuals (55 to 80 years of age), and documented an inverse relation. Higher baseline TL predicted a greater decrease in body weight, BMI, waist circumference, and waist to height ratio. A logistic regression analysis predicted that the risk of remaining obese after 5 years was lower in those who started off with a greater TL, and intervention further helped maintain their long TL.[11]

Taken together, the results of these studies firmly establish the association between obesity and telomere length, while the PREDIMED-NAVARRA study confirms that dietary intervention can delay the inevitable course of aging.

Diet and TL

Numerous studies have evaluated the impact of diet and dietary restrictions on TL. One such report found a positive correlation between TL and high fiber intake in women, but a negative correlation with polyunsaturated fatty acids.[12] Presence of anti-oxidants in the diet was also deemed important. A diet rich in the antioxidant omega-3 fatty acids slowed down the rate of telomere shortening, while the absence of these dietary components had the opposite effect.[13]

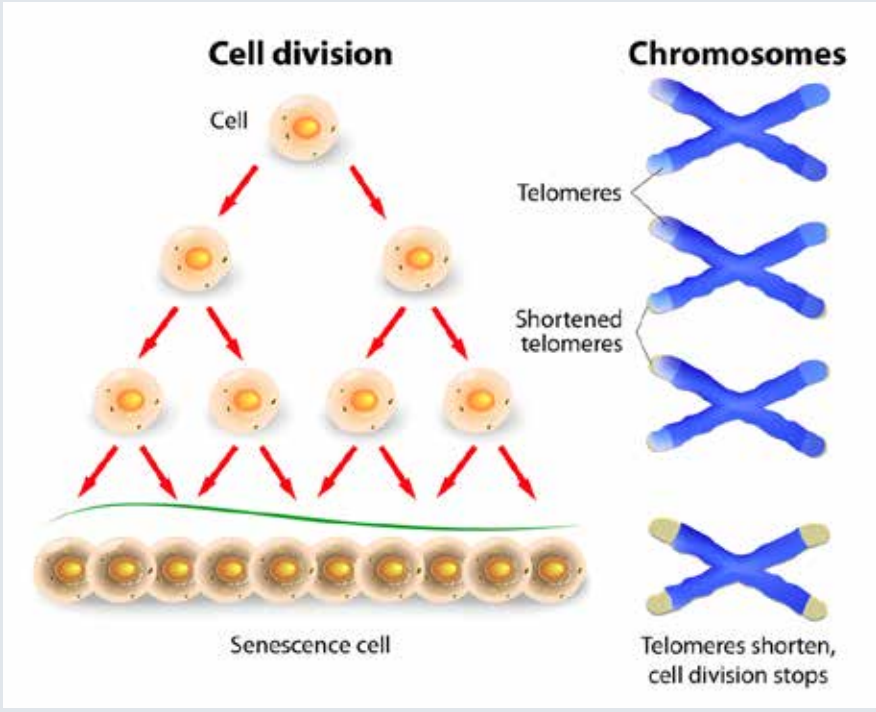
In addition to controlling what you eat, reducing how much you eat could also prove beneficial in terms of longevity. Several studies, conducted in animal models, identified health benefits in reducing food consumption, including an increased lifespan (up to 66%) and delayed onset of age-associated diseasescc.[14]

What Is Being Done?

Reverting back to the salt in the equation–it improves flavor in our food, and also acts as a stabilizer, preservative, and binder. Although essential for basic bodily functions, such as muscle contractions and relaxation, conducting nerve impulses, and maintaining the body's balance of water and minerals, excess salt is definitely detrimental and can lead to hypertension, heart disease, and stroke.[15]

The United States Department of Agriculture's (USDA's) dietary guidelines recommend that the daily sodium intake not exceed 2300 mg, while those in high-risk populations (persons ≥51 years old, African Americans, and those suffering from hypertension, diabetes, or chronic kidney disease) should limit their daily intake to 1500 mg.[16] However, considering that

Figure 2. Telomeres and Aging



Telomeres, which cap the ends of chromosomes, shorten with age, a process accelerated by various cellular stresses such as cell division, oxidative damage, free radicals, inflammation, etc. Shortened telomeres result in senescence (aging) or cell death.
Source: Woodrow Wilson School of Public and International Affairs; http://bit.ly/1sCnkSF.

nearly 70% of adults in the United States are at risk of developing heart disease due to high salt consumption, the Harvard School of Public Health, in conjunction with AHA and the Center for Science in the Public Interest, have called for the government to lower the recommendation of daily intake to 1500 mg.[15]

The CDC recommends small and smart changes to reduce salt consumption: being careful about buying high-sodium food products, providing children with fresh fruits and vegetables instead of processed and packaged foods (which are usually high in salt), and working with schools to improve the nutritional quality of meals.[17] Additionally, in partnership with state, local, territorial, and tribal health departments, the CDC is funding numerous programs to confront the growing obesity problem among children, including active transport to school, encouraging school-based physical education classes, and increased access to locally grown produce.[18]

With the increasing awareness raised by diverse organizations, and the Let's Move campaign spearheaded by frst lady Michelle Obama, a recovery path has been laid, though fruition is a long way coming. **EBDM**

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PEER EXCHANGE

AJMC Peer Exchange: Nationwide, Patient-Centered Strategy Needed to Battle Obesity, T2DM

Mary K. Caffrey

Fighting the nation's related epidemics of obesity and type 2 diabetes mellitus (T2DM) will take a nationwide strategy that increasingly tailors treatment to individual patient needs. Additionally, new approaches are needed to improve patient adherence and encourage lifestyle changes, which will lead to a healthier population.

That was the consensus of an expert panel convened by *The American Journal of Managed Care* as part of its conference, "Patient-Centered Diabetes Care: Putting Theory Into Practice," held April 10-11, 2014, at the Princeton Marriott at Forrestal in New Jersey.

Panelists taking part were **Jeffrey D. Dunn, PharmD, MBA,** senior vice president, VRx Pharmacy Services, LLC, Salt Lake City, UT; **Yehuda Handelsman, MD, FACP, FACE, FNLA,** medical director and principal investigator, Metabolic Institute of America, Tarzana, CA, and president-elect of the American Association of Clinical Endocrinologists (AACE); **Maria Lopes, MD, MS,** chief medical officer, AMC Health, New York City, NY; and **Kari Uusinarkaus, MD, FAAFP, FNLA,** associate medical director, adult primary care and health management, Colorado Springs Health Partners, Woodland Park, CO.

Peter Salgo, MD, professor of medicine and anesthesiology at Columbia University and associate director of surgical intensive care, NewYork-Pres-

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byterian Hospital, served as moderator. The 90-minute discussion covered the challenges to treatment, including woeful adherence rates to therapies despite recent advances in medication; how to weigh medical therapy against surgical options; and indications for the newest classes of diabetes therapies, the dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 receptor agonists, and sodium glucose cotransporter 2 (SGLT2) inhibitors.

The discussion opened with a snapshot of obesity and diabetes in the United States, where, according to the latest figures reported by the American Diabetes Association (ADA), nearly 26 million people are affected by diabetes, almost all of them with T2DM. Increases in diabetes have closely followed rising rates of obesity by state in recent decades, a point Handelsman noted when he said that California now "is where Mississippi was" years ago.

Handelsman said that "turning the tide" on diabetes would require a "nationwide, proactive intervention," with government health agencies taking a role. The trends are not good, the panelists agreed. Uusinarkaus said that though his home state of Colorado is statistically the nation's fittest, "Our obesity has finally crept up.…The trends are certainly in the wrong direction."

The statistics outlined by Salgo are alarming: he quoted an ADA study that shows the economic costs of diabetes are $245 billion a year in the United States, including $176 billion in direct medical cost (28% is for medication).

When Salgo asked if therapies alone could do the trick, given the distressing statistics on lifestyle modification, Handelsman insisted that past failures could not be a reason to give up options like better diet and exercise. "We know changing lifestyle works," he said.

Yehuda Handelsman, MD, FACP, FACE, FNLA

The challenge comes when it's time to pay for intensive, personalized efforts to help patients exercise and make better food choices over the long haul. These interventions are expensive, and not all insurers or employers are willing to include these items in a health plan.

Lopes agreed that prevention has to be part of the solution if the nation is to "bend the cost curve" on treating diabetes and its many complications. Tailoring treatment to individual patients is essential, she said.

Peter Salgo, MD

"We have to figure out what works, and more importantly, what does not work. A lot of this is going to be predicated on data from real-world situations," Lopes said. The panelists agreed that methods such as using newsletters or mailed reminders to diabetes patients were outdated and simply did not work. Group counseling has produced better results, Lopes said.

New therapies that help patients lose weight, alongside controlling diabetes, offer promise, because the patient can be motivated by seeing progress; studies show that glycated hemoglobin (A1C) levels drop along with excess pounds, even when the amount lost is initially small.

New therapies that help patients lose weight, alongside controlling diabetes, offer promise, because the patient can be motivated by seeing progress; studies show that glycated hemoglobin (A1C) levels drop along with excess pounds, even when the amount lost is initially small. Uusinarkaus said the promise of significant weight loss can help motivate a patient, who might refuse an injectable drug for diabetes, to give it a try.

New Agents: The SGLT2 Inhibitors

Salgo led a section of the exchange on the SGLT2 inhibitors, which are the latest tool for clinicians to combat T2DM. The excitement around these drugs comes from their ability to reduce A1C levels and blood pressure, and even aid weight loss, independent of what is happening with insulin and beta cell function.

Jeffrey D. Dunn, PharmD, MBA

As Handelsman noted, the basic mechanism of SGLT2 inhibitors has been understood for more than 40 years, but it was only recently that drug development progressed to harness what researchers have known. The kidney has an important role in glucose metabolism. In a patient without T2DM, the kidney reabsorbs glucose and returns it to the body, with SGLT2s accounting for 90% of this process and SGLT1s handling the other 10%. Normally, when the body reabsorbs a certain level of glucose, the rest is discharged in the urine. In T2DM patients, however, this mechanism runs off course, and SGLT2s uptake more glucose than is healthy. The new SGLT2 inhibitors block that process, at least to a point, precipitating more discharge of glucose through the urine.

Maria Lopes, MD, MS

Kari Uusinarkaus, MD, FAAFP, FNLA

"We know the kidney reabsorbs glucose," Handelsman said. "When you stop it, you really reduce a lot of exposure to glucose." He said that in time, this mechanism may be shown to limit some of the more serious long-term effects of T2DM.

Salgo noted that the mechanism of SGLT2s upends one of the fundamentals from diabetes care from decades past: letting persons with T2DM "spill sugar." Tests that measured sugar levels in the urine are no more, and have been replaced with modern blood glucose measurements.

The SGLT2s currently approved by FDA are canagliflozin, which Salgo said starts at a 100-mg dose, and dapagliflozin, which he said starts at 5 mg. Both can be used as monotherapy or in combination with other drugs. As Handelsman explained, while the weight loss effects of these drugs may seem modest (perhaps about 5 pounds), when SGLT2s are added to other therapies that also produce weight loss, the overall effect can be enough to encourage a patient to make lifestyle changes.

Who is a good candidate for SGTL2 inhibitors? Uusinarkaus said that typically, T2DM patients will already be on metformin, but if they remain obese or hypertensive, adding SGLT2 inhibitors may reduce these effects. In his review of the literature, "They do seem to be a little more potent than the DPP-4s."

Due to the way the drugs work in the renal system, however, Uusinarkaus said SGLT2 inhibitors are not recommended for patients who lack good renal function.

Is the weight loss effect beneficial? Lopes said, "Any degree of weight loss is good in these patients, especially since they are obese."

Whether the weight loss is clinically meaningful is measured not only in pounds lost, she said, but also in the way the weight loss affects other comorbidities. When A1C levels and blood pressure readings improve, "That's quite important to reduction of cardiovascular risks as well."

View of Payers, Pharmacy Benefit Managers

Dunn said payers and pharmacy benefit managers are open to new approaches and are not unwilling to pay for relatively expensive new therapies if they see signs of progress. Payers and employers balk, he said, when a patient is taking up to 4 drugs and still not achieving control of A1C or blood pressure.

"Every plan out there has thrown everything under the sun at diabetes," Dunn said. Plans cannot afford to provide intensive monitoring of every person with diabetes, but it does make financial sense to identify those patients most at risk of hospitalization or serious complications, and make highly targeted efforts to guide them to better health. "We need risk stratification and coordination," he said. "It has to be done on the right patients."

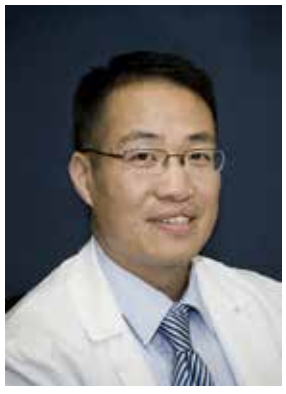
Dunn also called for shared risk among providers, payers, and the pharmaceutical companies that develop new, expensive treatments. Right now, he said, the risk is all on the payer, and that cannot continue. **EBDM**

Editor's Note: To view a webcast of the Peer Exchange, visit http://www.ajmc.com/ajmc-tv/peer-exchange.

Benefits, Risks of SGLT2 Inhibitors Explored at Session

Mary K. Caffrey

If the size of the crowd at the Moscone Center on June 15, 2014, in San Francisco, California, was any sign, interest is high in the new class of drugs to treat type 2 diabetes (T2DM), the sodium-glucose co-transporter 2 inhibitors (SGLT2s). These drugs, the focus of a symposium at the 74th Scientific Sessions of the American Diabetes Association (ADA), have gained notice for their role in eliminating glucose from the body while helping patients lose weight.



Edward C. Chao, DO

The symposium, "The Role of SGLT2 Inhibitors in the Treatment of Type 2 Diabetes," gave attendees an overview of how these new drugs harness the renal system to improve health measures, and how they can be used both alone and in combination with other drugs.

Edward C. Chao, DO, associate clinical professor of medicine at the University of California San Diego, walked the audience through the drug's physiological process. Clifford J. Bailey, PhD, FRCP, professor of clinical sciences and director, Biomedical Sciences Research, University of Birmingham, United Kingdom, reviewed recent studies on the drugs' benefits; Lawrence A. Leiter, MD, FRCP, FACP, FAHA, professor of medicine and nutritional sciences, University of Toronto, Canada, discussed safety issues; and Zachary T. Bloomgarden MD, MACE, clinical professor of medicine, Mount Sinai School of Medicine, laid out "unanswered questions" surrounding this new class.

While multiple SGLT2 inhibitors are under development, the session focused largely on canagliflozin and dapagliflozin, which have been approved by the FDA; presenters offered some data on empagliflozin, which has been approved in Europe and awaits FDA action.

Understanding the potential of SGLT2 inhibitors in T2DM starts with understanding the role of kidney in glucose metabolism, Chao said. Normally, the kidney reabsorbs glucose and returns it to the body; when glucose exceeds the body's reabsorption capacity, it passes out through the urine. However, this "job" of the kidney can result in hyperglycemia when too much glucose is reabsorbed, especially when glucose remains at chronically high levels. The role of the kidney in contributing to hyperglycemia was suspected in the time of the ancient Greeks, Chao said, but it took until the 1930s for this mechanism to be confirmed.

Sodium-coupled glucose co-transporters, especially SGLT2, are active in the reabsorption process. Chao said SGLT2 is normally responsible for 90% of the glucose absorption, with SGLT1 handling the remaining 10%. Thus, new drugs in the SGLT2 inhibitor class work to limit this process, allowing glucose to pass out in urine.

It's becoming clear, Chao said, that SGLT2 inhibitors do not have an unlimited capacity to eliminate glucose. Studies show that once a maximum level of glucose excretion is reached, higher doses of these new drugs do not eliminate more glucose. That's why there is interest in studying a combination of inhibiting SGLT2 and SGLT1, he said. It's also clear that because SGLT2 inhibitors have a distinct role, apart from the effects of insulin or another relatively new drug class, the incretin mimetics, that SGLT2 inhibitors can be used in combination with other therapies for additional benefits.

Lawrence A. Leiter, MD, FRCP, FACP, FAHA

The weight loss benefit of SGLT2 inhibitors is especially profound, said Bailey. If patients who need to lose weight can stick to a diet of 1500 to 2000 calories a day, and up to 300 calories of glucose are passed out through the urine, the effect on weight loss can be rapid, he said. However, there are some indications that the weight loss effect may bottom out, in part because after a while, patients become hungry and eat more.

> *"The weight loss benefit of SGLT2 inhibitors is especially profound. If patients who need to lose weight can stick to a diet of 1500 to 2000 calories a day, and up to 300 calories of glucose are passed out through the urine, the effect on weight loss can be rapid."*
>
> —Clifford Bailey, PhD, FRCP

It's the primary benefit, reduced levels of glycated hemoglobin (A1C) that interests clinicians the most, Bailey said. SGLT2 inhibitors are especially beneficial in patients who cannot take metformin, which is often the first drug prescribed for T2DM. However, Bailey said, the SGLT2 inhibitor class should be considered early on, even if metformin is used.

"If you give these to newly diagnosed patients, the combination of dapagliflozin and metformin, the results are better," he said, adding that combinations of dapagliflozin and insulin can also be effective.

Benefits of canagliflozin for reducing both A1C levels and weight are also evident, Bailey said. "It's more likely that you're going to see these agents in combination with metformin. We can also use as a triple therapy," along with insulin, he said. He repeated a theme heard at several sessions at ADA: acting aggressively early on, instead of waiting until T2DM progresses to add drug combinations, will be the right call for certain patients, especially if they need to lose weight.

Leiter addressed side effects, especially vaginal irritation in women and urinary tract infections (UTIs), which would be the result of higher glucose in the urine. However, Leiter said, thus far studies show that the side effects are not severe, that UTIs occur in the lower and not the upper urinary tract, and that generally, side effects have not been severe enough to cause patients to stop taking the drug.

"The highest occurrence is in the first 4 months, with less than 1% withdrawal from clinical trials as a result of infections," Leiter said.

What about volume depletion, which can result if patients become dehydrated? Leiter said these symptoms, along with skeletal risks, generally occur only in the oldest patients. As for cardiovascular risks, Leiter said trials going on right now will yield data that will tell clinicians much about longer-term effects.

What are the next questions in SGLT2 research? Bloomgarden said there are many, including why the drug class isn't more potent. Additional studies will examine relationship between SGLT2 inhibitors and glucagon, as well as the possible need for controlling dietary sodium to thoroughly understand the effects of this new class. **EBDM**

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Can Early Use of Insulin, GLP-1 Halt Diabetes Progression?

Mary K. Caffrey

For years, the standard for treating type 2 diabetes mellitus (T2DM) has been step therapy. Newly diagnosed patients are told to make change in their diets and to exercise more. Then, most start metformin. If T2DM progresses, doctors add drugs from among the dozen other classes, either alone but typically in combination. Insulin is added last, after a slow progression of deteriorating beta cell function and, perhaps, complications such as retinopathy or kidney disease.

Ravi Retnakaran, MD

But what if treatment for newly diagnosed T2DM looked more like care in cancer? What if insulin came *first*, for just a few weeks, and the decline in beta cell function could be arrested or even reversed? What if the "maintenance" therapy, after the short intervention with insulin, was not metformin but 1 of the newer, more powerful drugs approved in recent years?

On June 13, 2014, experts at the 74th Scientific Sessions of the American Diabetes Association (ADA) said this concept holds promise, even though the panelists had to hold back discussing results from several trials involving glucagon-like peptide (GLP-1) agonists in combination with insulin, which were presented late in the conference. While the results varied depending on the precise drug combination involved, more than 1 trial reported glycated hemoglobin (A1C) levels falling from above 8% to below 6.5% in groups of patients after they received GLP-1/insulin combo therapy. (Results for xultophy, the injectable mixture of Novo Nordisk's long-acting insulin Tresiba and its GLP-1 agonist Victoza, were described in 1 report as "the most talked about" in San Francisco.) [1]

The session, "Initial Treatment of Type 2 Diabetes—New and Not-So-New Ideas," held at the Moscone Center in San Francisco, California, began with Sunder Mudaliar, MD, of the Center for Metabolic Research at the University of California at San Diego. Mudaliar gave an overview of the concept of glucolipotoxicity. The theory emerged in a 1985 paper by Roger H. Unger, MD, and Scott Grundy, MD, PhD, who wrote that severe hyperglycemia can irreversibly damage beta cells, but halting it could, in turn, stop the progression and perhaps restore function.[2]

More recently, Mudaliar said, the work of Vincent Poitout, DVM, PhD, on glucolipotoxicity examined the relationship between glucose and fatty acids. Poitout states that when levels are chronically elevated, they harm beta-cell function in the pancreas; over time, this leads to reduced insulin secretion.[3]

Glucose and fatty acids, "are bad actors when they act together," Mudalair said. While needed at some level in the diet for fuel, they become toxic in high concentrations, and they do damage when those concentrations remain high over long periods. He reviewed multiple studies that showed how an intense period of hyperglycemia can have detrimental effects.

To halt glucolipotoxcity, Ravi Retnakaran, MD, an endocrinologist from the University of Toronto and Mount Sinai Hospital of Toronto, has studied giving T2DM patients short courses of insulin for periods of 4 to 8 weeks. This must be done early in the cycle of the disease; as diabetes progresses he said, the loss of beta cell function is so severe that it cannot be restored. Trying insulin early, Retnakaran said, raises the possibility of halting the decline, even though, "We usually don't think about reversible and irreversible factors of beta cell function."

Retnakaran's work has compared insulin delivery through a pump and through injections.[4] In 2013, he co-authored a meta-analysis of studies involving early use of insulin, which found 66.2% of patients achieved a drug-free "remission," after 3 months, although the effect was not sustained long-term after insulin stopped.[5] The quest now is to find a maintenance therapy that can help the patient retain this improvement. Retnakaran's 2010 pilot study with the dipeptidyl peptidase-4 (DPP4) inhibitor sitagliptin showed that therapy did not achieve the desired effect.

Why the GLP-1 class? The GLP-1 receptor is the gene expressed in pancreatic beta cells. Drugs in this class copy the process of natural incretins by helping trigger the release of insulin after meals, thus restoring blood sugar levels. Because of their link to the feeling of saiety after eating, these drugs also have the effect of contributing to weight loss,[6,7] which Richard E. Pratley, MD, said makes them particularly attractive to patients.

Pratley, of the Florida Diabetes Center in Orlando, further discussed early use of GLP-1 therapy, reviewing various benefits of this class relative to metformin. It's an ideal early monotherapy, he said, for patients who are metformin intolerant, who are overweight or obese, who are at risk of hypoglycemia, and who have "no barrier to injection." (After the session, Retnakaran discussed the issue of patients' fear of needles in his insulin studies; he said that when patients know that insulin treatment will not be forever, their objection to injection typically fades.)

Lawrence S. Phillips, MD, of Emory University in Atlanta, discussed "pattern care," which involves early combination therapy. Thanks to trials involving the newer classes of drugs, researchers have the ability to look at groups of patients who followed a regimen for a period of time and then stopped. Across several studies Phillips presented, the patients who were treated early and then stopped did see progression in their diabetes, but it never "caught up" to control group patients. This suggests the value of early intervention, he said, because the "legacy effect" lasts well beyond the period when the drug is taken.

> *"It's important to get patients to their A1C goal at least once during their treatment, because of studies that show the more often this happens, the slower the progression of the disease."*
>
> —Lawrence S. Phillips, MD

It's important, he said, to get patients to their A1C goal at least once during their treatment, because of studies that show the more often this happens, the slower the progression of the disease. "If we screen patients every 2 to 3 years, we can find patients when they have prediabetes," he said.

Treating these patients with better diet, exercise and perhaps therapy can help keep A1C levels down. Instead of targets such ADA's level of 7% or the 6.5% advocated by the American Academy of Clinical Endocrinologists, Phillips advocates targeting a level between 5.5% and 5.7%. "If we keep the A1C at 5.5, we preserve beta cells, and fewer complications develop later." **EBDM**

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Sessions Highlight Strides in "Artificial Pancreas" Technology

Mary K. Caffrey

"Are we there yet?" The opening line in the recent editorial in *Diabetes Care*,[1] appearing just ahead of the 74th Scientific Sessions of the American Diabetes Association (ADA) in San Francisco, sums up the hopes of those in the type 1 diabetes mellitus (T1DM) community, as they await word that "artificial pancreas" technology nears FDA approval.

Edward Damiano, PhD

Results presented at ADA on June 15, 2014, show that not only is the technology improving, but also that it is advancing on multiple fronts. Competition is important to the T1DM community, and it is becoming apparent that patients will have choices. This could help drive down prices for devices when they reach the market.

The "bionic pancreas" being developed by Edward Damiano, PhD, associate professor of biomedical engineering at Boston University, grabbed most of the attention, as results were simultaneously published in the *New England Journal of Medicine*.[2] The article, which highlighted separate studies among adults and teenagers, showed increased glycemic control with the investigational technology, especially among the adults overnight. "At home" studies, the next important step in the road toward FDA approval, will start soon among several study groups. Sue A. Brown, MD, assistant professor in the Department of Medicine at the University of Virginia, said such a study will begin there in July 2014.

Current technology requires T1DM patients to use an insulin pump and a continuous glucose monitor (CGM), but the patient largely tells the pump what to do. Overnight insulin regulation can remain tricky. Systems under study involve the use of specially programmed smartphones, which run algorithms that finely regulate release of insulin, more closely resembling what occurs in a person with a healthy pancreas. The Boston University model also dispenses the hormone glucagon, which commenters told *The New York Times* was a "clear advance."[3] Persons with T1DM and their advocates seemed to react favorably to the developments at the ADA conference. By contrast, some reacted negatively last fall when Medtronic, Inc used the term "artificial pancreas" to unveil its Minimed 530G with Enlite, whose "threshold suspend" technology was described by the company and in news reports as a major step forward in glycemic control.[4] However, in the view of many T1DM patients, the device did not represent an advance worthy of the "artificial pancreas" label.

That experience did not mute the anticipation at the San Francisco meeting, which saw hundreds crowd a small lecture hall for what was officially billed as highlights from the journal *Diabetes Care*. Two talks within the June 14, 2014, symposium, from William V. Tamborlane, MD, professor of pediatrics (endocrinology) at the Yale Diabetes Research Center, and Boris Kovatchev, PhD, professor in the Department of Psychiatry and Neurobehavioral Science and director of the University of Virginia's Center for Diabetes Technology, filled an overflow room and left dozens camped out in the hallways to watch the proceedings on a small screen.

Boris Kovatchev, PhD

Results that were published online ahead of the ADA sessions show that closed-loop technology of diabetes being developed at the University of Virginia trimmed the number of hypoglycemic episodes without adverse events.[5] Kovatchev's presentation featured photos of laptops that were running the insulin-regulating algorithms for the emerging technology only 4 years ago. Today's smartphones do the job in a more convenient package. Would this mean that persons with T1DM could soon manage their disease with the same portable device that most people carry in their pocket? Brown indicated this is possible. She said the phones used in clinical trials are disabled for other functions only because that's what FDA protocols require.

Some T1DM patients who took part in the University of Virginia trial in January are also well-known bloggers, and they did more to generate buzz than any marketing campaign ever could.[6] Kovatchev, whose center has received significant funding from the National Institutes of Health to work on artificial pancreas technology,[7] offered this progress report June 14, 2014: algorithms, which decide how much insulin to deliver, are ready. The technology is almost ready, but needs some fine-tuning. What's left is putting the devices into clinical settings on a broad basis, which will generate the results that FDA must evaluate before giving approval. That's what the "at home" tests will do next.

Artificial pancreas technology has raced forward since 2012, when the FDA published its road map outlining what the agency needed to see for approval.[8]

Boston University results. Results were published from 2 studies involving 20 adults and 32 adolescents with T1DM who wore a "bionic pancreas" for 5 days. Instead of the patient programming insulin delivery, the device was managed by an algorithm, which received data from a CGM and automatically controlled subcutaneous delivery of insulin and glucagon. In the adult study, the mean plasma glucose level during the study period was 138 mg/dL, and the mean percentage of time with a low glucose level (<70 mg/dL) was 4.8%. After using the device for 1 day, mean glucose levels were lower than mean levels during the control period (133 ± 13 vs 150 ± 30 mg/dL, P <.001.) Time with a low glucose reading was lower (4.1% vs 7.3%, P =.01). Among the adolescents, the mean plasma glucose level during the period using the device was also lower than during the control period (138 ± 18 vs 157 ± 27 mg/dL, P =.04), but the percentage of time with low glucose readings were similar (6.1% vs 7.6%, P =.23%). The authors reported significantly better control among the adults at night, and a reduction of more than 50% in the amount of carbohydrates given to treat hypoglycemia.[2]

University of Virginia results. Abstracts presented June 15, 2014, included results from a study of 10 adults, who stayed at a research "home" that is part of the university campus. The study's aim was to fine-tune insulin delivery overnight, essentially "resetting" the patient to near normal glycemic levels.[9] Brown said the technology aimed for an average 7 am reading of 120 mg/dL, and came in with an average of 119.3 mg/dL, compared with 152.9 mg/dL, P <.001, under standard care. And this happened using lower amounts of insulin, 6.1 units compared with 6.8 units, P =.1, under standard care. According to the study, improved glucose control carried over to the next day. **EBDM**

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Results Presented on Motivating Patients With Diabetes

Mary K. Caffrey

It's well-known that it's hard to treat type 1 (T1DM) or type 2 diabetes mellitus (T2DM) if patients fail to take prescribed medications, stick with diets, or follow blood glucose–monitoring regimens. Motivating at-risk groups, such as teenagers with T1DM, or minority populations with T2DM, is especially challenging.

The June 14, 2014, poster session at the 74th Scientific Sessions of the American Diabetes Association (ADA) meeting, held at the Moscone Center in San Francisco, California, included the track "Diabetes Self-Management Education: New Methods," with ideas for both T1DM and T2DM populations.

Teens and Young Adults With T1DM. In an interview earlier this year with *Evidence-Based Diabetes Management*, Robert Kritzler, MD, a pediatric endocrinologist who is also deputy chief medical officer, John Hopkins Health Care LLC, said the transition from the early teenage years to young adulthood is a challenging time for those with T1DM.[1] In short, these patients have all the normal challenges of moving from childhood to adulthood, and when one adds diabetes management to the mix, responsibility for self-care isn't always perfect.

A pair of abstracts at Saturday's poster session looked at this population. A study led by Kathleen C. Garvey, MS,[2] reported results from a survey of members of the American Association of Diabetes Educators. The 771 respondents (17% response rate) were overwhelmingly female (96%) and had typically practiced 12 to 15 years. Among the findings:

Most felt that reviewing a young adult's pediatric records prior to the first adult visit was important (88%), but only 22% reported having time to do so.

Most had access to endocrinologists (82%) or dieticians (93%), but fewer had access to mental health referrals (58%). Half reported they would prefer better access to mental health care for their young adult clients.

Those without access to mental health referrals reported more problems with young adults suffering from depression, substance abuse, eating disorders, or developmental disabilities.

The educators endorsed more access to education on young adult behavior (90%), better reimbursement (52%), and young adult support groups (83%).

A second study examined whether using social media as a tool for glucose management would be as effective as clinic visits in young T1DM adults.[3] The authors, from Skopje, Macedonia, used Facebook and Skype with a group of 124 teens and young adults aged 16 to 23 years. They were randomized into 2 groups: the first was treated with standard clinic visits, and the second with social media platforms and Medtronic's Carelink program. After 6 months, the groups swapped methods of care.

After 1 year, glycated hemoglobin (A1C) levels dropped as follows: from an average of 7.8% to 6.4% in the first group, and from 7.9% to 6.3% in the second group. Both groups maintained A1C levels during the 6 months after the changeover. The authors, led by Goran Petrovski, MD, PhD, concluded that both methods worked, but that the young adults preferred the social media visits to coming to the clinic.

Robert M. Mayberry, PhD, MS, MPH

At-Risk Populations With T2DM. Poor medication adherence is a problem across medicine, but it's a particular problem among the demographic groups with disproportionate levels of T2DM. Patients who are poor, less educated, and lacking access to better food or knowledge of how to follow a healthy diet are also less likely to stick with a medication regimen. Several abstracts Saturday examined efforts to improve adherence to medication and lifestyle changes among adults with T2DM—and showed just how stubborn the problem can be.

Robert M. Mayberry, PhD, MS, MPH, professor of epidemiology at Morehouse School of Medicine in Atlanta, Georgia, and his co-authors incorporated evidence-based medication use into patient self-care at a federally qualified health center (FQHC). A prior study found that 90% of African American adults with T2DM at this center did not take medication as prescribed. Mayberry's study engaged a community health worker and used motivational interviewing (MI) techniques to adapt an education program to these patients. A group of 460 adults were randomly assigned to a worker using MI techniques, as well as peer support, or a worker delivering general education. Patients were followed each month for a year. The group receiving the MI intervention showed significant improvements in A1C levels right after the intervention, but there was no significant difference in A1C improvement between the 2 groups. However, the intervention group showed improvement in scores on the PACIC survey (Patient Assessment of Chronic Illness Care).[4]

Results from the IDEA trial (Improving Diabetes through Examining and Advising)[5] examined whether patients who knew the nature of their diabetes risk would be more willing to stick with a lifestyle modification program. Low, moderate, and high-risk scores were assigned to 192 patients at baseline, and they were divided into 2 groups. In the first group, patients were told their risk at the outset; in the other, they were not told until week 12. The groups started with similar characteristics, and at 12 weeks there was little difference in attendance or weight loss (average of 10.08 lb for intervention group vs 9.66 lb for control). At 12 weeks, both groups were given risk information, including the previously unseen baseline for the control group. At 24 weeks, the control group continued to lose weight (2.63 lb average), while the intervention group gained (0.93 lb average). Thus, the knowledge of a baseline did not affect compliance with a lifestyle intervention, but the researchers concluded that those who were given information about their prior risk, and how much they had improved, were shown to have improved adherence. **EBDM**

Results from the IDEA trial (Improving Diabetes through Examining and Advising) examined whether patients who knew the nature of their diabetes risk would be more willing to stick with the lifestyle modification program.

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Diabetes Navigator Program Reduces A1C Levels for Patients in Alabama

Mary K. Caffrey

Deploying diabetes patient navigators among patients in Birmingham, Alabama, who were at high risk for developing type 2 diabetes mellitus (T2DM) produced measurable reductions in glycated hemoglobin (A1C) levels, and increased the patients' perception that their care was improving, according to researchers who presented results at the 74th Scientific Sessions of the American Diabetes Association.

In 2012, the American Academy of Family Physicians Foundation (AAFP) and Sanofi US launched a collaboration to not only better connect T2DM patients with community resources, but also to convince those at risk that they could manage their disease. Results from the effort, called Cities for Life, were reported June 14, 2014, during the ADA meeting, which was held at the Moscone Center in San Francisco, California.

"Diabetes care involves patients doing what they need to do every day, 24/7, 365 days a year. Leading a healthy lifestyle makes all of the medicines work better," said Edwin Fisher, PhD, of the AAFP Foundation. Yet patients who live in "food deserts" or have few safe places to exercise may have a hard time maintaining healthy lifestyles, Fisher said.

Cities for Life aimed to fill that gap. The program connected patients already diagnosed with T2DM or those at risk of developing the disease with navigators, who not only helped identify local resources to help patients manage their disease, but also gave patients education and encouragement about why a healthy lifestyle mattered. Patients were assigned to a navigator by their primary care physician (PCP). While some elements of Cities for Life were available to everyone in Birmingham, including a website with diabetes care resources, a group of 179 at-risk patients were tracked closely. Most in this group (77.5%) were African American women, and nearly all were overweight or obese. Patients in the closely watched group heard from navigators an average of 6 times during the intervention.[1]

Edwin Fisher, PhD

Fisher said Cities for Life benefited from enthusiastic, highly effective navigators as well as the participation of 80 community leaders who served on an advisory board. One Birmingham City Council member took a special interest in the program, Fisher said, ensuring that it would receive staff support and follow-up. Community leadership and awareness makes a difference, Fisher said.

Abstracts presented at ADA included a presentation of outcomes, with Natalia Loskutova, MD, PhD, as the lead author. Data showed that the 179 closely watched subjects started the 9-month intervention with average A1C levels of 7.7% and were able to drop that average to 7.1%. Slight improvements were seen in blood pressure and cholesterol levels, and patients reported improvements in their perceived ability to manage their disease.[1]

Fisher said AAFP and Sanofi purposely selected Birmingham because it is located in a state that is among the top 10 in the country in T2DM incidence, and where health problems among the poor have long been seen to be intractable.[2] By going "to where the problem is," Fisher said, researchers hoped to show the potential value of patient navigators, whose role could be replicated within a Patient Centered Medical Home.

What makes a good navigator? Fisher said while most of the navigators in the Birmingham study had at least a bachelor's degree, professional credentials were less important than having the right personal qualities. "They have to be reliable, caring, and have 'emotional intelligence.' They have to be willing to be part of team," Fisher said. Navigators needed to understand when to push a little harder, when to hold back, and when a problem required a referral to a PCP or specialist.

How replicable is Birmingham's experience? "What's replicable is how we tailored it to the community," Fisher said. He was the formal presenter of a separate abstract that analyzed the program's effectiveness at the community level. Survey results showed Cities for Life increased community awareness of diabetes and patients' perceptions of support.[3] The project also revealed another challenge: the gap between providers' and patients' views of the level of family support for those with T2DM.[4] **EBDM**

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Afrezza, Inhaled Insulin, Wins FDA Approval

FDA Update

On June 27, 2014, the FDA approved Afrezza, an inhaled insulin for mealtime use, bringing this form of therapy back to the market after a 7-year absence.[1] The approval covers patients with type 1 (T1DM) and type 2 (T2DM) diabetes mellitus, and follows an extensive review process, one that required the drug's manufacturer, the MannKind Corporation, to perform additional clinical trials at FDA's behest 3 years ago.[2]

Inhaled insulin got its first try in 2006, when Pfizer brought Exubera to the market. But the oversized inhaler was cumbersome and unpopular with patients and physicians alike. The product failed miserably and was pulled a year later. By contrast, Afrezza's small inhaler fits in the palm of a hand, and T1DM advocates who spoke with *Evidence-Based Diabetes Management* in May said it appeared MannKind had done its homework with patients this time around.[3]

"(This) approval broadens the options available for delivering mealtime insulin in the overall management of patients with diabetes who require it to control blood sugar levels," Jean-Marc Guettier, MD, director of the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research, said in a statement released by FDA.[1]

Afrezza is not for every person who requires insulin. FDA's approval comes with a boxed warning, the strongest type, that the product should not be used by smokers or persons with chronic obstructive pulmonary disorder.[1] Nor is Afrezza a substitute for long-acting insulin; rather, it is a mealtime complement for that product for T1DM patients; those with T2DM can use Afreeza with oral therapy. The inhaled product is seen as a means to get T2DM patients who need insulin to use it when they might otherwise avoid it, due to fear of needles.

According to the FDA, the approval includes requirements for 4 postmarketing studies for Afrezza: a clinical trial to evaluate pharmacokinetics, safety, and efficacy in pediatric patients; a clinical trial to evaluate long-term risks of lung cancer and cardiovascular function; and 2 studies to evaluate dose-response and within-subject variability.[1] **EBDM**

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Integrated Treatment for Diabetes, Depression Gains Notice, With Help From ACA

(continued from cover)

Table. Changes in Outcomes in Control, TEAMcare Trial

Outcome	Unadjusted Estimate Intervention Group	Change	Unadjusted Estimate Control Group	Change	Estimated Difference (95% CI)
A1C%					
Baseline	8.14 ± 2.03	0.81	8.04 ± 1.87	0.23	-0.56
6 months	7.42 ± 1.32		7.87 ± 1.93		
12 months	7.33 ± 1.21		7.81 ± 1.90		
LDL cholesterol					
Baseline	106.8 ± 35.4	14.9	109.4 ± 36.7	8.0	-9.1
12 months	91.9 ± 36.7		101 ± 36.6		
Systolic BP, mm Hg					
Baseline	135.7 ± 18.4	4.7	131.9 ± 17.0	-.0.4	-3.4
6 months	131.9 ± 15.2		133.5 ± 20.4		
12 months	131.0 ± 18.2		132.3 ± 17.4		
SCL-20 score					
Baseline	1.74 ± 0.59	0.91	1.65 ± 0.60	0.51	-0.41
6 months	0.84 ± 0.68		1.26 ± 0.72		
12 months	0.83 ± 0.68	1.14 ± 0.66			

Source: *N Engl J Med.* 2010;363:2611-2620. A1C indicates glycated hemoglobin; BP, blood pressure; LDL, low-density lipoprotein; SCL-20, Symptoms Checklist depression screen.

"Depression raises the risk 60% that the patient will develop type 2 diabetes," Wayne J. Katon, MD, of the University of Washington, said in an interview with *Evidence-Based Diabetes Management*. Once a patient has T2DM, untreated depression can make it hard to follow diets or stick with medication, he said.

Many of these connections have been known for years. In 2001, a study in *Diabetes Care,* the ADA's flagship journal, concluded that the presence of diabetes doubled the odds of comorbid depression.[5] The difference now is the push to coordinate care for the constellation of diseases, rather than treat mental health in a silo.

What's driving the shift? There are many factors, but the most important one is the ACA, which requires providers and health plans, as well as new entities called accountable care organizations (ACOs), to deliver better care while cutting costs. This has forced the healthcare system to confront how inattention to mental health drives up spending on the medical side. The 2014 report prepared for APA by the actuarial firm Milliman, Inc, got a full airing in New York City, including the finding that better integration of primary and mental health care could save $26 billion a year.[6]

In 2012, 14% of the enrollees on commercial plans had mental health claims, but these patients accounted for 28.7% of the medical spending.[6] Taxpayers pay for lack of coordination too. Mental health patients make up 9% and 20% of the enrollees in Medicare and Medicaid, respectively, but these enrollees accounted for 26.3% of the medical spending in those plans.[3] At the APA session, "Levering Psychiatric Expertise: Integrated Care and Healthcare Reform," panelists agreed that psychiatrists and PCPs who fail to embrace integrated delivery models will suffer financial consequences.[3]

Washington's TEAMcare Approach

The pioneers integrating primary and mental health care, particularly for patients with T2DM, are at the University of Washington, where the TEAMcare design was developed and studied in a clinical trial.[7] Patients were randomly assigned to receive usual care or collaborative care; patients in the second group had their care across multiple diseases—including depression, T2DM, and cardiovascular disease, managed by a specially trained nurse who ensured that cases were reviewed at weekly sessions with the care team.

The University of Washington group reported its results in the *New England Journal of Medicine* in 2010.[7] Patients receiving collaborative care for 12 months had 58% improvement in glycated hemoglobin (A1C) levels relative to the control group. Low-density lipoprotein measures and blood pressures improved by wider margins **(Table)**, as did scores on the Symptoms Checklist (SCL-20) depression screen. Patients receiving collaborative care were more likely to have adjustments to insulin or to antihypertensive and antidepressant medications. Patients who received the intervention also reported higher levels of satisfaction with their care.[5] The cost of care for this group was lower—an average of $594 per patient for the year.[4]

The Washington results have gained notice. Katon, who was the lead author on the *NEJM* article, took part in both panel discussions at APA and gave a workshop on practical ways to bring collaborative care to a practice.[3,8] Co-author Paul Ciechanowski, MD, MPH, presented the TEAMcare approach at the ADA symposium, "Bending the Curve: Behavioral Health Efforts in Diabetes and Healthcare Reform."[4] Katon and his University of Washington colleagues are now bringing TEAMcare concepts to practices around the country.[9]

As Ciechanowski and others explained at the ADA session, the key ingredient in collaborative care is the weekly case review, where PCPs, mental health professionals, care coordinators, and diabetes educators track who has missed an appointment, whose A1C levels should be taken, and whose unexplained physical symptoms could be a sign of a stress.[4] Another component is better use of electronic health records, although some state regulations constrain mergers of medical and mental health records.

A Long Time Coming

The need for collaborative approaches to diabetes and mental healthcare seems so obvious—so why has it taken so long?

In an interview, Katon listed many challenges:

Acute versus chronic conditions. Primary care has historically meant "acute care," such as treatment of a symptom or injury, while mental health services work best over time.

Confronting stigma. Most patients will show up at a PCP when stress manifests itself as a physical symptom, but the stigma of mental healthcare often means they won't follow up on a referral to a psychiatrist. It's easier to get past this when the mental health provider is part of the PCP's team.

Adherence. Getting patients to take medications is a problem across chronic conditions, but it's especially troublesome in the mental health arena. And the divide between primary care and mental health care has often meant that needed adjustments to antidepressants never occur. When medication doesn't work or side effects appear, patients may stop taking it.

Coverage. Historically, the biggest barrier to coordination of primary and mental health care has been the separation of coverage by payers. Limits on mental health visits and restrictions to higher-cost medications have made continuity of care and affordability difficult for many patients. ACA's enshrinement of mental health parity should help change this, although enforcement is just beginning.

Doctors themselves can be a barrier to better coordination, even in settings like the TEAMcare project in Washington. But if they can be won over, Katon explained at APA, these one-time doubters can be the strongest supporters.

He described a colleague, a former athlete-turned-PCP who would not make a mental health referral for 2 years. Then this doctor spent months working to alleviate his patient's unexplained back pain, without success. Katon, the psychiatrist on the team, interviewed the patient and learned of multiple family problems in the home, including addiction, unemployment, and money woes among the patient's adult children. Katon treated the woman's depression and helped her learn to set limits, which rid her of pain. In the process, Katon won over her primary care doctor.

Changing Incentives Opens Doors

Katon has high hopes for the movement toward the Patient-Centered Medical Home (PCMH), which should mean better coordination of care. Standards revised this spring by the National Committee on Quality Assurance (NCQA), which offers PCMH accreditation, call for better integration of behavioral health services into primary care.[10] In June, NCQA took comment on revisions that will boost accountability for antidepressant medication management and proactive assessment of drug and alcohol abuse, as well as numerous measurements in diabetes care.[11]

"The ACO movement, the vertical organization with medical specialty care, and

(continued on SP306)

Behavioral Health Session Tackles Diabetic "Burnout," Mental Health Delivery

Mary K. Caffrey

Diabetes is a medical condition that not only damages the body, but can also crush the spirit of those who have it. A lifetime of following diets, counting carbohydrates, following medication schedules, managing insulin injections, and visiting a fleet of doctors can wear down people with diabetes, even if they are doing everything right.

So, how should doctors serve those who suffer depression alongside the disease, either type 1 (T1DM) or type 2 diabetes mellitus (T2DM)? This was the theme of the June 14, 2014, symposium at the 74th Scientific Sessions of the American Diabetes Association (ADA), held at the Moscone Center in San Francisco, California.

At "Bending the Cost Curve: Behavioral Health Efforts in Diabetes and Healthcare Reform," attendees first heard from William Polonsky, PhD, CDE, associate clinical professor at the University of California at San Diego and head of its Behavioral Diabetes Institute. The symposium then featured 3 speakers who shared efforts to better coordinate care, especially for those whose symptoms or history suggest they are most likely to land in the hospital.

Polonsky delivered the Richard R. Rubin Award Lecture, which he titled, "Important Lessons My Patients Have Taught Me." His premise: decades' worth of papers, studies, and efforts to force patients to make lifestyle changes have gone overboard. In Polonsky's current view, if patients aren't responding, it might be time to stop blaming them, and for doctors to "look in the mirror."

"Does behavior matter? Yes, it matters a lot," he said. But "evidence of the power of collaborative action planning," in which doctors and patients agree on diet and exercise goals, is sorely lacking. "Why is it so hard?" Polonsky asked. "Habits are hard to change."

"Diabetes is a lot of work. The day someone is diagnosed, they've just been given a new job for the rest of their life," one that doesn't pay and has "no days off," he said. It's time for doctors to "step back and think differently" about what they expect from persons with diabetes.

Real change, Polonsky said, requires taking notice of 3 steps:

- The importance of taking time
- The importance of the mundane
- The importance of ATMs, or "actions that matter"

Taking time, he said, requires doctors to gradually warm their patients up to the idea of change, to their buy-in, to not push so hard that patients don't come back. When patients don't meet goals, he said, it's likely because "We have been focusing on the behavior rather than what's behind the behavior."

Motivational interviewing, for example, is getting lots of attention. But a review of 4 studies on its effects since 2010 showed 0.1% difference in glycated hemoglobin (A1C) among patients studied. Setting goals pateints won't buy into may be worse than doing nothing, Polonsky said.

Acknowledging "the mundane" asks doctors to isolate obstacles to meeting goals. Many patients show symptoms that indicate "diabetes fatigue" or "burnout" from handling the disease every day, said Polonsky, but they are erroneously diagnosed with depression and prescribed antidepressants. He hinted at data that were formally presented later at the conference, which showed that overall rates of depression in T1DM and T2DM may not be as high as previously believed.

(On June 15, 2014, the ADA released a study co-authored by Polonsky and led by Lawrence Fisher, PhD, ABPP, of the University of California at San Francisco. In the study, persons with diabetes whose scores on a standard questionnaire showed they were suffering depressive symptoms were prescribed 1 of 3 interventions. None of these interventions treated depression per se, but instead helped them to manage their diabetes. After 12 months, participants in all 3 intervention groups were able to lower their scores on the questionnaire.)[1]

Change can come in small steps. Polonsky showed data from a patient who was asked to check his blood glucose immediately before and immediately after a 45-minute walk for 7 days. The average postwalk drop each day was 35 mg/dL, and the results were a revelation to the patient. Seeing the concrete benefit of exercise was far more convincing than another lecture, Polonsky said.

"Actions that matter" are recommendations that give both doctor and patient "bang for your buck," he said. "Instead of giving the patient a list of a dozen things to change, focus on one that's really important, like taking medication properly.

Collaborative Models. Paul Ciechanowski, MD, MPH, of the University of Washington, and Mark Williams, MD, of the Mayo Clinic, made presentations on the collaborative care approach, in which primary care physicians and psychiatrists work in teams, along with care coordinators and diabetes educators. They key element of this approach is the systematic case review, involving the team reviewing the progress of each patient in the practice, usually once a week. Team members are given assignments for the following week, and Ciechanowski said everyone is held accountable for each patient's progress—not just the patient.

The TEAMcare approach, first featured in the *New England Journal of Medicine*,[2] was later found to be associated with a per patient savings of $594 in a cost-effectiveness evaluation, which analyzed claims for medical services over 24 months in a capitated environment.[3] (TEAMcare's website said savings in fee-for-service environments are $1100 for the same period).[4]

Ciechanowski said the collaborative model has several advantages: it addresses comorbid conditions, and patients with diabetes and mental health issues often have 4 or more diagnoses; it recognizes "clinical inertia," the phenomenon of putting patients on antidepressants but not adjusting the dose as needed; and it offers psychic benefits to the providers who get support from one another and feel less strained.

Williams noted that this "population management" approach, so different from the "disease-based" approach in which so many were trained, really requires a different way of thinking. This method forces providers to look for those patients who may not be "noisy" and demanding of attention, but are nonetheless not well. Those quiet patients are the ones who are often missed, he said.

Saving Lives, Costs in Type 1. Michael Harris, PhD, of the Oregon Health and Sciences University, presented a model to reduce hospitalization days among youth with T1DM. Even with strong family support, teenagers may struggle with regimens as they begin managing their disease on their own. But among the Medicaid population that Harris' group treats, conditions like high rates of parental unemployment, single parenthood, or even homelessness makes staying on insulin or diets more perilous.

The program, Novel Interventions in Children's Healthcare (NICH), pairs youth who have had multiple hospitalizations with "interventionists," who do everything from coordinating medical care to attending meetings with school officials, to making home visits. Early success stories included eliminating hospital stays for Oregon youth who have previously been admitted several times a year—in 1 case, 9 times in 8 months for diabetic ketoacidosis (DKA). DKA is usually the result of the teenager or the parent failing to keep adequate insulin or supplies on hand.[5]

These life threatening episodes tax both the patients and the hospitals that serve them; as Harris noted, Medicaid reimbursement rates often mean DKA incidents cost the provider more than they are reimbursed. Youth that NICH targeted made up 4.5% of the diabetic population in the Portland, Oregon, region but were consuming 50% of the healthcare resources, Harris said.

Success starts with understanding what Harris called "the context" of the behavior. "If you don't know the context in which the behavior is occurring, you can't change it," Harris said. NICH's first patient was a 15-year-old female who previously had 2 DKA episodes over 4 years. Then, in 2012, she had 12 in a year. The NICH interventionist uncovered upheaval in the home and a mother unwilling to provide supervision. "We moved her into a great-aunt's home, where she has stayed and thrived," Harris said.

Hospitalization has not been eliminated from this group, but it has been dramatically reduced. "Every single person enrolled experienced no or reduced hospital stays," he said. NICH saved Oregon Medicaid $116,814 in a year, cutting hospitalization costs from $158,616 to $41,702. Hospitals likely saved more, beyond what Medicaid was paying.

Being an interventionist is a 24/7 job, so duties rotate among a dozen staff members. All are actively encouraged to take "down time," Harris said. But the interventionists often resist because of the rewards that come with the job. "There's so much ownership of this," Harris said. "You can effect change that no one else can." **EBDM**

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(continued from SP304)

the focus on keeping people out of the hospital will all help," Katon said. Healthcare reform is forcing practices and health systems to scrutinize where patients with psychiatric disorders are overrepresented in treatment of comorbid conditions. The movement promises to tackle what has been a hurdle in promoting collaborative care: how to pay for the care coordinators or diabetes educators who make these models hum. Too often, Katon said, practices that did the right thing saved money, but the savings flowed to the payer, not to those delivering better care.

The arrival of ACOs and shared savings means "there's an incentive to get that money back," he said. He expects that Medicare's tracking of 30-day hospital readmission rates to be especially powerful in ensuring that mental health patients with comorbid conditions get not only care but also support services upon discharge.

Research into the connections is advancing as well, looking beyond the behavioral associations to biochemical roots. An article published last month, based on preclinical work on mice, suggests that decreased serotonin transporter function may be the common thread between depression and insulin resistance.[12] Better coordination of care may help doctors distinguish between true depression and "fatigue" from dealing with symptoms. Preliminary results presented in San Francisco found that measures of depression dissipated among many patients who received interventions aimed at helping them manage their disease.[13]

"What's important about this," said Lawrence Fisher, PhD, ABPP, of the University of California San Francisco and lead author of the study, "is that many of the depressive symptoms reported by people with type 2 diabetes are really related to their diabetes, and don't have to be considered psychopathology. So they can be addressed as part of the spectrum of the experience of diabetes and dealt with by their diabetes care team."[14] **EBDM**

Learning What Stress Does to the Mind Is Key to Understanding What It Does to the Body

Mary K. Caffrey

Modern life is full of stress, and understanding how stress affects the brain is essential to developing ways to prevent its harmful effects on the body, according to Gregory Fricchione, MD, of Harvard Medical School.

Fricchione's May 4, 2014, talk, "Mind/Body Medicine: The Link Between Clinical Medicine and Public Health," gave attendees at the 167th Annual Meeting of the American Psychiatric Association in New York City a lesson in the brain's evolution, alongside insights on how stress plays out in the population as obesity, type 2 diabetes mellitus (T2DM), depression, and cardiovascular disease.

The development of vaccines, antibiotics, and other drugs have allowed the world's doctors to tame many communicable diseases over the past century. It's the noncommunicable diseases that are causing increased suffering and cost to the US healthcare system and, more broadly, to the world economy, said Fricchione. He quoted data from a report that the Harvard School of Public Health prepared for the World Economic Forum, which stated that neuropsychiatric disorders, cardiovascular disease, chronic respiratory disease, cancer, and diabetes will cost $47 trillion by 2030.[1]

"For psychiatry, the story gets even more intense," Fricchione said. The common thread among these diseases is the brain and body response to stress, so the key to stemming rising costs and economic loss is to learn, "what we can do as psychiatrists to help out patients mount the best defense against noncommunicable disease, and especially stress."

Bending the curve, he said, "cannot only mean interventions once you have an illness. You have to push it upstream to ask what you can do for health promotion and disease prevention."

Fricchione said that understanding the pressure the human body and mind face starts with understanding the concepts of attachment theory, allostasis, and resiliency. The sense of security that comes as humans attach to each other is especially important for children, and if it is threatened or severed, that sense of "loss" shows up later, in the form of heart disease, cancer, chronic lung ailments, skeletal fractures, sexually transmitted diseases, and liver failure.

Allostasis refers to the body's natural tendency to work toward stability; when confronted with stress, the body has to work much harder to handle the "allostatic load." Afflictions like heart disease and diabetes also befall those who bear too great of a burden.

"This has to be a core ingredient in how we plan medicine, and in how we plan public health (responses)," Fricchione said. With rising rates of diabetes and obesity, especially among children, he said, "Shouldn't we be having a Manhattan Project in this country to deal with this problem?"

By contrast, when the body is unbalanced and feels a sense of "insecure attachment," that leads to the body developing defenses, including the "use of external regulators to alter mood," and "maladaptive protective factors."

"When stress exceeds resiliency, we see burnout. We see compassion fatigue. Stress can become overwhelming and persistent, and this leads to a downgrading of function," he said. "When stress cannot be metabolized by the allostatic brain mechanism, both health and performance suffer." Thus, the connection between stress and heart function, and stress and visceral pain.

What does all this mean for public health? Payers like Kaiser are recognizing the role that stress plays in disease. For example, there is increased awareness of the need to address stress among caregivers for the ill. Efforts to repair the attachment response will simply make people feel better, Fricchione said. **EBDM**

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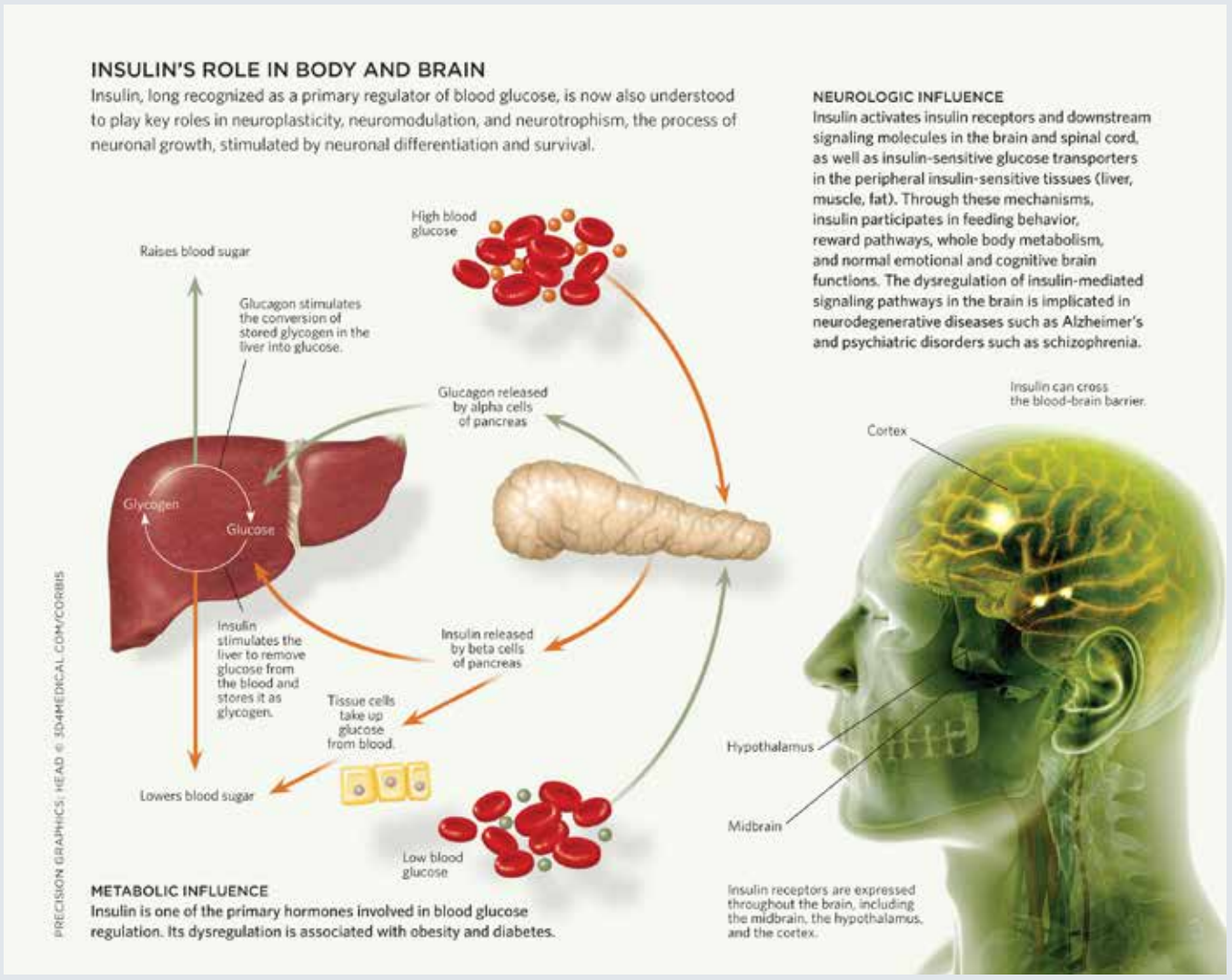
Aging and Cognitive Decline in Diabetes
(continued from cover)

Figure. The Peptide Hormone Insulin Regulates Meabolic Processes and Neuronal Functions[2]

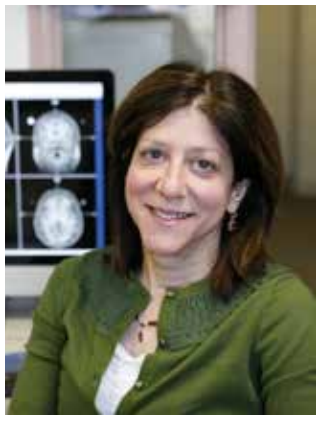


Cognitive Decline and Diabetes

The managed care statistics make it imperative that we try to understand and regulate some of the risk factors of reduced cognition. Based on numerous recent studies, as well as historical evidence, the Alzheimer's Association has recognized diabetes as a risk factor for cognitive disease.[6]

Persons with type 2 diabetes mellitus (T2DM) experience compromised verbal and nonverbal memory, reduced attention, and reduced processing speed, while type 1 diabetes mellitus patients additionally suffer from an impaired visuospatial performance, psychomotor efficiency, and general intelligence.[7] A study conducted in over 800 elderly men and women found that chronic, uncontrolled hyperglycemia can result in slowly progressive functional and structural abnormalities in the brain, with a 65% higher risk of Alzheimer's disease in those with T2DM.[8] A mouse model that evaluated the effect of aging and diabetes on learning and hippocampal synaptic plasticity, observed significant learning impairments in aged diabetic rats compared with controls.[9]

"Older individuals with T2DM are at a higher risk of developing Alzheimer's than the younger population," said Gail Musen, PhD, assistant investigator in the section of Behavioral and Mental Health and an instructor in psychiatry at Harvard Medical School, in an interview with *Evidence-Based Diabetes Management*. Musen's research is focused on identifying risk factors for Alzheimer's disease in persons aged 45 to 65 years suffering from T2DM. "T2DM increases the risk of Alzheimer's disease. Why? We don't know the reason for that yet, although there are reports of insulin resistance or certain vascular problems being responsible for this." Musen said that these patients show only a slight decline in their cognitive abilities that emerge as interesting patterns in the brain magnetic resonance imaging (MRI). "However," she said, "among the older population, those above 65 years of age, a rapid decline in cognitive abilities is observed, highlighting a different etiology between the 2 populations."


Gail Musen, PhD

In Alzheimer's disease, "The default mode network is most susceptible to the build-up of amyloid plaques and hypometabolism," she said. There are no visible early signs of the disease in 20- to 40-year-old individuals, so awareness of family history of cognitive impairment in T2DM patients would be a good indication. "If T2DM is the primary risk factor, it's easier to control," with medication, diet, and exercise. "However, if there are genetic factors involved, that'd be a lot more difficult to regulate." Musen's research group is working toward identifying risk factors for early disease intervention. "Unfortunately, we do not as yet have any reliable serum or blood markers available," she said, although proteins like sirtuin 1 have been projected as early markers of Alzheimer's.[10]

According to Medha N. Munshi, MD, head of Joslin's Geriatric Diabetes Clinic and assistant professor of medicine at the Beth Israel Deaconess Medical Center, "Older diabetes patients are usually more compliant with medication adherence and disease management. When they don't, you wonder why?" Speaking with *Evidence-Based Diabetes Management,* Munshi explained why she was interested in the phenomenon of cognitive dysfunction in the geriatric diabetic population. Her clinical observations in the older patient population that she treated demonstrated that cognitive dysfunction, depression, and an overall declining functional status were a barrier to achieving good glycemic control.


Medha N. Munshi, MD

Munshi's research group assessed these unrecognized barriers by screening adults over 70 years of age for the presence of depression, functional disabilities, and cognitive dysfunction. The finding: 32% of men and 34% of women reported depressive symptoms, which could influence functional disability. Patients recognized to have cognitive dysfunction had poorer glycemic control, probably due to an incorrect dose or timing of insulin or of their oral medication, omission of meals that can lead to hypoglycemia, etc.[11]

According to Munshi, these patients had a fairly good memory–the problem was with executive dysfunction–so integrating their treatment regimen was an issue, resulting in compromised self-care abilities.

MRI of the brain of 614 diabetic patients observed that a longer duration of high fasting plasma glucose level is associated with lower normal and total gray matter volumes, essentially a reduction in the total brain volume.[12,13] The study found that patients who had been diagnosed for 15 years or more had less gray matter than those who had the disease for 4 years or less. While previous studies had attributed the reduced brain size to a reduction in the blood flow, the authors of this study, conducted at the University of Pennsylvania, observed an accelerated rate of degeneration of the brain tissue in hyperglycemic patients, which they defined as a "neurodegenerative insult on the brain." Follow-up studies, evaluating the effect of aggressive treatment in slowing down the rapid cognitive decline, are ongoing.[13]

A Gap in the Knowledge Base

When asked about the efforts being undertaken by treatment institutes and diabetes organizations, like the American Diabetes Association (ADA), in raising awareness about cognitive impairment as a comorbidity of diabetes, Munshi acknowledged that "there is a big gap in the knowledge base–not just among patients and caregivers, but also providers themselves." She continued, "There are not many programs that address some of the additional comorbidities in the older diabetic patients, such as depression, cognitive dysfunction, and polypharmacy. At Joslin, each patient is screened for cognitive decline, unlike most diabetes care providers."

Can Overcoming Insulin Resistance Slow Down the Process?

A clinical trial, conducted as a part of the ACCORD Memory in Diabetes (MIND) study, evaluated the potential of intensive glycamic therapy to reduce glycated hemoglobin (A1C) to <6%, compared with standard therapy that would reduce A1C to between 7% and 7.9%. Of the 2977 patients randomized in the study, 1358 patients received intensive therapy and 1416 received standard therapy. Brain MRIs of these patients presented a significantly lower (26%) decline in the total brain volume of patients receiving intensive therapy compared with those receiving standard therapy. Surprisingly, while the cognitive outcomes were no different between the 2 groups, the intensive therapy was associated with increased mortality, an increase in hypoglycemic events, and weight gain, without any cardiovascular benefits, in the main ACCORD trial.[14] The results of this particular trial do not support the use of intensive therapy to improve cognitive outcomes.

However, insulin and insulin-mediated signaling pathways are known to regulate normal emotional and cognitive brain functions, and may contribute to memory and learning. Historical data points to an association between glucose metabolism and cognitive impairment.[2] Therefore, a different approach might be essential.

A recent proof-of-concept clinical trial, that Munshi participated in, did just that—intranasal insulin delivery to the brain was observed to improve cognitive performance in 15 older T2DM patients, without any effect on blood glucose levels. Binding of insulin, an important neuromodulator, to its corresponding receptors in the brain is regulated by insulin transport through the blood-brain barrier (BBB). Insufficient delivery of this peptide hormone can reduce perfusion and cortical activity, with corresponding effects on cognition **(Figure 1)**. Intranasal delivery bypasses the BBB and also avoids systemic effects of insulin. The authors conclude that the shared insulin signaling in vascular and metabolic pathways can provide new therapeutic targets to prevent brain atrophy and consequent cognitive decline in older T2DM patients.[15]

Cognition and Disease Management

Managing a complex disease like diabetes is extremely difficult and requires the patient to rigorously follow specific disease-management protocols. Impaired cognition could result in cardiovascular effects or severe hypoglycemic events, making it imperative to develop strategies to reduce the risk of cognitive impairment.[14]

A retrospective study conducted by Munshi and her colleagues, evaluating the barriers to glycemic control in the older diabetic population, identified that communication with an educator who is familiar with a patient's barriers can improve self-care frequency, help maintain functionality, and lower stress in the patients.[16] The study concluded that telephone follow-up with the patients in-between clinic visits would greatly improve diabetes control in the elderly, cognition-impaired population.

Taken together, there still seems to be a lack of awareness on cognitive impairment as a risk factor for diabetes, and improving the understanding among patients, caregivers, and physicians is essential. Additionally, treatment plans should incorporate therapeutic strategies for brain health, especially among older T2DM patients. **EBDM**

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Commentary

Value-Engineered Translation: Developing Biotherapeutics That Align With Health-System Needs

(continued from cover)

these evaluation criteria as technologies progress from preclinical testing through clinical testing is not indicative of whether the resulting technology represents a good investment from either commercial or health-system perspectives. Achieving regulatory approval is only indirectly related to criteria that determine reimbursement and health-system adoption of the therapy.[1]

Here we describe the Value-Engineered Translation (VET) framework that couples development decisions along the translational continuum with the production of a "reimbursable evidence dossier." It assists technology develop-

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ers in comprehending the evidence requirements of healthcare payers, both public and private, in different markets. Concomitantly, it supports payers in evaluating a broader range of factors for novel bio-therapeutics that may address unmet healthcare needs. Finally it benefits the public and patients, who require better and more cost-effective therapeutics and diagnostics, by informing decisions on health insurance coverage and out-of-pocket expenses. We illustrate the utility of the framework with real world biotherapeutic development examples, noting that a similar analytical framework is applicable to therapeutics, 'omics'-based diagnostics, combination therapies, or codependent technologies. We begin, however, with a brief description of the changing health technology assessment environment.

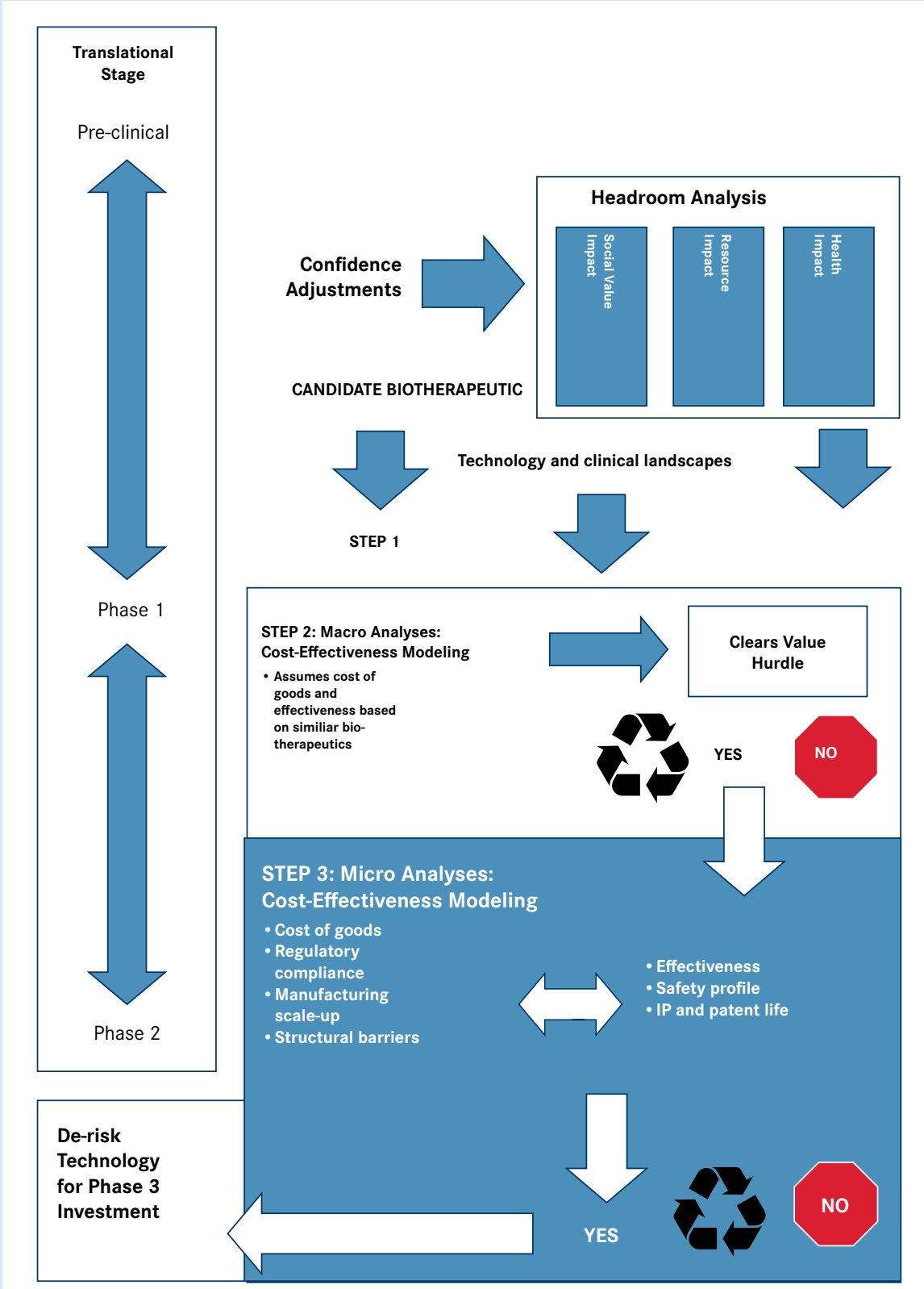
The Case for Health Technology Assessment in Major Markets

Health Technology Assessment (HTA) is a process by which the evidence for the safety, effectiveness and value of technologies is systematically identified, critiqued, and synthesized. HTA informs the reimbursement decisions of payers—should funding for a technology in a particular indication be introduced, maintained, limited, or withdrawn? HTA dates back to the 1976 United States Congressional Office of Technology Assessment report, "Development of Medical Technologies: Opportunities for Assessment."[2] During the 1980s, HTA continued to develop in the United States, notably in the Blue Cross/Blue Shield Technology Evaluation Center (TEC) and its collaborative relationship with David M. Eddy, MD, PhD, of the Kaiser Permanente Care Management Institute, which began in 1993.

However, from the late 1980s to the present day, the role of HTA in health coverage has grown most rapidly outside the United States. HTA agencies operate at national and state/provincial levels in most countries with publicly funded health systems. Notable examples include the Canadian Agency for Drugs and Technologies in Health (CADTH); Australia, which requires economic evaluations to be included in submissions to its Pharmaceutical Benefits Advisory Scheme; and the United Kingdom National Institute for Health and Care Excellence (NICE), which has pushed the role of HTA in decision making with explicit decision criteria supported by increasingly sophisticated methods. To support technology developers, NICE now offers early scientific advice to companies to help them design studies and develop evidence portfolios that meet the needs of reimbursement agencies. Similarly, in Europe, licensing authorities host joint HTA/regulatory scientific advice meetings with biopharmaceutical companies. As the European Union represents 27% of the global biopharmaceutical market, planning to meet the needs of HTA organizations, as well as licensing authorities, is an increasingly important component of pharmaceutical R&D and clinical trial planning.

The United States has the world's most expensive health system, with some of the poorest outcomes in terms of average lifespan and infant mortality among developed countries. Healthcare consumed 17.2% of the gross domestic product (GDP) of United States in 2012, and spending outpaced GDP by 2.0% to 2.3% from 1950 to the global recession in 2007, with some slowdown in the rate of

Figure 1. The Value-Engineered Technology Framework



The Value-Engineered Technology Framework comprises 3 steps: Step 1 is a headroom assessment, which integrates considerations of the health and resource impacts of a candidate technology and whether social values may modify our assessments of those impacts. Steps 2 and 3 are based on the availability of more specific evidence and comprise increasingly sophisticated economic models to assess the likelihood of clearing market access hurdles and the value of alternative R&D investments in terms of their impact on that likelihood.

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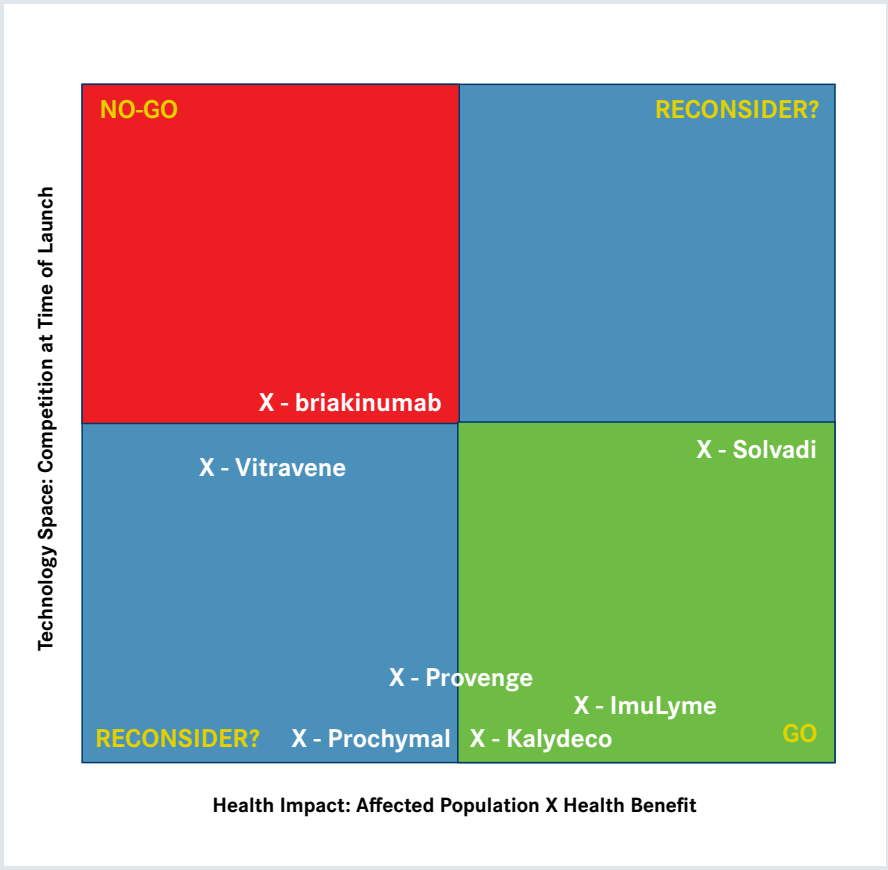
Figure 2. Technology Headroom



A hypothetical plot of two factors that influence headroom for a given technology/indication dyad. The X-axis identifies the health benefit and the Y-axis identifies competing technologies at the time of product launch (current and prospective). For illustrative purposes, we have plotted where the novel bio-therapeutics discussed in this commentary might fall. Note that considerations of social value may drive a no-go decision even for otherwise valuable technologies (e.g., ImuLyme) and vice-versa. A third axis would be resource impact—or costs/benefits to other parts of a health system.

growth since. The high rate of increase in healthcare expenditures is due to a combination of factors, many of which are likely to worsen in the coming decades. These include an aging population and the high cost of new technologies that do not necessarily improve health outcomes compared with existing standard of care. The greatest call on federal coffers comes from the Medicare and Medicaid programs. The former covers all citizens aged 65 years and older and some persons with disabilities; the latter covers individuals below an income cutoff. Medicare covered 46 million people in 2009, 33.2 million were enrolled in Medicaid, and an additional 150 million Americans were covered by private insurance, largely through their employers. The remainder of the population was uninsured.

While US law expressly prohibits CMS from considering cost-effectiveness in national coverage determinations (NCDs), its management stresses the importance of cost control. Jacqueline Fox describes an "open secret" in health policy—CMS considers cost when issuing NCDs.[4] Indeed, one analysis suggests that coverage decisions are influenced by the availability of cost-effectiveness evidence,[5] even though clear evidence of an implicit cost-effectiveness threshold was lacking.[6] Fox calls for CMS to be given the power and obligation to develop transparent processes to consider the cost of new medical treatments before covering them,[4] a call echoed in a 2014 report for RAND Health.[1] This report further called for an alignment in incentives for development of safe and effective health technologies with incentives for the development of technologies that present the greatest value to health systems and patients. Of necessity, value implies considerations of cost-effectiveness.

Several recent developments support our contention that cost will factor increasingly into US healthcare markets. First, in the early part of this century, CMS publicly re-engaged with HTA, implementing Coverage with Evidence Development (CED), where coverage is linked to the collection of additional evidence to inform subsequent reviews of the coverage decision.[7] CED was consistent with the development of conditional reimbursement programs in other Western healthcare systems since the mid-1990s.[8] Access with Evidence Development is now recognized as the term of art for such systems.[9]

Second, the limitation on CMS to consider only whether a diagnostic or therapy is "reasonable and necessary" is largely restricted to hospital and physician services. Coverage of self-administered therapies, including some biologics, is determined by private sector insurance plans and additional state subsidies. These plans may supplement Medicare/Medicaid, be employer based, or be purely private, but all consider costs and many engage in HTA.[10] For example, the TEC may be the most durable HTA program in the world;[11] Washington State Health Authority operates an explicit HTA program;[12] and the California Blue Shield Foundation has supported the California Technology Assessment Forum since 2003.[13] More recently, a group of New England states (Maine, Massachusetts, Connecticut, New Hampshire, Vermont, and Rhode Island) established the Comparative Effectiveness Public Advisory Council (CEPAC) to support clinicians, patients, and policy makers in using comparative effectiveness information.[14]

Third, the Patient Protection and Affordable Care Act (ACA)[15] established the Patient- Centered Outcomes Research Institute (PCORI), a nonprofit corporation, to conduct comparative effectiveness research in a manner that does not discriminate on a number of grounds, including against the elderly and the disabled. PCORI provides the secretary of Health and Human Services with information to compare the effectiveness of treatments, and cost may be an "outcome" measure in the information as long as PCORI does not make recommendations based on cost per quality-adjusted life-year (QALY) thresholds. Entities such as CEPAC support clinicians, patients, and policy makers in using comparative effectiveness information.[14]

The ACA has also influenced existing trends toward increased price sensitivity in health insurance.[1] These trends include increased deductibles in many private insurance plans and declining prevalence of employer-based plans. Added to these are the ACA's excise tax that targets generous employer-sponsored insurance plans, and the high cost-sharing rates in lower-premium plans offered on health insurance exchanges instituted by the ACA. With insurers now limited in denying coverage to those with pre-existing conditions, logic would suggest choosing the options of decreased coverage of expensive technologies and/or increased co-payment. The value of HTA and the innovative payment mechanisms developed under the Access with Evidence Development umbrella is that these provide evidence-based and tried-and-tested mechanisms for bearing down on technology costs.

Other initiatives target physicians to weigh the costs of care in their decisions.[16] Both the American College of Cardiology and the American Heart Association have stated that they will integrate cost and value information in their guidelines, as has the American Society of Clinical Oncology. The guidelines will incorporate published evidence on the cost-effectiveness of interventions, increasing health price transparency. Finally, the ACA enables groups of providers of hospital and physician services, known as Accountable Care Organizations, to receive a share of efficiency gains if they meet quality performance standards.[17]

In this reimbursement climate, breakthrough technologies such as Vertex Pharmaceutical's Kalydeco for cystic fibrosis, approved by the FDA in 2012, and Gilead's Sovaldi for hepatitis C infection, approved by the FDA in late 2013, are experiencing substantial pushback from payers, due to the prices their manufacturers wish to charge. The former is specific to only 4% of individuals with cystic fibrosis with a specific gene mutation, and costs $307,000 a year per patient, well above most reimbursement thresholds. The latter is priced at $84,000 for 12 weeks and $168,000 for 24 weeks of treatment. It is yet to be seen whether new hepatitis C treatments about to enter the market, and discussion of combination therapies, will drive down the price of this drug.

Thus, value assessment is an increasingly real and immediate component of the market access process in the United States, as it has been for many years in other developed countries. The necessary corollary is that value assessment becomes part of the clinical translation process.

Value-Engineered Translation Framework

The value-engineered translation (VET) framework was designed to evaluate translational candidate biotherapeutics for their potential to clear value-based reimbursement hurdles.[18] It comprises 3 distinct steps along the translational continuum—headroom analysis, macro analyses, and micro analyses—as shown in **Figure 1**. It provides developers with information at specific points in the process to inform "go-no-go" and research prioritization decisions. For technologies that clear all 3 stages, the framework provides a reimbursement portfolio to incentivize investment in, and inform design of, costly phase 3 clinical trials. The portfolio is a starting point for designing the final evidence

package to submit to HTA agencies for reimbursement decisions.

This discussion will focus on the first phase. It comprises a headroom assessment, which integrates considerations of the health and resource impacts of a candidate technology and whether social values might modify our assessments of those impacts. The second and third phases of the VET framework are based on the availability of more specific evidence and comprise increasingly sophisticated economic models to assess the likelihood of clearing market access hurdles, along with the value of alternative R&D investments and their impact on that likelihood.

Headroom Analysis

Headroom analysis evaluates any unmet need for a candidate technology for a specific indication to support a price consistent with an acceptable return on the investment in clinical translation (**Figure 2**). In other words, it considers the scope for therapeutic or health system benefits of a technology relative to other existing technologies or those expected to be on the market at the time of product launch. This phase may commence as soon as a technology or indication dyad has been specified. It first assesses the maximum health gain that could be achieved if a new therapy restores the affected individual to his or her full health, with consideration for age and gender. However, if existing therapies are successful in restoring a patient's health, then it will be very difficult for a new therapy to justify a premium price on the basis of health delivered.

Fortunately, in a value-based decision framework, improvements in the cost of care are also valued, as they reflect potential health gain for other people served by the health system. Thus, the second component of the headroom assessment considers whether the candidate technology could achieve savings elsewhere in the system that would be valued by the budget holders, as releasing resources to provide healthcare to others.

The final component of the headroom assessment contemplates whether the characteristics of the technology, the disease, or the affected population would modify the value of the health benefits or resource savings for the decision maker. For example, many jurisdictions incentivize technology development for rare/orphan diseases and for pediatric populations.

The assessment of headroom draws upon insights from clinical landscaping, which maps how the condition is currently managed in target healthcare systems, and technology landscaping, which draws upon patent, clinical trials, and trade and publications databases to identify potential competitor technologies likely to be on the market at the expected time of product launch. The former assessment specifies current headroom and the latter determines the likely headroom at the time of market access. Combined, these analyses determine whether the technology is likely to be a first to market, a fast follower, or a me-too, all of which would influence the ability of a developer to command a premium price.

The final component of the headroom assessment combines the methods of evidence synthesis and Bayesian expert elicitation. It examines the preclinical and early clinical data for evidence of publication bias, which forms the basis for adjusting expectations about the scope of the new technology for "over-confidence" bias.

Why Should Health Technology Developers Consider Headroom?

Here, we present retrospective and prospective examples of how early analysis of headroom may aid in decisions along a translational continuum. The first example illustrates the need for analysis of future market prospects—technologies may fail close to clinical adoption if the expected health benefit shrinks at the time of market entry. Vitravene (fomivirsen), an antisense therapy developed at the National Institutes of Health and licensed by Isis Pharmaceuticals, Inc, was approved by the FDA in August 1998 to treat cytomegalovirus retinitis (CMV-R). During its development in the 1990s, AIDS had transformed CMV-R from a rare disease into one of the most common ocular infections in the United States. When approved for use, Vitravene was a biomedical breakthrough as the first FDA-approved antisense therapy. While Vitravene was in phase 3 clinical trials, Highly Active Anti-retroviral Therapy (HAART) regimen, the "3-drug cocktail", was developed to suppress HIV replication and allow the immune system to recover. As a consequence, the number of new cases of CMV-R declined by nearly 75%. When Vitravene reached the market, distributed by Novartis Ophthalmics AG, HAART had been standard therapy for about a year. New cases of CMV-R were less common, and many existing cases no longer needed treatment; in other words, the health crisis that Vitravene was designed to address had receded and sales of the product were much lower than predicted. As a result, Novartis no longer markets Vitravene, but Isis Pharmaceuticals still cites Vitravene as evidence of its "ability to meet FDA and European regulatory requirements for safety and efficacy, and for the commercial manufacture of antisense drugs."[19]

The ACA has also influenced existing trends toward increased price sensitivity in health insurance. These trends include increased deductibles in many private insurance plans and declining prevalence of employer-based plans.

The second example illustrates that delays in evidence development for regulatory approval and legal rights may lead to a loss of headroom if they enable a competitor to enter the market, making a therapy a fast-follower rather than a first-in-class. In 2008, Abbott Laboratories (now AbbVie) began marketing an anti-TNF-alpha human monoclonal antibody, Humira, as a therapeutic for anti-inflammatory disease, including psoriasis. The antibody was derived from a phage display library obtained from Cambridge Antibody Technology (CAT).[20,21] Abbott disputed the royalty payments to CAT on products it developed from antibodies it had licensed. Abbott lost the court case in 2004, resulting in royalty payments to CAT of 5% instead of 2% on net sales.[22] At the same time, Abbott was developing another anti-inflammatory therapeutic, anti-IL-12/23 human monoclonal, briakinumab, also obtained from CAT. Despite Abbott's positive phase 3 results in 2009 for treating psoriasis, the FDA demanded additional data.[23] Later that year, Centorcor Ortho Biotech Inc (now Janssen Biotech) received FDA approval for its anti-IL12/23 monoclonal StelaraTM (ustekinumab).[24] In 2011, Abbott announced it had withdrawn its application with the FDA and the European Medicines Agency for briakinumab, partly because of a competitor and in part to avoid competing with its existing market for Humira.[25]

The example of 2 FDA-approved recombinant Lyme disease vaccines from the late 1990s illustrates the potential negative impact of social values on headroom for a technology. While social values can lead decision makers to approve technologies that would otherwise not be considered cost-effective, they can also produce a contrary effect. In 1998, FDA approved SmithKlineBeecham's (now GlaxoSmithKline's) LYMErix. Pasteur Merieux Connaught (now Sanofi) conducted phase 3 trials of its vaccine ImuLyme at the same time, but never applied for FDA approval. LYMErix trials demonstrated only 76% efficacy and required 3 doses. Additionally, it was approved for a restricted population: persons aged 15 to 70 years who lived in endemic areas and who engaged in activities with frequent exposure to ticks. After 1 year on the market, reports of adverse events began to appear and the media covered stories about "vaccine victims." A class action lawsuit was filed against the company. While the FDA did not find a higher rate of adverse reactions among a small group who received the vaccine, some studies suggested HLA DR4+ patients who received the vaccine might be at a higher risk for developing chronic treatment-resistant arthritis. The FDA convened a public meeting in 2001 to discuss the risks and benefits of the vaccine. After a highly contentious

Delays in evidence development for regulatory approval and legal rights may lead to a loss of headroom if they enable a competitor to enter the market, making a therapy a fast-follower rather than a first-in-class.

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An HTA framework that starts with an analysis of available headroom is valuable from an R&D investment standpoint only when supported by further economic modeling, as the evidence of safety and efficacy mount.

discussion, the FDA made no changes to the use and labeling of the vaccine, but required the manufacturer to provide data from a phase 4 (postmarketing) trial. With all the negative publicity, sales fell off and GlaxoSmithKline withdrew the vaccine from the market in 2002.[26]

Our work with the regenerative medicine community is leading to greater awareness of cost-effective development of related technologies.[18] Two current examples in regenerative medicine are Osiris Therapeutics Inc's Prochymal, a stem cell therapy to treat steroid-refractory graft-versus-host-disease (GVHD), which was the first off-the-shelf regenerative medicine therapy to gain regulatory approval in Canada in 2012. The conditional approval, requiring ongoing collection of evidence, was only for children with the rare condition. No provincial health plan in Canada has approved reimbursement for the therapy—evidence that regulatory approval is no longer equivalent to market access.

The FDA approved Dendreon Corporation's Provenge (sipuleucel-T) in 2010 as an autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. However, Provenge has struggled since its approval due to its administration procedure and the cost. Physicians balk at the $93,000 cost of a course of therapy for an expected 4 month survival benefit for prostate cancer patients. Research found that 57% of physicians indicated a maximum price of $30,000 for this scale of benefit.[27] Physicians were concerned with the ability of patients to pay or copay for expensive therapies, the need for preauthorization from insurance companies, and the minimal benefit to patients. At the time Dendreon sought FDA approval, Provenge was a first-in-class immunotherapy. However, the FDA required further evidence of efficacy, which delayed the launch. Now Provenge struggles for market share against rival drugs: Xtandi, from Astellas and Medivation and Zytiga from Johnson & Johnson. The company's share price and workforce now reflect its decline in fortunes.

From a prospective standpoint, the key lesson for health technology developers is that reimbursement considerations influence all markets. An HTA framework that starts with an analysis of available headroom is valuable from an R&D investment standpoint only when supported by further economic modeling, as the evidence of safety and efficacy mount. For example, a simple plot of disease burden (patient population and potential health impact of the technology) plotted against existing and prospective technologies, is a valuable basis for R&D investments, from both funding and research career perspectives. For example, the headroom for an expensive stem cell therapy for myocardial infarction—with limited benefits for patient survival and quality of life compared to a plethora of existing technologies—is low when compared with an expensive stem cell therapy for severe sepsis or a treatment for triple-negative breast cancer, which present an increased health gain, especially when alternative therapies are lacking.

In conclusion, it is imperative for stakeholders in translational research—whether funding agencies that invest public moneys in health R&D, researchers who invest their careers, or industry that brings products to market—to consider uncertainties in clearing increasingly high reimbursement hurdles. A well-structured HTA does not lead to certainty in a changing environment, but it identifies risk factors and promotes investment in technologies with a high likelihood of successful clinical adoption and reimbursement. **EBDM**

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